Aims and Scope

*Trends in Anaesthesia & Critical Care* aims to be a leading biomedical review journal, providing reviews and comment on highly topical subjects and the latest breakthroughs in basic, clinical and translational research. This includes basic and clinical research aimed at understanding disease processes and clinical practice of importance to anaesthesia and critical care. The aim is to stimulate debate on new research, cover controversial topics, or provide a new framework for, or interpretation of, an old problem or current issue, or speculate on the implications of recent research and clinical advances in health care infrastructure concerns at national or international levels. Many of these subjects also raise ethical, legal and financial issues and TACC may include articles on such matters.

The journal's objective is to provide a platform for discussion, analysis and debate of these topics across a diverse, multidisciplinary audience of basic scientists and clinicians, who share the common goal of understanding anaesthesiology, pain, pharmacology, critical care and related subject areas with a view to new clinical practice. Communication of the emerging concepts and ideas will facilitate progress in exciting and evolving field of anaesthesia and critical care.

Reviews and Opinion articles form the foundation of each bimonthly issue. Reviews objectively chronicle recent and important developments. Opinion articles provide a forum for debate and hypothesis. The Focus section includes short articles highlighting topical issues and providing comment on recent research papers of particular note. Articles are carefully commissioned, peer-reviewed and edited to provide authoritative, critical and accessible insights.

*Trends in Anaesthesia & Critical Care* also welcomes correspondence. Letters may address topics raised in recent issues of the journal, or other matters of general interest to the field. The decision to publish rests with the Editor-in-Chief at all times. The author(s) of articles discussed in a Letter will normally be invited to reply.

If you are interested in suggesting an article for consideration, please submit a one-page summary with a list of key references to tacc@elsevier.com. Authors should note that all articles are peer reviewed and publication cannot be guaranteed.

Editor-in-Chief

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The age of 21 years has a particular meaning to many individuals and to many groups and cultures. It is usually equated with 'coming of age' in some form. The journal Current Anaesthesia and Critical Care (CACC) was 21 years old in 2010. CACC was unique when it was born. Continuing Medical Education (or Continuing Professional Development, CPD) was well established and journals existed in many specialties but not in Anaesthesia or Critical Care. CACC was the first such journal for these important specialties. Over the years, more CPD journals appeared for our specialty, some of which have disappeared again while CACC lived on. The world of education progresses and with it CPD itself has changed. The Royal College in the UK and other National Societies and Institutions across the world quite correctly now takes the central role and the internet is being used for provision and recording of CPD. So the need for such CPD journals has waned and this, sadly, has included CACC. It was with great reluctance that we have made the decision to cease to publish CACC. The World Wide Web, however, has guaranteed that the valuable information which it contained would live on.

"The bird meanwhile had become a fireball; it gave one loud shriek and next second there was nothing but a smouldering pile of ash on the floor" CACC luckily did not catch fire - we decided on a controlled end to its publication. The phoenix which Harry Potter witnessed was immediately reborn from the ashes and this is exactly what is happening here. Current Anaesthesia and Critical Care has become reborn as Trends in Anaesthesia and Critical Care (TACC).

Readers may already be familiar with the highly successful 'Trends' series which has been published for over 30 years. 'Trends' is a very exclusive family and it is a great pleasure to be joining it. It has, of course, a different format to CACC and we will be following the Trends format with TACC. This will be a journal for reviews and opinions and not for original articles. Reviews will be concise and balanced, and focussed on recent research or clinical practice in rapidly progressing or emerging areas. They will provide a view on a recent exciting paper or a group of related papers in the primary literature. Opinions will present a personal viewpoint on an important topic, intending to stimulate debate or further research. We of course invite letters to the editor related to any previously published article.

All articles in TACC are peer reviewed. There will be something for everyone. They will be aimed at the full audience range to include students, trainees, basic scientists, clinical scientists, clinicians and specialists. Articles will cover subjects relating to the fields of anaesthesia, critical care, pharmacology, pain, clinical practice and related areas.

"Fascinating creatures, phoenixes. They can carry immensely heavy loads, their tears have healing powers and they make highly faithful pets". We cannot offer all of this but we hope that you will enjoy reading TACC.

Reference

EDITORIAL

Ethics, consent and pharmacology

The reader could be forgiven for pondering the links between these three fundamental issues in the practice of anaesthesia and critical care. At a superficial level, the link is very simple – all three are addressed in this first issue of Trends in Anaesthesia and Critical Care. This is not, however, the limit of the relations between these three topics.

Ethics in medicine has existed since time immemorial. Ethics in society has probably existed since the human race began to populate the Earth. Modern society would not be able to function without the codes of conduct, ethics and morality which govern our behaviour and existence. Basic human rights are but one example of some of the practical application of codes of conduct within our society. Codes of medical ethics exist across the globe and have strong similarities all over the world. Every country has its medical regulatory body each of which provides a code of conduct for its members – based on codes of ethics. In this issue, Lawson examines models and principles of ethics and how they relate to original philosophical theories, putting them into the context of current ethical teaching in the practice of medicine.

Amongst the codes of ethics and behaviour for every doctor is to ensure that their patients are kept fully informed of their condition and treatment. The old paternalistic approach where doctors told patients what was going to happen without any involvement of the patient in the decision making process is no longer acceptable. Patients’ expectations have changed enormously over the last 15–20 years and it is now essential to involve each patient in the decision making process and seek their opinion (and agreement, or not) to the procedure. This includes an explanation of the various risks, benefits and potential complications inherent in the procedure or treatment. Written consent for anaesthesia is necessary in some countries, but not all. Consideration of consent seems always to be topical and the steady stream of litigation alleging lack of information continues.

The obstetric service is a particularly complex area for consent. Understanding and balancing the amount of information available and required is not an easy task in the context of obstetric anaesthesia. Drs. Jackson and Cox explore some of the complex issues surrounding consent on the labour ward. The pregnant cardiac patient provides a significant challenge for the anaesthetist and also for the obstetrician and both consent and management strategies may be difficult. In some institutions these cases are commonly managed by 2 consultants, one with a specific interest in obstetrics and one cardiac and Dr. Iyer and colleagues address this issue.

Pharmacology underpins much of the practice of anaesthesia. It is not normally necessary to involve a patient in (or seek consent for) decisions as to the choice of drugs in anaesthesia. Occasional situations do arise, however, where such discussions do occur. The author encountered several such situations in the immediate time following the unfortunate demise of the singer Michael Jackson. It had been reported in the press that the use of a particular anaesthetic agent might have been contributory to his death. The choice of anaesthetic agent was introduced into the preoperative discussions by several patients, apparently seeking assurance that such a dangerous drug would not be used in their care.

Opioids are one of the oldest drug families known to mankind and are fundamental to the pharmacological management of acute and chronic pain. We have advanced considerably since the use of extracts of poppy. Before I (the author) studied medicine, I trained as a pharmacist and my father was also a pharmacist (practising in the 1940s–1980s). Well do I remember bottles of tincture of opium extract on the shelves. The modern day opioids still exhibit the well-known opioid related side effects (e.g. respiratory depression, miosis, constipation) but we are now appreciating the fact that some of the newer agents seem to have additional side effects, especially in cases of long-term use. Dr. Humble addresses some of these issues.

Much of ophthalmic practice is undertaken under local anaesthesia given topically and also by local injection. Most drugs used for an effect on the eye are given topically in order to localise the effect to the eye and avoid systemic side effects. The thin conjunctiva allows rapid absorption of pharmacological agents. Topical administration has its drawbacks and Drs Gunayadin and Cok explore the hazards of topical administration of drugs to the eye.

Transfer of the critically ill patient across large distances is essential, particularly in some continents and also in military situations. This area has developed into its own subspecialty. It requires teams of dedicated professionals with particular skills and training. Another area with similarly special considerations is expedition medicine. Infections are commonplace in the critical care unit, of interest amongst which is viral hepatitis. A much rarer infection is Dengue fever. The reader will find a great deal of useful information in this issue with respect to these topics.

Finally three focus reviews are included, each of which takes a clinical situation, illustrated by a recent case, and provides a short review on the subject. The TURP syndrome, intrathoracic gastric rupture and Eisenmenger’s syndrome are those covered in this issue.

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What is medical ethics?

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1. What is ethics?

Ethics, or moral philosophy, is a branch of Philosophy concerned with norms and values, rights and wrongs and what ought or what not ought to be done. In other words coming after reflection, argument and analysis, to a sense of what one ought to do under given sets of circumstances. The relationship between physician and patient has been of interest since ancient times, principally concerning the moral obligations of physicians in preventing disease and treating the sick and injured. The physician was deemed to be acting for the good. However the revelation that physicians had been involved in unethical experimentation, and other atrocities, upon humans in Nazi Germany during WW11 seems to have been a turning point questioning the assumption of the good of the physician, leading to The Nuremberg Code on research ethics in 1946 and subsequent declarations.

In the past forty years, technological advances such as artificial ventilation, transplantation and dialysis, along with rise of the concept of autonomy and the decline in paternalism, changed both the ability of medicine leading to prolong life but also the attitude of patients and society to the newfound abilities of medical science. An example still debated is when might it be right to withdraw artificial ventilation and whether withdrawal is ethically different from withholding it? Medical ethics (or Bioethics) has become the study and critical analysis of the ethical issues that arise in the interrelationships between law, medicine, life sciences, theology and biotechnology.

2. Ethics and the law

The law is important and relevant and the practice of healthcare takes place within a framework of laws and regulations relevant to the particular jurisdiction. The fact that something is legal however does not entail that is moral. Nor is the converse true. The Apartheid laws in South Africa and the Anti Jewish Penal Codes in Germany in the 1930s are example of “laws” which we might consider to be unethical. Abortion was legalised in the UK in 1967. Does this mean it was morally wrong before the law changed but not afterwards? There is a distinction and the American jurist; Earl Warren put the relationship succinctly in 1964;

In civilized life, law floats in a sea of ethics. Each is indispensable to civilization. Without law, we should be at the mercy of the least scrupulous; without ethics, law could not exist.3

3. Common sense and subjectivity

A common criticism of formal ethics discussions is that the problems that are discussed can be dealt with a bit of common
sense. Training as a healthcare provider and applying common sense is all you need, not studying moral theory. There is an element of truth to this, for in day-to-day practice doctors and nurses have for generations worked in an ethical manner. Notwithstanding the various “evil” doctors and nurses in history for the most part the training and self-selection of people in the caring professions ensures a high level of “ethical conduct”, and simply learning moral theory does not make one more ethical than learning the ten commandments makes one a Christian. However, we are more often now presented with problems which common sense cannot solve. In the event of a Pandemic flu how will we decide whom to ventilate, would it be morally correct (if illegal) to assist the death of a suffering patient at their request and what is the difference between withholding and withdrawing treatment? These problems are not commonsensical and require explicit moral deliberation to resolve them. It also commonly said that morality is all subjective, however there are common moral norms in most societies such as prohibition of murder or incest. Even when there is a lack of consensus on a matter, for example as in assisted suicide, does not mean there is no objective truth to be found or that it is not worthwhile looking for it.

4. Ethics and religion

For religious believers the answers to ethical problems are often to be found in sacred texts such as the Bible or the Koran and in the various commentaries and discussions that have flowed from them. There are two main problems with using religion as a basis for ethics. The major and most fundamental problem was formulated by Plato in the Euthyphro. Is the good simply good because God commands it, or does God command it because it is good? If the former is true then morality is mere obedience to an arbitrary will. If the latter is true then morality is independent of the will of God, so recourse to knowledge of the divine, at least in ethics, is redundant. A second problem arises, as reliance on religious tenet will involve applying such principles to situations unheard of or undreamt of when the religion was first promulgated. It is not always easy to reconcile ancient religious texts with modern medicine. Another problem is how to convince those who don’t share a religion that they should accept its ethical tenets.

5. Ethical models

Ethics is, broadly speaking, divided into four basic theories of right and wrong actions. Utilitarianism, Deontological or rights based theories (Kantianism), Virtue Ethics (into which we may include feminist ethics) and the Four Principles approach. The four principles approach, which is the most commonly taught model in medical schools, is based on the concepts (or principles) of Justice, Beneficence, Non-Maleficence and Autonomy. It is perhaps the pre-eminent theoretical model used in the health sciences. Virtue Ethics has its roots in the ancient Greek philosophy of Aristotle. Virtue ethicists believe that the rightness or wrongness of an action is embedded in the character of the individual. The deontological approach is most famously associated with the German philosopher Kant, who argued that agents must act rationally and consistently to be moral. Finally Utilitarianism is a moral theory, which weighs the consequences of an act. The morality of an act is crystallised by the consequences, this sort of analysis is exemplified by the usage of outcome measures for populations such as in vaccination.

5.1. The four principles

Beauchamp & Childress first unveiled the four principles approach to medical ethics in 1979. Since that time they have become very popular and have become the standard model for medical ethical discourse and teaching in UK medical schools.

5.1.1. Autonomy

Respect for autonomy is the principle of respect for decision-making capacities of autonomous persons allowing them to make reasoned informed choices. Autonomy can be divided into autonomy of thought, that of intention and that of action. Respect for autonomy has developed into a professional obligation, which is both a negative obligation—we must not constrain autonomous choice; and a positive obligation we must ensure that patients are able to be autonomous as much as is possible. This entails proper disclosure of information relevant to the decision-making process and actively looking to promote autonomy by ensuring understanding. In the context of illness it is probable that there is some degree of impairment of autonomy. In the critical care setting all aspects of autonomy may be significantly impaired.

5.1.2. Beneficence

Healthcare professionals have a moral obligation to act in such a way as to benefit their patients. This is the principle of beneficence preventative medicine and in public health programs. This principle of beneficence has its limitations though. How much risk is it obligatory for a doctor or nurse to take when treating a patient? Those HealthCare Professionals in the armed forces have voluntarily taken on a different level of risk, but in the event of a pandemic infectious disease it is arguable how much risk doctors and nurses are obliged to take. Beneficence also has to be tempered with other factors. An autonomous patient has a right to refuse or decline a treatment even if it is thought to be in his or her best interests, the respect for individual autonomy trumps beneficence in this example. Beneficence has also to be tempered by Non-Maleficence and Justice.

5.1.3. Non-Maleficence

The principle of non-harming is also central to medicine. However it is a truism that all treatment has the potential to do harm. Invasive monitoring on the ITU involves a risk of complication and will cause some discomfort or pain as will any surgical procedure. The harm caused needs to be proportional to the benefit.

5.1.4. Justice

Justice in this context is concerned with the fair distribution of health resources.

Doctors often feel that this “distributive justice” impacts on the relationship between them and the patients under their care, arguing that their obligations are to their patients and that the responsibility for allocation of resources does not function at the bedside. However marginally beneficial intensive care may be justifiably limited on the basis of societal consensus that its cost is too high in relation to the value of its outcome. The American Thoracic Society bioethics task force stated in 1997 “extraordinary expenditures of resources for marginal gains unfairly compromise the availability of a basic minimum level of healthcare services for all.” Such issues have great relevance in the context of dealing with pandemics.

The four principles approach has proved very popular and is amenable to use in many differing situations and forms a workable template in practice. However it does have limitations. It is difficult to see how one orders the principles in complex situations and how one settles conflicts between principles. In much common discourse solutions to ethical problems have been reduced to a simple recitation of the four principles without consideration of
the abstract concept of what the principles actually mean, as if a solution can be simply achieved just by invoking the principles. Clearly interpretation of them in the context of a problem is desirable. However notwithstanding any criticisms, the success of the four principles approach is testament to their utility.

6. Utilitarianism

For the purposes of generalisation utilitarianism can be defined as a consequentialist philosophy whereby actions are held to be right or wrong by virtue of their consequences. It has its roots in the writings of Jeremy Bentham and John Stuart Mill and is fundamentally based on the “fact” that suffering is evil and happiness is good. Acts are considered right when they maximise net welfare. The rightness of an act (or healthcare intervention) is crystallised in terms of the welfare of the persons, or population, concerned. The sum of the positive and negative effects are aggregated. Thus for any given healthcare intervention the overall balance of benefit over harm is what is assessed by a consequentialist analysis.

Healthcare planning, strategic decisions over resource allocation and decisions as to how to allocate resources in pandemics or emergency situations are good examples of where consequentialist analysis is used in contemporary healthcare. The large scale economic analyses of the National Institute for Health and Clinical Excellence using such tools as the QALY, the quality adjusted life year, and vaccination programs also have a consequentialist, aggregating basis to them. The herd immunity produced by vaccination may not necessarily benefit a specific person nor might an identifiable person benefit from a treatment recommended by NICE but in both cases the health gains to the population are maximised. Utilitarianism has always suffered from the problem of consequentialist conception of morality and virtue that any means can be used to justify a good enough end. To use a controversial issue, if autism were actually caused by the MMR vaccine in a small number of children then the net benefits to the population would justify this harm to them when viewed through a consequentialist lens. This seems to be almost counter intuitive, conflicting in some way with our common morality.

Utilitarianism can be seen as too demanding and also to a certain extent diminishes individual responsibility. For each action or decision, an agent makes a calculation of net benefit to determine whether the consequence produces an overall increase in happiness of all concerned, at that point and in the future. Imagine a field of dominoes laid out in random patterns, how could you predict which will fall when a single domino is pushed over? A utilitarian would also state that I, having pushed the first domino over, must have responsibility for all the other falling dominoes. This may be true of the dominoes but human beings are not dominoes and make decisions as to how to act. The utilitarian removes their responsibility for their actions because their “falling” is a consequence of the first domino falling. As Benn points out “the results of assigning responsibility so promiscuously is that no one is really responsible for anything”.

Utilitarianism implies that people should give up what they have at all times to benefit others who are in greater need. This is not consistent with social mores now or in the past. In advocating the approach that all should behave in such a manner it devalues those who do so, as it does not distinguish between obligatory actions and supererogatory. A supererogatory action is one that goes beyond what we might call the call of duty, the normal and accepted degree to which we should act. The demand to maximise happiness, however defined, would have implications for how can we define the geographical limitations of our obligations. We would be obliged to forego intensive care in the UK until those resources had been used to bring the level of healthcare in developing countries up to our basic standard. A laudable aim, but not practical in a political or sociological sense.

7. Deontology and Kant

Deontological moral theories are broadly speaking in opposition to consequentialist theories in that the morality of an action is a function of the act itself rather than the consequences. Moral rightness consists of acting rationally and consistently, independent of empirical or other motives. Emmanuel Kant, an eighteenth century Prussian philosopher is seen as a father of modern deontology. He believed that humans had autonomy of will and could by acting rationally in accordance with a “supreme moral law” ensure the rightness of their actions. He formulated the “categorical imperative” that stated that we should always treat rational human beings as an end in itself and never merely as a means to an end. He stressed that we should only act on principles that we would wish to become universal laws, and stressed the independent moral worth of a person.

Kantianism has been criticised for being too absolute, he was unequivocal that the supreme moral laws applied without exception. Thus to lie, even to save a life, would be a moral wrong. The absolutist stance also gave no weight to concepts such as being good, caring or helping others and seems out of keeping with our “common morality”.

More recently W D Ross in the early 20th century refined deontological concepts stating:

The moral order... is just as much part of the fundamental nature of the universe (and... of any possible universe in which there are moral agents at all) as is the spatial or numerical structure expressed in the axioms of geometry or arithmetic.

He described seven prima facie duties;

Fidelity — Fulfilling promises (implicit and explicit)
Reparation — Making up for wrongful acts
Gratitude — Repaying for past favours
Non-maleficence — A duty to not injure others
Justice— Promoting the distribution of happiness
Beneficence — A duty to improve the condition of others Self-improvement.

Despite criticisms of lists and the absolutist nature of deontology it has strong contemporary resonance. The general medical council has a list of “duties of a doctor”.

Make the care of your patient your first concern
Protect and promote the health of patients and the public
Provide a good standard of practice and care
Treat patients as individuals and respect their dignity
Work in partnership with patients
Be honest and open and act with integrity.

8. Virtue Ethics

Virtue Ethics has its roots in ancient Greece in the teachings of Plato and Aristotle. Plato discussed four key virtues: wisdom, courage, temperance and justice. Aristotle considered that when people acquire good habits of character, they are better able to regulate their emotions and their reason. Virtue ethicists thus think that right and wrong cannot be defined in terms of pre-set moral principles or rules. The distinction is made between right and wrong by being sensitive to situations in a moral sense or expressing fundamentally good or admirable character traits. In virtue ethics, the motives and character of the agent are what
counts. They help us reach morally correct decisions when we are faced with difficult choices.

As a principle for developing good moral characters, being virtuous is appealing. As a means of solving difficult ethical problems though it seems to have some disadvantages. How do we determine what is the “right” sort of character and how does just having the right sort of character ensure a correct decision? Similarly how do we distinguish or rank differing virtues. Perhaps as an ethical model it says more about the psychology of morality than the nature of moral truth.

9. Which model and when?

No one model can provide a solution to all ethical dilemmas and it would be surprising if were so. Kantianism seems to grate against human psychology, utilitarianism may be too demanding, virtue ethics a bit fuzzy and the four principles may seem a little too simplistic. They all have their shortcomings. We may though make a broad distinction between macro ethical problems such as resource allocation across society and choices as to what treatment is best for a given disease and the micro ethics of dealing with patients on an individual level. Healthcare in general has a strong utilitarian basis as described above. Optimising which treatment for sepsis involves pooling data and producing a population based recommendation. That recommendation may not be valid for an individual, indeed we cannot be certain that any treatment will work definitely for a given individual, but we know we can maximise the outcome for a group. At the micro level whilst, a degree of maximising outcome occurs the relationship between the doctor or nurse and the patient is more about being “a good person”, doing the right thing for him or her. It is perhaps at this level that the four principles come into their own. Using medical ethics helps us formally conceptualise what are often complex issues. The varying models give us tools to explain the moral reasoning behind our analyses and decision-making process.

Conflict of interest
None.

References
1. Miriam Webster online dictionary.
Consent on labour ward

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SUMMARY

Consent is relevant to all areas of anaesthetic practice, but labour ward presents one environment where consent can be particularly problematic. This article investigates issues surrounding the timing, content and delivery of information prior to anaesthetic procedures as well as the capacity to consent in labour and the emergency setting.

1. Introduction

Consent to anaesthetic intervention in the labour ward presents a number of issues and there are several scenarios in which the anaesthetist on labour ward becomes involved in the consent process. Changes in case and statute law relating to consent, along with women’s changing expectations, demand a less paternalistic approach than has been traditional. Many anaesthetists have yet to modify their practice to reflect fully these changes in society and the law. In contrast to the day to day practice of general anaesthetists, labour analgesia requires consent to be sought by the anaesthetist for a standalone procedure, rather than in combination with a surgical procedure. Also, this may not be an elective procedure, in the sense that the request may be made with minimal planning or forethought by the woman for a procedure that needs to be conducted shortly after the consent process. Obviously this presents a number of difficulties which we will investigate further.

The labour ward anaesthetist will also be involved in the consenting process, together with the obstetric team, for a number of other procedures, mainly in the operating theatre, although not exclusively. These can either be elective, semi-elective or emergency procedures (Caesarean section, postpartum haemorrhage, instrumental deliveries, manual removal of placenta, perineal suturing, cervical suture insertion or removal) but the same guidance on consent still applies and there are many different factors that need to be taken into account in each scenario. Particularly difficult is the emergency scenario, where there is little time, and other distractions exist that complicate the consent process. We will explore these areas in more depth and consider consent for elective and emergency caesarean section under both regional and general anaesthesia.

2. Consent

It is beyond the scope of this article to tackle all aspects of the consent process within medical practice. We will focus on those aspects specifically relating to the consent process in and around labour ward.

So, what is consent? There has recently been a huge increase in the guidance written on consent, exploration of consent in medical practice as a whole and within, more specifically, anaesthetic practice. Patient awareness of consent and specifically the desire for more information and more choice has dramatically changed.

The General Medical Council (GMC) introduced updated guidance on 2nd June 2008 and the Mental Capacity Act 2005 came into force, in England and Wales, in October 2008. In Scotland there is separate guidance on the capacity to consent contained within the Adults with Incapacity (Scotland) Act 2000. The Association of Anaesthetists’ of Great Britain and Ireland has also written guidance on consent for anaesthesia and the advice specific to obstetric anaesthesia is summarised in Table 1. These documents have clarified much of the thinking about the consent process for doctors and within healthcare as a whole. Inevitably, however, there still remain aspects that are difficult to clarify with generic guidance documents and even by statute law. These issues will continue to be discussed within medical journals and legal circles and will develop over time in response to these, and other, documents.

There are three main components to valid consent:

- Information
  - The patient must have sufficient information to make a choice
3. Overview of consent on labour ward

The guidance surrounding consent on labour ward has evolved over the years. Whereas in the past it might have been common practice to assume consent, provide minimal information and minimal documentation with the defence of ‘acting in the patient’s best interests’, such practice is no longer acceptable as demonstrated by the increasingly litigious outcomes and legal rulings.

The previous requirement to give a patient as much information as the average man or woman in the street would want has been replaced by an expectation that doctors will give patients as much information as they want or need. The GMC clarify that we should provide the appropriate information and documentation concerning pain relief and anaesthesia during labour and delivery. This information must be prepared in conjunction with an anaesthetist, and arrangements should be in place to ensure that any patient who wishes to discuss techniques with an anaesthetist may do so. Nevertheless, the patient must still be provided with appropriate information at the time of the procedure, the details of which must be documented.

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9.4 Obstetrics

9.4.1 The adult parturient is presumed, like all adults, to have capacity. This may be compromised by drugs, fatigue, pain, or anxiety, although the compromise will need to be severe to incapacitate her.

9.4.2 Labour is the wrong time to burden women with excessive information. It is important that every obstetric unit provides antenatal advice for women concerning pain relief and anaesthesia during labour and delivery. This information must be prepared in conjunction with an anaesthetist, and arrangements should be in place to ensure that any patient who wishes to discuss techniques with an anaesthetist may do so. Nevertheless, the patient must still be provided with appropriate information at the time of the procedure, the details of which must be documented.

9.4.3 Birth plans often include references to analgesia and anaesthesia. If a woman obviously loses capacity during labour, the birth plan should be treated as an advance decision, and any documented refusal of therapy must be respected. However, a presumption of capacity remains in these circumstances. Therefore, competent women who request epidural analgesia during labour, despite recording a refusal in their birth plan, should have their request respected, although they should be asked to countersign any documentation concerning consent for the procedure.

9.4.4 In law, a competent pregnant woman can refuse any treatment for any reason, even if this puts the unborn child at risk of harm or death. An emergency court order may be requested in such circumstances, but will only be granted if the court concludes that the woman lacks capacity.

9.4.5 In general 16 and 17 year-old parturients are to be regarded as adults from the point of view of making decisions about interventions, and children younger than this may be competent depending upon the circumstances. However, young parturients are probably more likely to become temporarily incompetent under the emotional and physical stress of labour. Units should therefore have guidelines in place to ensure that these patients receive antenatal information and advice and, if necessary, anaesthetic referral.

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<td>Birth plans often include references to analgesia and anaesthesia. If a woman obviously loses capacity during labour, the birth plan should be treated as an advance decision, and any documented refusal of therapy must be respected. However, a presumption of capacity remains in these circumstances. Therefore, competent women who request epidural analgesia during labour, despite recording a refusal in their birth plan, should have their request respected, although they should be asked to countersign any documentation concerning consent for the procedure.</td>
</tr>
<tr>
<td>In law, a competent pregnant woman can refuse any treatment for any reason, even if this puts the unborn child at risk of harm or death. An emergency court order may be requested in such circumstances, but will only be granted if the court concludes that the woman lacks capacity.</td>
</tr>
<tr>
<td>In general 16 and 17 year-old parturients are to be regarded as adults from the point of view of making decisions about interventions, and children younger than this may be competent depending upon the circumstances. However, young parturients are probably more likely to become temporarily incompetent under the emotional and physical stress of labour. Units should therefore have guidelines in place to ensure that these patients receive antenatal information and advice and, if necessary, anaesthetic referral.</td>
</tr>
</tbody>
</table>

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- Capacity
  - The patient must be competent
- Voluntariness
  - The patient must be able to give their consent freely

We will explore further these main areas as well as looking at specific scenarios common on labour ward.

3.1. Information

Without adequate information patients are unable to make informed decisions about their treatment. However, how does one decide what information should be given — is it more important to impart the information the clinician views as important or rather the information the patient thinks is important? The GMC’s guidance on the sharing of information and discussion of treatment options is comprehensive, but not tailored to any one speciality (Table 2). So, the GMC clarify that we should provide the appropriate information to the situation and give the information the patient wants. Essentially we need to tailor the information provided to the individual.

There have been a number of studies investigating what women want to know regarding regional analgesia and anaesthesia. The results vary depending on when the patients are asked, which raises the question of when it is best to impart this information. There are a few issues surrounding the timing of the giving of information. First labour and delivery do not happen without warning, there are months before the actual delivery allowing, theoretically, plenty of time for planning, education and documentation. Theoretically this should work but, as we know, this is not as easy to achieve for a variety of reasons. Second, pregnancy, particularly a first pregnancy, is a very busy, stressful and confusing time for mothers.

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMC guidance on the sharing of information and discussion of treatment options.</td>
</tr>
</tbody>
</table>

The exchange of information between doctor and patient is central to good decision making. How much information you share with patients will vary, depending on their individual circumstances. You should tailor your approach to discussions with patients according to:

- their needs, wishes and priorities
- their level of knowledge about, and understanding of, their condition, prognosis and treatment options
- the nature of their condition
- the complexity of their condition
- the nature and level of risk associated with the investigation or treatment

You should not make assumptions about:

- the information a patient might want or need
- the clinical or other factors a patient might consider significant, or
- a patient's level of knowledge or understanding of what is proposed

You must give patients the information they want or need.

You should explore these matters with patients, listen to their concerns, ask and respect their views, and encourage them to ask questions. You should check whether patients have understood the information they have been given, and whether or not they would like more information before making a decision. You must make it clear that they can change their mind about a decision at any time.
Whilst we, as the potential doctors involved in a patient’s care, have our own agendas regarding planning and discussion of care, the patient themselves may have an entirely different agenda that may not include any discussion at all about the possibility of hospital care during their planned delivery. There are many different views as to how labour should be conducted by many different interested parties. Prospective mothers may only consider the potential ‘medical’ implications and interventions briefly and not lend as much weight to the issues that we, as doctors and anaesthetists, consider to be the important ones.

### 3.1. Timing of information

Antenatal education of anaesthetic issues could be ideal if there were the time for appropriately senior anaesthetists to teach in this type of forum and the ability to target the correct audience (i.e. those who were going to require an intervention) who were then able to retain the information without the need to repeat the same process at the point of delivery. However, there is very little input from anaesthetists antenatally, and women receive information from many sources. They may have been given the impression that labour is not particularly painful and that analgesia is usually not necessary. They may have decided in advance that they would prefer not to have regional analgesia and be disappointed if they then feel they need it. Consent to an anaesthetic intervention is still all too often discussed with the anaesthetist between contractions in a distressed situation. Over recent years there has been a move to greater availability of anaesthetic antenatal clinics in many hospitals. This has allowed discussion of anaesthetic issues to a targeted audience but will never be able to accommodate every pregnant woman. There is also a greater awareness amongst expectant mothers of anaesthetic issues, in particular analgesic options. Recent pressure groups may go on to influence patient desire to consult anaesthetists prior to labour.

### 3.1.1. How much information?

The next factor to determine is how much information to provide to women and this can vary depending on the timing, external influences (i.e. category I caesarean section), and type of anaesthetic (regional vs general anaesthetic) being discussed. A recent study showed that women’s views on the provision of information regarding regional analgesia in labour varied widely. Their preferred level of risk at which they wanted to be informed varied from 1:1 to 1:1 000 000 000 and concluded that anaesthetists should be flexible in their disclosure of information when obtaining consent for regional analgesia and consider the particular wishes of the patient rather than follow rigid centralised guidelines. These sentiments are reflected in a similar study investigating the risk information for general anaesthesia on labour ward. This, again, showed that women varied widely in the range of risk information they felt they should be informed about prior to a general anaesthetic (1:1 to 1:1 000 000 000), specifically on labour ward. It also showed that women vary in their background knowledge of general anaesthetic risks and this may also differ between hospitals.

Other studies have suggested that while women want to know most, or all, of the risks associated with regional anaesthesia in labour, many do not want to know the incidences quoted.

Anaesthetists differ in the amount of information they routinely provide in their consenting process. The level of risk at which a complication should be discussed is controversial. A level of 1% is often quoted but is out of date and, as already discussed, this figure must now take into account the wishes and expectations of the individual woman. Women should be informed of the risk of any complication, however unlikely, that the average person would want to be told about prior to treatment.

### 3.1.2. Written vs verbal consent

Apart from certain treatments carried out under the Mental Health Act and some forms of fertility treatment, there is no legal requirement to obtain written consent. The presence of a signed consent form does not automatically confirm that valid consent has been obtained. Consent can be verbal alone and still be valid, however documentation of the discussion is recommended. Indeed the GMC states that ‘you must use the patient’s medical records or a consent form to record the key elements of your discussion with the patient’. Within obstetric anaesthesia the majority obtain verbal consent and make some record of the discussion on either an anaesthetic form or within the patient notes. A recent study of Australian anaesthetists showed that over 80% of respondents obtain verbal consent and 20% have no record of the consent or its discussion.

Gerancher et al investigated the ability of parturients to recall information provided at the pre anaesthesia discussion to determine if written consent added to this discussion improved recall. The ability to recall information 5–7 months after labour was increased in the group given written information and required to give written consent.

Clearly also important is the ability of women to recall this information that we have decided to impart. It is at this point that we have to start addressing the capacity of a particular woman to consent and it is to this we will now turn our attention.

### 3.1.3. Verbal vs written information

Over recent years there has been a proliferation in written information available for women approaching labour or surgical delivery explaining their options for analgesia and anaesthesia, in English as well as many other languages. Studies have attempted to look into the retention of information dependant on the method of information delivery. A study assessing the benefit of providing written information (Obstetric Anaesthetists’ Association (OAA) information sheet) antenatally showed that ‘the OAA leaflet improves women’s knowledge of analgesic techniques’. There remains, however, little consensus amongst anaesthetists about what information to provide.

The OAA has attempted to standardise the information given to expectant mothers and to this end has produced a variety of written information as well as information in other media, such as DVDs. The written information is available in a large number of different languages and this proves a valuable resource.

Language barriers between women and medical staff present particular problems and, due to the unpredictable timing of events on labour ward, will continue to cause problems despite the expansion of translation services in many NHS trusts over the last decade. Individual translators for women throughout the course of their labour would be prohibitively expensive and the alternatives of using relatives, friends, incidentally fluent staff or telephone based translation services are less than ideal. Without huge financial investment this situation is unlikely to change in the near future. Perhaps the best solution is to facilitate and encourage antenatal discussion, in a planned setting, with the backup of written information in the patient’s own language. However even this requires careful planning and expansion of staffing and already stretched services. The foreign language translations of the OAA information leaflets, free to download from the internet, can be invaluable.

### 3.1.4. Written vs verbal consent

Finally we must also mention the fact that not everyone agrees as to exactly what information should be given regarding regional anaesthetic techniques and general anaesthesia on labour ward. There is no consensus regarding the risks to disclose or even the incidences of those risks. We address this later in this article.
3.2. Capacity

3.2.1. Consent, capacity to consent and the Mental Capacity Act

Having discussed the current position regarding the content and timing of the consent process we now turn our attention to the debate as to whether women in labour can lack the capacity to consent. Commonly referred to as ‘informed consent’, many of the issues have been addressed through the Mental Capacity Act (MCA) which is discussed below. Scotland has its own legislation, the Adults with Incapacity Act 2000, which contains similar principles. Northern Ireland currently has no primary legislation on capacity. Decisions about medical treatment and care when people lack capacity must be made in accordance with common law, which requires decisions to be made in a person’s best interests.1,16

So, can a woman who has written in her birth plan that she “does not wish to have an epidural under any circumstances” change her mind once she has experienced labour and then request epidural analgesia?

The Mental Capacity Act2 came into effect in England (and Wales) in October 2007 and has obvious implications for anaesthetists. It sets out 10 key principles that underpin the legal requirements in the Act:

- ‘A person must be assumed to have capacity unless it is established that he lacks capacity’
  - Every adult has the right to make his or her own decisions and their capacity to do so should be assumed unless proven otherwise
- ‘A person is not to be treated as unable to make a decision unless all practicable steps to help them do so have been taken without success’
  - The patient must be given all appropriate help understanding what is proposed before it is decided that he cannot make a competent decision
- ‘A person is not to be treated as unable to make a decision merely because he makes an unwise decision’
  - Individuals retain the right to make what may seem to be eccentric or unwise decisions
- ‘An act done, or decision made, under this Act for or on behalf of a person who lacks capacity must be done, or made, in his best interests’
  - Any decision made on behalf of a patient who lacks capacity must be in their best interests
- ‘Before the act is done, or the decision is made, regard must be had to whether the purpose for which it is needed can be as effectively achieved in a way that is less restrictive of the person’s rights and freedom of action’
  - Anything done for an individual should be the least restrictive of his basic rights and freedoms

The Act also sets out in detail how to assess capacity stating that in order to be able to give consent a person must be able:

- to understand the information relevant to the decision
- to retain that information
- to use or weigh that information as part of the process of making the decision
- to communicate that decision

There have been a number of studies investigating issues surrounding informed consent both internationally and nationally, both before introduction of the MCA, and after.

Jackson et al3 questioned 60 women in labour immediately after request for epidural analgesia and assessed degree of understanding of the information supplied and the ability to make a free decision. They concluded that labouring women are capable of giving informed consent. Interestingly, only 48% of their patients wanted specific figures quoted for complication rates.

A recent study18 investigated the capacity of women in labour to consent as assessed by women while still in labour. Preliminary data showed that women generally felt that they had received enough information to make a decision but a significant proportion revealed that they did not satisfy the individual components of the MCA during labour. Despite this, most felt satisfied with the process and that they had been able to give their full consent to the procedure. This suggests a potential conflict between women’s wishes and views and the MCA.

Anaesthetists’ opinions on the ability of women in labour to consent have also been investigated. Saunders et al questioned 124 perinatal anesthesiologists from the United States and found that 68% suggested that “patients in active labour are able to give informed consent for labour epidural analgesia”. While this formed the majority of opinion there were 28% who did not feel that “informed consent” was possible in labour.20

So, to return to the initial question posed: can a woman who has written in her birth plan that she “does not wish to have an epidural under any circumstances” change her mind once she has experienced labour and then request epidural analgesia?

Ultimately it is the decision of the anaesthetist seeking consent, and therefore performing the proposed procedure, to satisfy themselves that a woman is able to make an informed decision at the point of consent. The principles of the MCA help to clarify the points that should be satisfied and the underlying principle is that women must be assumed to have capacity unless suspected and proven otherwise. That would suggest that a woman is able to change her mind if the severity of labour pains provides new information that she can use in her decision making process. Good documentation of any subsequent discussion would be advised.

3.3. Voluntariness

The final component to valid consent, according to GMC guidance, is the requirement for the patient to be able to give their consent freely. This requires that women are allowed to make their decisions without pressure from others such as relatives, friends or indeed those seeking the patients consent. Ideally the woman should be given the time and opportunity to consider their options before deciding to proceed with a proposed treatment.

Perhaps relevant to this is the ability to provide information in the woman’s own language and ensuring that any decision is the woman’s own. Ideally relatives or friends should not be used for providing translation due to the risk of either incorrect translation or the inability of the woman to express her true opinion. Clearly this is a complicated matter as it is impossible to provide independent translation services in person all year round on labour ward, however efforts should be made to ensure that a woman’s choice is voluntary and their own.

4. Anaesthesia in the emergency setting

It will be clear to anyone who has worked on labour ward that conditions for obtaining consent are often suboptimal. In an emergency there may be little time to discuss all the implications of the procedures being planned. This excuse cannot be used in the elective setting, such as for elective caesarean section. However, the boundary between emergency and elective procedures is often hazy on the labour ward. Indeed the categorisation of caesarean
section into different grades of urgency has resulted in a, sometimes disputed, scale of timing regarding the length of time between decision to deliver and actual delivery. This results in pressures to proceed that affect any discussion between obstetrician, anaesthetist and woman that will undoubtedly affect any consent obtained. It is important to be aware of these influences and the principles remain that women retain capacity to consent unless evidence that this is not the case. As doctors we must continue to act in a woman’s best interest at all times and strive to provide all the information the woman requires before making a decision. In the emergency situation we may not be able to provide anything other than the most basic and essential of information and this is obviously the appropriate management. As always’ good documentation of the rationale of the decision and the extent of any discussion with the patient, however brief, is essential. Also important is their agreement for the anaesthetist to act quickly without much discussion in certain circumstances and this should also be recorded in the notes. So saying “We need to deliver your baby quickly so I am going to give you a general anaesthetic right now” can be acceptable if the woman agrees with this briefly outlined plan. If, however, she wishes to delay the process for further discussion, that is her prerogative. Most obstetric anaesthetists, and obstetricians, are skilled at a timely intervention of “we are really worried about your baby”, or something similar, in these situations. However, rapid intervention should not be forced on a woman if they do not appear happy with the process.

5. Consent on labour ward – a practical guide

We have reviewed some of the research and current guidance, and addressed some of the practical difficulties surrounding consent on labour ward. However, how is this translated into our practice on labour ward? Clearly, individual practice varies and always will, as ultimately it is the individual anaesthetist’s responsibility to ensure they are satisfied that their practice is of a high standard and in line with peers.

As previously mentioned there is no consensus as to which risks to disclose to women on labour ward or even the exact incidences of those risks. Indeed the risks may vary from hospital to hospital. Recently, however, the OAA has published guidance as to the risks associated with both general anaesthesia and regional analgesia. Table 3a and b summarise the guidance from the OAA although it should be noted that this lists more risks than are likely to be discussed in detail with all patients. Specifically, the risk of nerve damage is often categorised by anaesthetists into minor and temporary, minor and permanent and major, rather than being discussed in more detail with appropriate estimates of risk for each.

Table 3a
Risks of having an epidural or spinal to reduce labour pain.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>1 in 5 (spinal)</td>
</tr>
<tr>
<td>Failure/Inadequate block</td>
<td>1 in 20 (epidural)</td>
</tr>
<tr>
<td>Post dural puncture headache</td>
<td>1 in 100 (epidural)</td>
</tr>
<tr>
<td>Neurological injury</td>
<td>1 in 500 (spinal)</td>
</tr>
<tr>
<td>Epidural abscess</td>
<td>1 in 10000 (Temporary)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1 in 50,000</td>
</tr>
<tr>
<td>Epidural haematoma</td>
<td>1 in 100,000</td>
</tr>
<tr>
<td>Total spinal</td>
<td>1 in 1700</td>
</tr>
<tr>
<td>Total spinal</td>
<td>1 in 900</td>
</tr>
<tr>
<td>Severe neurological injury</td>
<td>1 in 250,000</td>
</tr>
</tbody>
</table>

Table 3b
Risks of general anaesthesia.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest infection</td>
<td>1 in 5</td>
</tr>
<tr>
<td>Sore throat</td>
<td>1 in 5</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>1 in 10</td>
</tr>
<tr>
<td>Difficult airway</td>
<td>1 in 300</td>
</tr>
<tr>
<td>Aspiration</td>
<td>1 in 300</td>
</tr>
<tr>
<td>Corneal abrasion</td>
<td>1 in 600</td>
</tr>
<tr>
<td>Dental damage</td>
<td>1 in 4500</td>
</tr>
<tr>
<td>Awareness</td>
<td>1 in 250–1000</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>1 in 20,000–20,000</td>
</tr>
<tr>
<td>Death or brain damage</td>
<td>Less than 1 in 100,000 (death)</td>
</tr>
</tbody>
</table>

Very rare (brain damage) – exact figures do not exist

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Other aspects to consider discussing regarding regional anaesthetic techniques include the risk of conversion to general anaesthesia, motor block, analgesia (diamorphine or fentanyl) and consequent pruritis and post operative analgesia. As already stated it is ultimately the responsibility of the anaesthetist performing the procedure to satisfy themselves that they have provided adequate information for an individual woman and guidance often varies from hospital to hospital.

6. Summary and conclusions

Providing information to patients and obtaining informed consent is a complex skill developed over years of practice. There is now an expectation that it should be performed well.

The combination of statute and case law, guidance from formal bodies and research about current practice and opinion of anaesthetists and the wishes of parturients can guide our practice in obtaining informed consent.

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None declared.

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References
REVIEW

Management of the pregnant cardiac patient

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Keywords:
Pregnancy
Cardiac disease
Anaesthesia

SUMMARY

Heart disease is a leading cause of maternal death. The aim of this review is to consider the most common causes of cardiac disease in pregnancy, highlight factors that should be recognized by the clinician, and address recent advances in the anaesthetic management of these patients.

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1. Incidence

Heart disease accounts for 48 of all maternal deaths over the period 2003–2005. The maternal mortality for cardiac disease was 2.27 per 100,000 maternities in 2003–2005. The relative incidences of various types of cardiac disease as a cause of maternal death are listed in Table 1. Failure of communication between members of multidisciplinary teams; lack of clear policies for the management of cardiac problems; and failure of individual clinicians to diagnose cardiac problems accurately or to appreciate the severity of these conditions when identified were the common causes.

2. Principles of anaesthetic management

Management of pregnant women with severe pre-existing cardiac problems should be undertaken by multidisciplinary teams in tertiary centres. However women with stable lower risk conditions may be safely managed in a district general hospital if the level of attention to detail and care required can be provided. Thorough assessment of women with pre-existing cardiac disease, optimization of cardiac status antenatally or preferably preconception is vital. Vaginal delivery is preferable in most cases, and with careful incremental regional anaesthesia is safe in most women with cardiac disease. The presumed advantages of vaginal delivery are minimal blood loss, greater haemodynamic stability, avoidance of surgical stress, and less chance of postoperative infection and pulmonary complications. Effective pain management is a necessity to avoid further increases in cardiac output from pain and anxiety. Regional anaesthesia has the advantages of reducing preload and afterload, and minimizing the fluctuations in cardiac output associated with labour as well as providing excellent analgesia. Anticoagulation needs to be reversed to allow regional analgesia to be performed. Planned elective delivery may be required in the most serious conditions particularly as some of these women will not reach term due to cardiac instability.

In patients undergoing general anaesthesia, the principles of anaesthetic management are as for any patient with cardiac failure: maintenance of normal to low heart rate to decrease oxygen demand, and prevention of large swings in blood pressure. The hypertensive response to intubation can be obtunded by, for example, the use of alfentanil 1–2 mg before careful titration of the induction agent. Thereafter a nitrous oxide–volatile–relaxant technique is suitable. But remifentanil has the advantage of allowing volatile use to be minimised, thereby reducing uterine atony and the potential for postpartum haemorrhage.

Careful monitoring of fluid balance is obligatory and invasive monitoring is recommended. Early critical care referral is essential for unstable patients and critically ill patients with pulmonary oedema, hypoxia, mental obtundation, hypotension, refractory oliguria or acidemia may require cardiac output monitoring, artificial ventilation and inotropic support.

3. Acquired maternal cardiac disease

The main differential diagnoses for acute cardiovascular deterioration in pregnant women include thromboembolism, eclampsia, haemorrhage, cardiac disease and sepsis. Cardiac disease including peripartum cardiomyopathy, myocardial infarction and aortic dissection accounts for approximately one in six maternal deaths (Table 2).

3.1. Peripartum cardiomyopathy

Peripartum cardiomyopathy is a poorly understood condition, with an incidence of 1:1500 to 1:4000 live births. It has been
defined as the onset of cardiac failure with no identifiable cause in the last month of pregnancy or within 5 months of delivery, in the absence of heart disease before the last month of pregnancy. It is associated with older maternal age, greater parity, black race and multiple gestations.

Viral myocarditis and an abnormal immune response to pregnancy have been implicated in the pathogenesis. Symptoms and signs that should raise the suspicion of heart failure include paroxysmal nocturnal dyspnoea, chest pain, nocturnal cough, new regurgitant murmurs, pulmonary crackles, elevated jugular venous pressure and hepatomegaly. The differential diagnosis includes myocardial infarction, sepsis, severe pre-eclampsia, amniotic fluid embolism and pulmonary embolism. The electrocardiogram usually demonstrates normal sinus rhythm or a sinus tachycardia but dysrrhythmias or other ECG changes may also be present. A diagnosis relies on the echocardiographic identification of new left ventricular systolic dysfunction. Patients usually exhibit cardiomegaly on chest X-ray.

Treatment of peripartum cardiomyopathy involves salt restriction, and the use of diuretics to decrease pulmonary congestion and volume overload. In patients with systolic dysfunction, afterload is usually reduced with vasodilators. Angiotensin-converting enzyme inhibitors are the mainstay of treatment postpartum, even in mothers who are breast feeding. Patients with poor cardiac function, as evidenced by an ejection fraction <35%, are at risk of thromboembolism and anticoagulation is indicated.

### Table 2

<table>
<thead>
<tr>
<th>Triennium</th>
<th>Congenital</th>
<th>Acquired</th>
<th>Ischaemic</th>
<th>Other</th>
<th>Total</th>
<th>Rate 95 per cent CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985–1987</td>
<td>10 (43)</td>
<td>9 (39)</td>
<td>4 (17)</td>
<td>23 (100)</td>
<td>1.01</td>
<td>0.68 1.52</td>
</tr>
<tr>
<td>1988–1990</td>
<td>9 (50)</td>
<td>5 (28)</td>
<td>4 (22)</td>
<td>18 (100)</td>
<td>0.76</td>
<td>0.48 1.21</td>
</tr>
<tr>
<td>1991–1993</td>
<td>9 (24)</td>
<td>8 (22)</td>
<td>20 (54)</td>
<td>37 (100)</td>
<td>1.60</td>
<td>1.16 2.20</td>
</tr>
<tr>
<td>1994–1996</td>
<td>10 (26)</td>
<td>6 (15)</td>
<td>23 (59)</td>
<td>39 (100)</td>
<td>1.77</td>
<td>1.30 2.43</td>
</tr>
<tr>
<td>1997–1999</td>
<td>10 (29)</td>
<td>5 (14)</td>
<td>20 (57)</td>
<td>35 (100)</td>
<td>1.65</td>
<td>1.19 2.29</td>
</tr>
<tr>
<td>2000–2002</td>
<td>9 (20)</td>
<td>8 (18)</td>
<td>27 (61)</td>
<td>44 (100)</td>
<td>2.20</td>
<td>1.64 2.96</td>
</tr>
<tr>
<td>2003–2005</td>
<td>4 (8)</td>
<td>16 (33)</td>
<td>28 (58)</td>
<td>48 (100)</td>
<td>2.27</td>
<td>1.67 2.96</td>
</tr>
</tbody>
</table>

* Includes one case which was not assessed.

### Table 1

<table>
<thead>
<tr>
<th>Type and cause of death</th>
<th>Indirect</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Sudden Adult Death Syndrome (SADS)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Peripartum cardiomyopathy</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Myocarditis or myocardial fibrosis</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Mitral stenosis or valve disease</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Infectious endocarditis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Right or left ventricular hypertrophy</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>or hypertensive heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>34</td>
</tr>
</tbody>
</table>

* Women who died from 45 days to one year after delivery and whose deaths were reported to and assessed by the Enquiry.

14
General anaesthesia may be necessary in anticoagulated patients, but the hypertensive response to intubation and surgical stimulation may increase shear stress in the aortic root, promoting rupture or progression of a pre-existing dissection. The best method of anaesthesia for Caesarean section remains controversial.

4. Pre-existing cardiac disease

Many cardiac problems can be identified or optimized in the preconception or antenatal period, particularly in those patients with congenital heart disease, prior cardiac surgery, or cardiac-related problems in previous pregnancies.

4.1. Congenital heart disease

Congenital heart disease is increasingly prevalent in women of childbearing age, due in large part to advances in the diagnoses and treatment of these conditions in recent decades. Acanthotic conditions such as atrial and ventricular septal defects or persistent ductus arteriosus with small or moderate left to right shunts are well tolerated, as is prior surgical repair of a coarctation of the aorta. Ebstein's anomaly, a condition in which the tricuspid valve is displaced apically and is usually incompetent, is also well tolerated, although in cases where it is associated with an atrial septal defect or Wolf–Parkinson–White syndrome cyanosis or arrhythmias may occur.

Cyanotic conditions that have been corrected surgically are associated with minimal increased risk to mother and foetus. Total repair of the tetralogy of Fallot reieves the cyanosis and the outflow obstruction of the right ventricle and, in the absence of major residual defects, pregnancy can proceed without minimal additional risk to mother or child. A successful outcome to pregnancy has also been reported after surgical correction of transposition of the great arteries, and even after the Fontan repair of a functionally single left ventricle. The success of pregnancy is determined by the functional status of the right ventricle in the former and the single ventricle in the latter.

5. Valve disease

In general, pregnant women tolerate valvular incompetence better than stenosis. This is because the reduced systemic vascular resistance (SVR) improves forward flow and limits the effects of regurgitation. Stenosis, in contrast, creates a fixed impediment to the increase in cardiac output that accompanies pregnancy and labour, possibly precipitating heart failure and arrhythmias. The incidence remains high in developing countries and therefore pregnant women who are recent migrants to the UK should be screened for valvular stenosis. The mitral valve is most commonly affected by rheumatic heart disease, the aortic valve much less so. In the UK, calcific degeneration of congenital bicuspid aortic valves is the leading cause of stenosis encountered in pregnancy. Pregnant women with heart valve disease no longer require routine antibiotic prophylaxis according to recent NICE guidelines.

5.1. Mitral valve

In mitral stenosis, a gradient develops across the valve between the left atrium and ventricle, the magnitude of which depends on the severity of the stenosis and the flow across the valve. In non-pregnant patients, symptoms correlate closely with the size of valve area. The increased cardiac output of pregnancy can exacerbate this situation, precipitating heart failure and ventricular arrhythmias in the final stages of gestation, labour and the postpartum period, and an associated high risk of acute decompensation, pulmonary oedema and cardiovascular collapse. In patients with severe mitral stenosis, mortality can be as high as 5%. Echocardiography is the investigation of choice in the diagnosis of mitral stenosis and can be used to assess the suitability of the patient's valve for commissurotomy.

Prenatal management is directed towards avoiding cardiac decompensation, with regular assessment for volume overload and pulmonary oedema. Treatment involves bed rest, oxygen therapy and diuretics. In severe cases, balloon mitral valvuloplasty is the treatment of choice, with excellent results. Most women with mitral stenosis can undergo vaginal delivery with epidural anaesthesia unless obstetrically contraindicated. Tachycardia, secondary to labour pain, increases flow across the mitral valve, producing sudden rises in left atrial pressure and potentially leading to acute pulmonary oedema. This tachycardia is relieved by epidural analgesia without significantly altering patient haemodynamics. Invasive haemodynamic monitoring detects sudden drops in SVR in the presence of a fixed cardiac output these can be treated with small bolus doses of phenylephrine, with volume expansion when necessary.

5.2. Aortic stenosis

Although the symptoms of aortic stenosis can be masked by left ventricular hypertrophy, preconception functional class provides a good estimate of the patient's ability to tolerate pregnancy. Together with clinical symptoms, echocardiographic estimation of valve area rather than pressure gradient has been shown to be a better guide to the severity of disease in pregnancy, where the hyperdynamic flow can overestimate the valve gradient.

Patients with severe stenosis do not tolerate blood loss, tachycardia and central neural blockade or vena caval compression well. The main objective is to avoid fluid depletion and hypotension. Early placement of arterial and central venous lines, maintenance of left uterine displacement and Caesarean delivery under general anaesthesia should be considered. Intravenous oxytocin at delivery can cause severe intractable hypotension and preplanning to avoid its use in these patients is prudent. Phenylephrine to restore coronary perfusion pressure has no adverse effect on left ventricular function and filling dynamics in patients with valvular aortic stenosis under general anaesthesia, and has also been used uneventfully in cases with severe stenosis. In patients with less severe disease, whilst single shot spinal anaesthesia is contraindicated, Caesarean delivery has been successfully managed by invasively monitored, incremental regional anaesthesia using both epidural and subarachnoid catheters. Balloon valvuloplasty is possible in pregnant patients, but the risk of severe regurgitation is high.

5.3. Valve prosthesis

Women with prosthetic heart valves who are asymptomatic or mildly symptomatic before conception tolerate pregnancy well. Infection, thromboembolism, particularly with older metal valves (Starr Edwards), and haemorrhage as a consequence of anticoagulation are all recognized complications of prosthetic valves in pregnant women. The possibility of teratogenicity, central nervous system abnormalities and increased foetal bleeding with the use of oral anticoagulants during the first trimester of pregnancy and the difficulty of maintaining anticoagulation with subcutaneous heparin means that these women have a very real treatment dilemma. The relatively high risk of thrombosis despite heparin treatment or the risk of severe foetal abnormality with warfarin. Subcutaneous heparin or low molecular weight heparin needs to be administered to maintain the activated partial thromboplastin time ratio at 2.5–3 times normal. Higher levels (3–4 times normal) are required for older valves. These levels can be difficult to achieve and maintain adequately.
6. Pulmonary hypertension

Pulmonary vascular disease is associated with a substantially increased risk of maternal death. Primary pulmonary hypertension is a rare disease that particularly affects young women of childbearing age. It is defined clinically by a persistently elevated pulmonary artery pressure (PAP), mean pressure >25 mmHg at rest, without an obvious aetiology.22 The mortality of mothers with primary pulmonary hypertension in pregnancy is thought to be as high as 30%.26 Secondary pulmonary hypertension has a reported 60% perinatal mortality and any parturient with this condition should be regarded as critically ill.27 Pulmonary hypertension is tolerated badly during pregnancy because of insufficient adaptation of the right heart to increases in cardiac output in association with a poorly compliant pulmonary vasculature. Postpartum intravascular volume shifts resulting from haemorrhage or diuresis are particularly poorly tolerated. The greatest risk occurs in the peripartum period and most deaths occur between 2 and 9 days postpartum.28 Right ventricular decompensation presents clinically as increasing dyspnoea, cyanosis, chronic cough, haemoptysis, early fatigue and syncope. Death results from irreversible right ventricular failure or arrhythmias. Pulmonary embolism is an important differential diagnosis.

The principles of management in the peripartum period are the avoidance of increases in pulmonary vascular resistance (PVR), and maintenance of right ventricular preload, left ventricular afterload and right ventricular contractility. In general, better results can be achieved by avoiding increases in PVR due to hypothermia, acidosis, hypercarbia, hypoxia, high ventilation pressures, and sympathetic agents such as epinephrine and norepinephrine. Most reports have recommended vaginal delivery under epidural anaesthesia, if feasible.29 The high, dense regional block required for operative delivery is potentially hazardous as it can result in a considerable reduction in right ventricular preload but successful outcomes have been reported.30 General anaesthesia may permit effective control of right ventricular preload, enable better control of PAP responses to surgical stimulation, and permit administration of inhaled or nebulized pulmonary vasodilators in a controlled fashion.30 An opioid-based technique minimizes increased pulmonary pressures during laryngoscopy and avoids the excessive negative ionotropic effects of inhalational agents.31 Nitrous oxide increases pulmonary vascular resistance and is to be avoided.32 Care must also be taken to minimize reduction of venous return by positive pressure ventilation. The choice of technique should be decided on an individual basis.

7. Cardiac transplantation

Women who have undergone heart transplantation tolerate pregnancy well provided the function of the transplant was stable before pregnancy.33 Complications in such pregnancies are related to the immunosuppressive therapy and include hypertension, pre-eclampsia, infections and episodes of acute rejection in the mother, and low birth weight and preterm birth in the infant.34 A transplanted heart is denervated, although it retains its own conducting system; it is devoid of functional autonomic innervation. The choice between spontaneous delivery and Caesarean section is based on obstetric indications.

8. Summary

The presence of adequate systems for early detection, appropriate referral to specialist centres and timely delivery with multidisciplinary support can minimize the serious consequences of poorly controlled heart disease in pregnancy. A high index of suspicion along with an awareness of the need for the appropriate anaesthetic technique, in combination with adequate and where necessary invasive monitoring are important in these cases.

There should be a low threshold for echocardiography in women with cardiorespiratory symptoms in the peripartum period. Coronary angiography and computed tomography may be necessary in the assessment of pregnant women with incipient, life-threatening, cardiac disease. Ergometrine must be used with caution. It is contraindicated in women with underlying ischaemic heart disease. The use of oxytocin boluses is a cause for concern. Manual uterine massage, uterine compression sutures, followed by slow oxytocin infusions, are the preferred approaches.35 Management of pregnant women with severe cardiac disease should be undertaken by multidisciplinary teams in tertiary centres. Cardiac status must be optimized antenatally and planning for elective and possible emergency delivery is essential. Invasive monitoring is frequently required in the management of pregnant patients with cardiac disease. Vaginal delivery is preferable, and carefully titrated regional anaesthesia is safe in most women with cardiac disease.

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References


New opioid side effects and implications for long-term therapy

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1. Introduction

A recent increase in the popularity of the prescription of opioids for chronic pain syndromes has benefited a great many people. Opioid induced side effects such as nausea, constipation, tolerance and addiction are widely known, but new detrimental effects are emerging in the clinical setting as well as in literature. They include hypogonadism, osteoporosis, immune suppression, cognitive impairment and hyperalgesia. The majority of people with chronic pain will have tried opioids and a significant number will be on these drugs indefinitely. In this review, we discuss the impact of some of these side effects and their implications for chronic opioid therapy.

2. Hypogonadism

A reduction in the level of sex hormones has been observed in survivors of cancer who have consumed opioids for long periods. This has been associated with significantly higher levels of depression, fatigue, and sexual dysfunction.1 Opioid induced androgen deficiency (OPIAD) has recently been identified in men taking long-term opioids through the oral,2 intrathecal3 and transdermal routes.4 OPIAD is a clinical condition characterized by a low serum testosterone and dehydroepiandrosterone (DHEA); clinical signs include diminished libido, erectile dysfunction, depression, fatigue, vasomotor phenomena, mild anaemia, osteoporosis, and sarcopenia.5 A study looking at the endocrine consequences of long-term administration of intrathecal opioids found that 25 out of 29 men had a low serum testosterone level and a decreased libido. In the same study all premenopausal women developed amenorrhoea or dysmenorrhoea, and had low serum Luteinising Hormone (LH), oestradiol and progesterone levels. Eighteen out of 23 postmenopausal women were found to have decreased serum LH and Follicle Stimulating Hormone (FSH) levels. Opioids also caused central hypocorticism (in 15%), and Growth Hormone deficiency (in 15%). However, DHEA levels were not measured in this study.3 A study of 54 men consuming oral opioids for non-malignant pain showed that 48 (89%) men had subnormal levels of either testosterone or oestrogen. This decrease in hormone level was also related to the type of opioid consumed and the dosage. Thirty-nine men out of 45 (87%) on opioids, reported normal erectile function before opioid use, and erectile dysfunction or diminished libido once they were commenced on opioids.2 In the same study 47 women aged between 30 and 75 years, who were receiving oral or transdermal opioids (fentanyl) for the management of non-malignant pain were compared to a control group of the same study 47 women aged between 30 and 75 years, who were not receiving opioid analgesia. It was found that testosterone, oestradiol, and DHEA levels were 48%–57% lower in the opioid using women. LH and FSH levels were around 30% lower in premenopausal and 70% lower in postmenopausal opioid users. These women also reported a change in their menstrual cycle and often its cessation. Oophorectomised women had a decrease of
testosterone by 39%. These women were not taking oestrogen supplements, indicating that there is an impairment of adrenal androgen production. Animal studies suggest that opioid induced hypogonadism may be due to suppression of hypothalamic-pituitary and testicular function.

Administration of exogenous DHEA and/or testosterone not only seems to correct the symptoms of hypogonadism, but may even improve the pain relief from opioids. It is uncertain whether hypogonadism itself increases neural sensitivity. Studies have shown that women on average have lower nociceptive (or pain) thresholds than men; one theory being due to women’s lower levels of testosterone.

A recent review highlighted the impact of opioids on the endocrine system. The authors concluded that patients on long-term opioid therapy should be screened routinely for symptoms of hypogonadism and laboratory abnormalities in sex hormones. They also recommend that patients who are diagnosed of opioid induced hypogonadism should be offered sex hormone supplementation after careful consideration of the risks and benefits and consultation with an endocrinologist.

3. Osteoporosis and increased fracture risk

A North American prospective cohort study of more than 8000 elderly women found that those taking opioids had an increased risk of fracture. A large cross-sectional survey of medication usage, combined with measurements of bone mineral density found that opioids and anti-convulsants were associated with a significant reduction in bone mineral density.

A large Danish case control study demonstrated an increased risk of fractures in patients using opioids. Most of the commonly used opioids were implicated with the exceptions of buprenorphine, pethidine, and dextropropoxyphene. Specifically, morphine was shown to increase the risk of the classic osteoporotic fractures of the hip, forearm and spine. CNS impairment with loss of balance was postulated, but the definitive mechanism for this was not proven.

It is suggested that the increased incidence of fractures in patients on opioid therapy might in fact be due to opioid induced osteoporosis. In a review of chronic pain patients who received opioid analgesics for over 10 years, Tennant noted that 20% of patients developed osteoporosis. Studies have shown that opioids may contribute to lowered bone mineral density and to increased fracture risk by interfering with growth of osteoblasts and inhibition of osteocalcin production by osteoblasts. Chronic hypogonadism induced by opioids has been postulated as a cause of osteoporosis.

4. Immune suppression

Optimal immunological function is paramount in facilitating recovery from physiological insults such as infection, trauma and surgery. Its importance in the development and response to cancer has also become apparent during the scientific analysis of the malignancy process. Recent studies have revealed that pain may impair immune function by its effect on the hypothalamic-pituitary-adrenal system as well as suppressing Natural Killer (NK) cells, which may be involved in the mounting of resistance to infection and cancer. As well as the effect pain itself has on the immune system, opioid therapy may also have a deleterious effect, impairing the function of other lymphocytes, macrophages and even antibodies. In the acute post-operative period, opioids may reduce nociception and therefore reduce the stress response to pain. Paradoxically, morphine may also decrease lymphocyte proliferation in the early post-operative setting.

Opioid induced immunosuppression may be peripherally and centrally mediated. Impulses from the central nervous system modulate immune function via the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Opioid and non-opioid receptors on immune cells themselves provide the peripheral route of concentration dependent immunosuppression. Using a mouse model, it has been demonstrated that NK cell activity and splenic T cell proliferative response to various stimuli were not affected by administration of morphine in μ-opioid receptor deficient animals but were suppressed in the ones in which receptors were preserved. This suggests that the immunosuppressive actions of opioids may be mediated through μ-opioid receptors.

While it has been shown that opioids suppress the immune system, this is a complex process that is not yet fully understood and the effect may be inconsistent between different drugs. Opioids such as buprenorphine, tramadol, oxycodone and hydromorphone appear to induce less suppression than morphine. The clinical relevance of these immunological effects cannot be quantified with any certainty at this stage. Nevertheless, this issue must now be acknowledged and taken into account in patient management especially in at-risk groups such as the elderly and the immunocompromised. In the setting of acute or cancer pain it would make sense to utilise these properties of this study with caveats to minimise suffering and promote recovery, however in the setting of chronic pain the optimum approach would be to utilise opioids at the lowest dose for the shortest time as part of a multimodal approach in order to avoid impairment of the immune system.

5. Cognitive impairment

It is intuitive to clinicians that the use of strong opioids will impair cognitive function however there is little published data to support this in the community setting. It should also be acknowledged that pain itself is associated with significant cognitive impairment. There is a complex interplay of multiple contributory factors in the maintenance of normal cognition and it is difficult to determine the extent to which these confounding variables contribute to cognitive impairment in the clinical setting. Tests such as the popular Mini-Mental State Examination (MMSE) were created as a convenient and useful screening tool for the development of dementia. However, the MMSE was not specifically designed to look for subtle cognitive impairment in the typical pain clinic patient and not surprisingly it is too insensitive for this purpose.

Research into opioid induced cognitive impairment has yielded mixed results. Sjogren et al. investigated the influence of specific factors on neuropsychological functioning and demonstrated statistically significant differences in the various assessment scores between pain clinic patients and their age-matched controls. Intriguingly, there were minimal differences between patients receiving opioids and those receiving none in most tests except for serial addition and sedation scores. This could, in part, be accounted for by the fact that the doses in the opioid group varied considerably and a significant number were taking what may be considered low to moderate dosages. Relatively low, stable opioid doses are unlikely to be associated with major effects on cognition, whereas higher dosages are associated with higher sedation scores and almost certainly, higher levels of cognitive impairment. In one study, patients taking intermittent opioids for cancer experienced significant cognitive impairment that lasted for 1 week after increasing their dosage. The relevance of this study with regard to cognitive dysfunction caused by long acting opioids and infusions is not known. Another study looking at cerebral function of cancer patients revealed small but statistically significant prolongations of continuous reaction time in patients on 30–920 mg of morphine per day.
compared to patients who were not receiving opioids.\textsuperscript{30} Patients who were on long-term oral opioids for chronic non-malignant pain performed poorly during neuropsychological tests for vigilance/attention, psychomotor speed and working memory when compared to healthy volunteers. However, it is uncertain whether other factors including pain itself contributed to these findings.\textsuperscript{31} Immediate-release morphine for breakthrough-pain produced transient anterograde and retrograde memory impairments and a decrement in two-target tracking in another palliative care study when taken on top of a sustained release opioid medication.\textsuperscript{32}

In the management of chronic pain, the emphasis is on maximising function and optimising quality of life.\textsuperscript{33,34} Pain is associated with cognitive impairment and therefore it is desirable where possible, to avoid compounding the problem by prescribing high dose opioids. Even subtle changes in cognition can have a profound effect in individuals who may already be impaired for a variety of reasons. Moderate to high doses can only be justified if the benefits outweigh the side effects and the available data does not support the chronic use of opioids in many patients.\textsuperscript{34}

6. Opioid induced hyperalgesia

Opioid induced hyperalgesia (OIH) may be defined as a decrease in the nociceptive (or pain) threshold caused by exposure to opioids. It has been known for more than a century that opioids can induce a paradoxical exacerbation of painful sensations in spite of their analgesic properties.\textsuperscript{35} The mechanism for OIH has not been determined conclusively but numerous cellular receptor systems have been implicated. Both peripheral and central mechanisms are thought to be responsible for the phenomenon. A number of animal studies have been done to elucidate the mechanism of hyperalgesia. Rats receiving intrathecal morphine for 8 days developed thermal hyperalgesia and anti-nociceptive tolerance, suggesting similar underlying mechanisms. The excitatory amino acid (EAA) neurotransmitter was thought to be involved because co-administration of the NMDA receptor antagonist MK-801 or the non-NMDA EAA-receptor antagonist 6-cyano-7-nitroquinolinic acid, 2-dione with intrathecal morphine blocked the development of OIH and tolerance. The intracellular messenger protein kinase C is also implicated in OIH and tolerance. Both phenomena were prevented by GM1 ganglioside, which inhibits protein kinase C\textsuperscript{36} and may have a role in neuremodulation.\textsuperscript{37} CXBK mice, a strain expressing the \( \mu \)-opioid receptors at a very low density, did not develop OIH in a protocol rendering wild-type mice hyperalgesic, suggesting a role for the \( \mu \)-opioid receptor system in the development of OIH.\textsuperscript{38}

It is most likely that relevant changes occur at multiple levels of the nervous system, including the brainstem nuclei, spinal cord neurons, glia, and primary afferent neurons.\textsuperscript{39} Glial cells have traditionally been considered to be relatively inert neural cells that added structural stability, but interest has grown in their role in pathological pain states. It is thought that opioids act at other non-opioid receptors located on glial cells and thereby trigger an inflammatory cascade that can sensitise neurons and lead to hyperalgesia.\textsuperscript{30} Tolerance and OIH can be demonstrated and distinguished in animal studies. In a clinical setting, distinguishing the two phenomena is much more challenging and often is impossible. However, it would seem extremely likely that the two states may exist simultaneously as both involve stimulation of opioid receptors and share neurotransmitter and receptor systems.\textsuperscript{35}

7. Discussion

Clinicians should be aware of the significant morbidity that may be associated with the long-term use of opioids. It would seem pragmatic to make use of advances at the pre-clinical level in order to optimise the management of patients with chronic pain. Indeed, the American Pain Society has recently published guidelines for chronic opioid therapy despite an apparent lack of robust high-level clinical evidence.\textsuperscript{40}

A strict well-defined trial of opioid therapy should be initiated with the explicit cooperation of the patient. If the goals of the trial are not met (e.g. limited efficacy) or there is opioid abuse the medication must be stopped.\textsuperscript{40} There is no universal convention for opioid dosages but patients should be started on a low dose, which can be gradually increased to control symptoms. If the patient is continually requesting a higher dose then, by definition, the pain is only minimally responsive and a reduction in dosage should be considered due to the risk of hyperalgesia.

Patients who are on high doses (more than 200 mg per day of morphine or equivalent) or long-term opioids for chronic pain should be reassessed at appropriate intervals for adverse effects and the prescription should only be continued if appropriate doses are effective and there is no aberrant behaviour.\textsuperscript{40} In general terms it is best to minimise the dose and if possible wean off the drugs altogether over time. Opioid rotation may be tried though strong evidence for benefit is lacking.\textsuperscript{40} Patients should be encouraged to engage in active coping strategies including physical and psychological therapy.\textsuperscript{40} Non-opioid drugs should be used as first-line treatment in conditions such as neuropathic pain where opioid therapy is often less effective.

8. Conclusion

Opioids have served mankind well and it would be hard to imagine a world without these compounds due to their integral place within modern health care. However, if all things should be consumed in moderation then opioids are certainly no exception. The emerging side effects of opioids such as hypogonadism, osteoporosis, immune suppression, cognitive impairment and hyperalgesia should be considered carefully when these drugs are used for chronic conditions.

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References

The principles of aeromedical retrieval of the critically ill

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SUMMARY

With the development of highly sophisticated tertiary care facilities, the need to move critical care patients between hospitals is becoming an increasing common phenomenon. In many areas the distances involved in these transfers and the urgency of the cases has led to the use of aerial transport of retrieval teams and their patients.

This article discusses the physiology of aeromedical transport and its effects on certain clinical conditions and the equipment used. The article also offers some practical advice on personnel, equipment and how to carry out a tasking in both fixed wing and rotary wing aircraft.

1. Introduction

With the development of highly sophisticated tertiary care facilities, the need to move critical care patients between hospitals is becoming an increasing common phenomenon. The need for such transports to be performed by specialised teams with appropriate equipment and planning is well documented.1-5 In many areas the distances involved in these transfers and the urgency of the cases has led to the use of aerial transport of retrieval teams and their patients.

All patient transport is associated with an increase in mortality and morbidity, but the aeromedical environment can be particularly hazardous and challenging. The most striking difference is obviously the effect of altitude. An increase in altitude will result in a reduction in partial pressure of oxygen in accordance with Dalton’s Law. Increasing altitude will also increase gas volume or where volume is restricted there will be a relative increase in pressure in accordance with Boyle’s Law. The temperature also decreases by approximately 2 °C for every 300 m of altitude gained and the partial pressure of water also falls reducing the humidity of the air. These environmental factors not only have clinical implications but can also have a marked effect on the equipment used. Table 1 gives a summary of the environmental and physiological changes with altitude.

2. Mode of transport

Any vehicle used for transportation of critical care patients should ideally be specially configured or at least modified to ensure a safe working environment. The essential requirements of any transport vehicle have previously been suggested and are listed in Table 2.6

When discussing aeromedical retrieval the mode of transport can be broadly be separated into rotary and fixed wing aircraft. The fixed wing group can then be further refined into jet and propeller driven aircraft.

Fixed wing aircraft have the advantage of having a greater range and being faster but this is somewhat offset by the need for a secondary road transfer at either end. There is reduced noise whilst in flight compared to most helicopters. On takeoff and landing of fixed wing aircraft, significant forces (fore/aft) are exerted on the patient. These forces can have quite dramatic effects on patients who have already met their physiological reserve. These effects are dependent on the patient’s orientation and the force exerted. They can lead to venous pooling in the lower limbs causing a decreased venous return and a corresponding fall in blood pressure. In the head injured patient the forces can inhibit venous flow leading to an increase in intracranial pressure. Fixed wing aircraft are also capable of flying in a greater range of weather conditions, thanks to de-icing capabilities, greater range, and higher operating ceilings; the latter dependant on cabin pressurisation – which should be regarded as mandatory for fixed wing air ambulances. The maximum pressure differential that can be generated between the cabin and the atmosphere will be dependent on the type of aircraft. Some jet aircraft are able to establish a sea level cabin whilst flying at 12,000 ft. However flying at this altitude will use more fuel.
thus limiting range and may be contraindicated by the terrain or weather. It therefore requires close consultation between the medical and aviation crew before a sea level cabin can be established.

Helicopters are extremely versatile aircraft and have maximum benefit over moderate distances between clinical facilities which both have easily accessed helipads. They are however expensive to operate and require extensive modifications to enable critical patient care.

A “donut model” has been used to demonstrate the efficacy of the different modes of transport over different distances (Fig. 1).7

Area A demonstrates the distance where there will be very little benefit from aeromedical retrieval. Beyond this is ring B, within which a rotary wing aircraft can benefit a proportion of patients by delivering advanced critical care to the scene faster than taking them to hospital by alternative transport. Ring C demonstrates the distance where there will always be a time benefit by transporting the patient by helicopter. The outer limit of ring C will be determined by the type of rotary wing aircraft used and the distance of secondary road transfer needed when using fixed wing aircraft. Beyond this ring, area D demonstrates the distances where fixed wing aircraft offer the greatest benefit.

The cost of aeromedical retrieval is intrinsically high but this can be offset on some fixed wing aircraft as the cabins can be configured to take multiple patients. It is unusual to be able to carry multiple patients in rotary wing aircraft as most of the models used have limited cabin space and payload. However the shorter transport times by rotary wing aircraft may justify their use where workload is high (hence the team is available for another retrieval sooner) and/or the transport is urgent.

3. Medical personnel

The team require the skills to independently maintain or preferable improve the care of the patient in transit. These will include diagnostic and procedural skills and the ability to apply these in an aeromedical environment. The use of inexperienced and junior staff in retrieval medicine has been demonstrated to be associated with increases in preventable mortality and morbidity.8,9

The team should ideally be a minimum of two people or if there are multiple patients a formula of \( n + 1 \) (\( n \) = number of critical care patients) has been suggested.10 The composition of the team should be similar to clinical frontline staff at the destination. This implies the use of a physician based team, although in some stable patients

Table 1
Changes with altitude.

<table>
<thead>
<tr>
<th>Altitude (feet)</th>
<th>Pressure (mmHg)</th>
<th>Alveolar PO2 (On Air)</th>
<th>Gas Space Expansion (%)</th>
<th>Std Temp (°C)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sea Level</td>
<td>760</td>
<td>103</td>
<td>-</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>733</td>
<td>96</td>
<td>+3.6</td>
<td>13</td>
<td>Minimum altitude above ground level for helicopter transfers</td>
</tr>
<tr>
<td>2000</td>
<td>706</td>
<td>94</td>
<td>+8</td>
<td>11</td>
<td>Likely altitude for most helicopter flights over sea level</td>
</tr>
<tr>
<td>3000</td>
<td>681</td>
<td>89</td>
<td>+12</td>
<td>9</td>
<td>Likely range of cabin altitude for standard flights in most turboprop air ambulance flights (e.g. Beech King Air Series)</td>
</tr>
<tr>
<td>4000</td>
<td>656</td>
<td>85</td>
<td>+16</td>
<td>7</td>
<td>Standard Cabin altitude for airliners and most jet aircrafts</td>
</tr>
<tr>
<td>5000</td>
<td>628</td>
<td>79</td>
<td>+20</td>
<td>1</td>
<td>Likely ceiling of helicopter operations</td>
</tr>
<tr>
<td>10,000</td>
<td>523</td>
<td>61</td>
<td>+45</td>
<td>¬</td>
<td>Threshold for hypoxic decompression in non-acclimatized individuals</td>
</tr>
<tr>
<td>15,000</td>
<td>429</td>
<td>45</td>
<td>+77</td>
<td>-14.5</td>
<td>Likely upper range of cruise altitude of turboprop aircraft. Decompression at these altitudes causes rapid loss of consciousness and death without O2</td>
</tr>
<tr>
<td>20,000</td>
<td>349</td>
<td>34</td>
<td>+117</td>
<td>-24.5</td>
<td></td>
</tr>
<tr>
<td>25,000</td>
<td>282</td>
<td>30</td>
<td>+170</td>
<td>-34</td>
<td>Cruise ceiling for airliners &amp; jets. Limit for survivable decompression even with 100% O2 for flight crew</td>
</tr>
<tr>
<td>40,000</td>
<td>141</td>
<td>&lt;10</td>
<td>+439</td>
<td>-56</td>
<td></td>
</tr>
</tbody>
</table>

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Table 2
Essential feature’s of transport vehicles.

- Readily available.
- Adequate operational safety.
- Capable of securely carrying at least one stretcher and intensive care equipment.
- Safe seating for full team, ideally with access to the head and side of the patient with enough access for observations and procedures.
- Adequate space and patient access for observation and procedures.
- Equipped with adequate oxygen/other gases for duration of transport.
- Fitted with medical power supply with appropriate voltage and current capacity.
- Appropriate speed (coupled with) comfortable ride, without undue exposure to accelerations in any axis.
- Acceptable noise and vibration levels.
- Adequate cabin lighting, ventilation and climate control.
- Fitted with overhead i.v. hooks and sharps/biohazard waste receptacles.
- Straightforward embarkation and disembarkation of patient and team.
- Fitted with appropriate radios and mobile communications.

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Fig. 1. The donut model of medical retrieval.
transport may be appropriate by suitably trained flight nurses. The use of multidisciplinary teams including physicians, nurses and paramedics further broadens the skill set available. In some circumstances, other medical specialties may also be needed for example a surgeon or a perfusionist. These personnel should be regarded as an additional to the standard team as it is unlikely they will be familiar with the aeromedical environment.

The team work closely dealing with stressful situations. Therefore it is essential that they work well together and have well developed communication skills. It is also desirable that the team are able to be adaptive and can act resourcefully in the limited transport environment.

Training and continued development is an essential part of the clinical governance of any aeromedical operation. Initially the training should involve the principles and practicalities of retrieval medicine, familiarisation with the equipment and vehicles and the relevant safety and emergency procedures. Following the period of initial training it is very useful for new personnel to do a number of accompanied missions with senior staff to hone their new skills. In service training and peer review of cases should be encouraged to further develop and refine skills.

4. Equipment

4.1. General considerations

Minimum standards for equipment and monitoring during the transport of critical care patients have been developed. All possible scenarios should be planned for. In aeromedical retrievals the weight and space available for equipment may be restricted. This requires intelligent design and selection of equipment so as to neither compromise patient or aviation safety. It should also be noted that equipment which is to be fixed in the aircraft will require inspection by the civil aviation authority. This is to ensure that the fixation will be secure under the large forces sometimes exerted in flight.

The aim should be to have a standardised set of equipment taken on all missions and then to add to this auxiliary equipment for specific scenarios. It is also essential to have some form of back up or redundancy for vital equipment and monitoring. A comprehensive equipment list has previously been suggested.

Portability is an essential aspect of all the equipment used. It must be possible to use this equipment within and outside of the transport aircraft. This will mean that electrical equipment must have a sufficient battery life to be used outside. These internal batteries should not be relied upon in flight unless the duration of the transfer is expected to be less than half the estimated battery life. There should be an alternative means of powering this equipment either from an external battery pack or directly from the aircraft. Ideally it should be possible to charge equipment when in flight. Spare batteries should not be relied upon unless the device(s) are amenable to rapid battery swaps without interruption to monitoring or therapy. Portability can be addressed further in a couple of ways. Equipment and monitoring can be aircraft mounted but readily detachable to accompany the patient or more conveniently a mobile intensive care module can be incorporated into the stretcher. This can either be in the base of the stretcher or as a “stretcher bridge” straddling the patient. Photographs demonstrating the CareFlight stretcher bridge are shown. These designs allow the patient and equipment to be assembled into one unit at the referral point. This reduces the loading and unloading time, the chance of disconnection of the ventilator and monitoring and the risk of leaving equipment behind. The benefits greatly outweigh the minor disadvantage of the increased weight (20–30 kg) and the slight increase in the centre of gravity of the stretcher.

4.2. Monitoring

Thorough clinical observation remains the mainstay of monitoring, although some clinical assessments such as auscultation are impossible whilst in flight. Therefore the monitoring employed should be at the same or a higher level to that received in an intensive care setting. Most modern transport monitors offer ECG, SpO2, non-invasive and multi-channel invasive pressures, capnography and temperature monitoring and some will also function as a defibrillator. Non-invasive blood pressure and pulse oximetry are extremely susceptible to artefact whilst in flight. Therefore invasive blood pressure monitoring is invaluable and shielding of the pulse oximeter probe may be necessary. As previously observed, once in the air the clinical team is very isolated and having back up equipment is essential. This particularly applies to monitoring equipment. A defibrillator can be utilised as a back up ECG monitor and there are numerous small hand held pulse oximeters and EtCO2 detectors which can be used. On longer flights it is also worth considering carrying compact biochemical and blood gas analysers, particularly when transporting patients with major respiratory or biochemical disturbances.

4.3. Respiratory support and ventilation

As previously discussed an increase in altitude will result in a reduction in partial pressure of oxygen in accordance with Dalton’s Law. Therefore those critical care patients dependent on a high FiO2 at sea level may require more aggressive management if they are to fly. Non-invasive ventilation has a limited role in aeromedical retrieval as most systems have extremely high gas...
consumption and are impractical except for very short flights. Management decisions regarding the level of respiratory support needed should be made prior to boarding the aircraft, as endotracheal intubation in flight is extremely difficult because of limited space.

All ventilated patients require a mechanical ventilator during transport. Manual ventilation occupies one team member and cannot reliably deliver constant volumes and a stable EtCO₂. Transport ventilators are a compromise between portability and features. The ventilator must be small, light and robust and be economical on gas consumption whilst being able to work independently of an external power source. The extent of the other features needed is determined by the level of care required by the patient. It should also be noted that increasing altitude can cause an increase in tidal volume in pneumatically controlled ventilators, necessitating setting changes in flight. Studies have shown that in accordance with Boyle’s law the pressure within the cuff of an endotracheal tube will increase with a gain in altitude. It has also been suggested that this increase in pressure can exceed the critical perfusion pressure of the tracheal mucosa at an altitude of as little as 2000–3000 ft. Anecdotally, saline has been used to fill the cuffs to avoid this increase in pressure. This practice is however technically quite demanding and an easier solution is to monitor and maintain a constant transmural cuff pressure – which will require bleeding and re-instilling air on ascent and descent respectively.

A suction system is required during all phases of the transfer. This may be a Venturi system, an electrical pump or manual aspirator. Oxygen driven Venturi systems have the advantage of being compact and more reliable than electrical systems, but consume high volumes of oxygen.

4.4 Infusions

Critical care patients often have multiple drug infusions running. It is however important to rationalise these infusions before transferring patients. This can be done by combining sedatives and stopping some infusions for transport and then giving boluses as required. Compact, lightweight syringe driver type pumps can be utilised for low volume infusions. It is particularly useful if these devices are compatible with all types of syringe. Fluid pressure bags and pump sets should be available to maintain intravenous flow rates as only minimal elevation of fluid bags is possible in most aircraft.

5. Special clinical conditions

5.1 Pneumothorax, pneumocephalus and intraocular air

Expansion of trapped air in pathological airspaces could potentially have disastrous consequences. Some smaller pneumothoraces may now be treated conservatively at sea level but great caution should be used when transferring these patients by air. The percentage volume increase of a small pneumothorax may have minimal clinical consequences but if the patient was to deteriorate the restricted environment of most aircraft makes placement of a chest drain or decompression of the chest exceedingly difficult in flight. These risks must be balanced with the potential morbidity of a prophylactic chest drain. In those patients with a chest drain, Heimlich or other similar one-way valves should be used for pleural drainage. Although these valves are widely used in aeromedical retrieval there are some concerns because once in use it is difficult to assess whether the valve is functioning or not. It is always useful to test the patency of the valve prior to its use. This is done using a syringe and blowing air across the valve. Underwater seal drainage systems should be avoided as they are not suitable for transport, owing to the likelihood of tipping and syphoning.

Aeromedical retrieval of patients with known pneumocephalus is often regarded with great concern. This is based on the theoretical risk of a tension pneumocephalus with potentially fatal results. There is very scant evidence of these occurrences in the medical literature. A recent review of 21 cases of aeromedically evacuation of those patients who had documented pneumocephalus claimed no patient sustained a temporary or permanent neurological decline as a result of air transportation. Although this is a small study group it can be concluded that pneumocephalus in a patient should not be an absolute contraindication to flight. To further mitigate the risk it is also sensible to fly at the lowest cabin altitude deemed safe by the pilot.

Intraocular air and penetrating eye trauma are other pathologies where the effect of altitude may have devastating consequences. These are theoretical risks. The clinician transporting the patient must balance this risk against the potential benefit of transferring the patient. A cabin pressurised to the lowest permit able level will reduce the risk.

5.2 Diving injury patients

With the ease of commercial air travel and increasing availability of dive sites in remote, exotic locations, decompression illness may occur at locations far from hyperbaric facilities. The need for urgent transport to a hyperbaric facility often involves aeromedical retrieval. A minimal increase in altitude however can worsen symptoms. Although a review of the literature found that no adverse events had been reported when transporting decompression illness patients below 500 ft. This is therefore another situation where a sea level cabin would be of great benefit. If transporting the patient by rotary wing aircraft detailed discussion with the aviation crew will be required to plan a flight route with the lowest possible altitude. In good weather this is often achievable by flying over the ocean.

6. Conclusion

This article gives an oversight of the principles employed when transporting a critical care patient by air. The table below highlights a few of the important “laws” which if followed will not only improve patient care but will also alleviate the stress of the retrieval team!

<table>
<thead>
<tr>
<th>Blair’s laws of air medical retrieval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The ideal situation and patient transport are mutually exclusive.</td>
</tr>
<tr>
<td>2. Only those complications not anticipated by the air medical team will actually occur. Big problems are usually little ones that were unforeseen.</td>
</tr>
<tr>
<td>3. Any resemblance between the expected and actual situations is usually coincidental.</td>
</tr>
<tr>
<td>4. Air goes in and out, Blood goes round and round; any variation on this is a BAD THING. i.e. first make sure the basics are done well</td>
</tr>
<tr>
<td>5. The best patient monitor is the one between your ears - provided it is switched on. i.e. clinical observation and intelligent interpretation remain the cornerstones of patient monitoring.</td>
</tr>
<tr>
<td>6. The length of sticky tape employed on the patient should not exceed the distance between the referring &amp; receiving hospitals (Anything up to this amount is OK). A small amount of time</td>
</tr>
</tbody>
</table>
spent securing i.v. lines, drains and ET tubes will pay dividends. All of these are extremely difficult to replace in flight! 7. There is no such thing as the “room next door” in the sky. This applies to equipment and staff. You must be able to deal with any situation that may arise.

Conflict of interest statement
None.

References

Expeditions and adventure travel are becoming increasingly popular. As these ventures continue to grow in popularity so too do the opportunities for doctors interested in expedition and wilderness medicine. A few doctors manage to make a career in expedition medicine but for the majority it remains a hobby that runs alongside their usual clinical practice. At the same time expedition and wilderness medicine is progressing as a specialty in its own right. This review aims to serve as an introduction to expedition medicine, to raise points for further consideration and to signpost the next steps for those that are interested in acting as an expedition doctor. The requirements of an expedition doctor and the possible medical problems faced are as heterogeneous as the environments travelled to and the groups travelled with. This review outlines a number of principles that hold true in pre-expedition planning, during the expedition and in the post-expedition phase.

1. Introduction

Regions and activities once the preserve of hardened explorers are now becoming increasingly accessible. A quick search on the Internet will show numerous adventures organised for charitable fundraising such as climbing Mt. Kilimanjaro or dog sledding in Norway. More adventurous (and financially solvent) individuals can be guided up the highest mountains or ski the last miles to the poles. The lines between adventure tourism, expeditions and remote travel are becoming increasingly blurred. As these ventures continue to grow in popularity so too do the opportunities for doctors interested in expedition medicine. A few doctors manage to make a career in expedition medicine but for the majority it remains a hobby that runs alongside their usual clinical practice. At the same time expedition and wilderness medicine is progressing as a specialty in its own right. This review aims to serve as an introduction to expedition medicine, to raise points for further consideration and to signpost the next steps for those that are interested in acting as an expedition doctor.

Expedition medicine requires a broad range of skills and knowledge that encompasses elements of general practice, pre-hospital and emergency medicine, travel medicine and infectious disease. The nature of the work means you are often the only doctor present with limited resources and definitive care may be a long way away. Anaesthetists make a significant proportion of expedition doctors, especially those interested in High Altitude or diving physiology. The UCL based Centre for Altitude, Space and Extreme Environment (CASE) research group are probably the best known after the well-publicised Caudwell Xtreme Everest expedition and research publications.

The requirements of an expedition doctor and the possible medical problems faced are as heterogeneous as the environments travelled to and the groups travelled with. However, a number of principles hold true in pre-expedition planning, during the expedition and post-expedition.

2. Planning

The planning phase for the expedition should not be underestimated; if the expedition goes well then the planning is likely to be majority of your work. Consider the expedition in terms of the role of the doctor, the expedition environment, the group, medical resources and kit, and evacuation plans.

3. Role of the expedition doctor

It is essential to have early and regular contact with the expedition leader to discuss what is expected of the expedition doctor. The extent of the doctor’s role will depend on the nature of the trip, the doctor’s medical and expedition experience and the personalities involved. If you take on the role of expedition doctor then you should be confident not only that you have necessary medical knowledge and skills but also that you have the personal and
outdoor skills to thrive in the wilderness environment. Consider what treatments and advice you are willing to offer to participants in the expedition before, during and after. You should also consider what duty of care you have for local expedition staff and how you will handle requests for medicine or help from the local population, particularly if it is for chronic conditions. During the expedition will you see non-urgent medical problems as and when, or decide to pre-arrange arrange consultation times? In a remote environment it can be a challenge to find a consultation area to see patients that respects their confidentiality and enables you to examine and treat as required and then document the event.

The expedition doctor should contact their defence organisation at an early stage to discuss suitable indemnity insurance. This is usually straightforward and inexpensive for the occasional trip. However indemnity to cover the treatment of US citizens or working in US territories can pose problems due to the high costs involved in potential legal cases. Doctors working for a commercial expedition company should discuss the possibility of arranging indemnity through the company’s own insurance.

Equally important is to ensure the expedition has sufficient travel, medical and evacuation insurance. A number of activities commonly encountered in expeditions are specifically excluded in most routine travel insurance schemes. The cost of search and rescue, evacuation, medical care and repatriation from remote environments can quickly escalate so ensure that the insurance policy has a sufficient maximum level of cover.

4. Expedition environment

When researching exotic pathogens for the risk assessment remember that common things occur commonly. A study of 440,000 expedition days found an injury incident rate of 1.18 per 1000 programme days, with over 50% of these injuries being athletic sprains and strains. One should not forget the risks of travelling to the expedition area, road traffic accidents are more common in developing countries and a tourist driving has a 6 fold increased risk compared to a local.

Gastrointestinal disturbances by far are the commonest cause of illness, much of which can be prevented by implementing a plan for hygiene and sanitation. Ensuring clean water or adequate decontamination of drinking water, suitable latrines and camp layout, safe food preparation and hand washing can mean the difference between success and failure in an expedition.

Some expedition environments are intrinsically more dangerous than others. High altitude mountaineering particularly as it combines altitude, changeable weather and cold, the risks associated with the terrain and prolonged evacuations. The mortality rate for those climbers that ascend above base camp on Mt Everest (5360 m to summit 8848 m) is 1.3%. Any doctor partaking in a trip ascending above 3000 m should be confident in the management of Acute Mountain Sickness (AMS), on Kili-manjaro (5893 m) a recent study of trekkers found 75% suffered with symptoms of AMS.

5. The group

In some cases the doctor may be involved in team selection, particularly if the expedition is likely to be very physically or psychologically arduous. However often the doctor joins alongside or after the majority of the group. The pre-assessment health questionnaire helps judge individuals’ suitability and to adapt the medical plan and equipment according to their medical needs. The pre-assessment questionnaire should comprehensive enough to highlight all significant past and ongoing medical problems, as well as collecting next of kin and GP contact details. Be aware individuals keen to go on an expedition may ‘play down’ the severity of chronic illnesses. Ideally any participant who declares a significant medical history should be seen in person for a more thorough assessment. Undeclared pre-existing medical conditions may subsequently invalidate travel insurance claims. Copies of the pre-assessment questionnaire should be carried on the expedition as a reference and copies left back at home as a backup.

Pre-expedition training weekends are an invaluable opportunity to eyeball each participant and develop a better understanding of personalities and capabilities within the group. It is also the best time to give the medical briefing to cover the risk assessment, the practicalities and importance of personal hygiene, an overview of medical evacuation plans and what personal first aid kits individuals should bring. If appropriate then it is a good opportunity to teach the group some pertinent first aid. Individuals may also need reminding to ensure relevant vaccinations are up to date, bearing in mind some vaccines can take up to 3 weeks before the onset of protection (e.g. Hepatitis A vaccine). Dental pain can ruin a trip so you should advise a dental check-up prior to departure, especially in polar or mountaineering expeditions as cold and high altitude can uncover hitherto asymptomatic dental problems.

6. Medical resources and evacuation plans

The only medical kit and diagnostic equipment available on a remote expedition is that which you carry in with you. Specifics will vary with the size of the group, pre-existing medical conditions, duration and location of the expedition and personal opinions of the doctor. There is some evidence-based recommendations for medical kits, but most is based on personal experience and common sense. It goes without saying that you should not take any special equipment or medication if you are not confident and competent in its use. Whilst thinking about what to bring in a medical kit you should also research the availability of re-supplies, the proximity of local medical resources, and the location of and likely evacuation time to definitive care. It is useful to know in advance where anyone in the group has useful medical skills or is a healthcare worker, particularly if you are the only doctor in the event that you become unwell (Fig. 1).

Obtaining the necessary drugs and equipment can be protracted and costly, you should ensure that the expedition leader has budgeted for this. A local or hospital pharmacist is a useful starting point for advice to avoid breaking GMC guidance of self-prescribing. If you decide to take controlled medication be aware that new Home Office guidance states a personal license is not

Fig. 1. The Asaro mud men of Papua New Guinea browse a popular medical textbook.
required for less than 3 months duration and less than 3 months supply of a controlled drug if prescribed with supporting documentation. However you must also contact the consulate of the expedition country and any country that you transit through to check local laws and procedures. Be aware that certain medications, e.g. codeine and prochlorperazine are controlled drugs in other countries, e.g. the UAE. All medication should be transported in clearly marked medical kit with a covering letter. Travel with and keep on you a copy of your GMC certificate and another form of medical ID, this may prove useful at boarders and if a participant is admitted to a local hospital. The medical kit and medications particularly will need to be protected and waterproofed for the transport; tupperware boxes can be very useful for this. Most medicines will need protecting from extremes of temperature. Even when you are aiming to minimise weight it is good practice to keep the information leaflets with the medications and pack an up to date BNF.

The Appendix lists what the author took to base camp on a recent 3 week expedition to climb Mt Aconcagua (6982 m) and adjacent peaks (oxygen and a gamow bag were available at the ranger stations) (Fig. 2).

Medical evacuation (Medevac) of a sick or injured patient should be well planned and researched in advance. Due to the limited resources and backup of an expedition doctor he or she should have a low threshold for deciding to evacuate. Medevac may require stretchers or mules, 4 x 4 vehicles, boats, helicopters or aircraft or any combination depending on circumstances. Consider how these resources will be contacted, how to relay the urgency of the evacuation and whether you as the doctor will travel with the patient perhaps then leaving the rest of the group without medical support. Essential contact details for local emergency services, embassies, transport options and hospitals should be checked on arrival in country. The finalised medical evacuation plan should be on a laminated sheet carried by multiple people in the group, it is recommended that individuals should always carry copies of their certificate of travel insurance along with a credit card and some local currency.

7. During the expedition

The expedition doctor should make a daily risk assessment to account for activities, the condition of the group and changing climate or altitude. In the majority of expeditions a doctor will only have to deal with minor injuries and ailments. However in the event of any serious incident or illness, reassurance or advice from a colleague back home can be just a phone call away. It may be worth pre-arranging possible contacts for this, but despite ongoing improvements in satellite technology due to the remote and unpredictable nature of expeditions being able to reach these contacts should never be relied upon.

As in usual practice it is essential to document any consultations and treatment given during the expedition. In the unlikely event of a claim resulting from a medical incident during an expedition there is little case precedence. The standard Bolam test will apply but the courts have recognised that “an emergency may overburden the available resources, if an individual is forced by circumstances to do too many things at once, the fact that he does one of them incorrectly should not lightly be taken as negligence” (Wilsher v Essex Area Health Authority).

8. Post-expedition

On return the doctor must follow up any illness or medical incidents encountered during the expedition. A report of any significant medical problem and treatment given should be sent to the relevant GP. Prior to dispersal the group should be advised on any specific latent disease risks that may present on return and be reminded to complete any malarial prophylaxis or vaccination courses.

9. Conclusion

Expedition medicine is an exciting and challenging part of medicine that you can practice in exciting and challenging environments. It is growing and maturing as a speciality. Making the first step and arranging the initial expedition can be daunting. For those who are interested the following websites, courses and books may be of use.

Conflicts of interest

None.

Appendix

Medication taken on Exercise Andean Trinity – a mountain- eering expedition to Mt Aconcagua and adjacent peaks, 8 people, 3 weeks. Individuals had personal supplies of basic analgesics and the majority were taking Acetazolamide prophylactically. Bold print indicates which medications were used.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin 300 mg</td>
<td>16 tabs</td>
</tr>
<tr>
<td>Paracetamol 500 mg</td>
<td>50 tabs</td>
</tr>
<tr>
<td>Codeine 30 mg</td>
<td>46 tabs</td>
</tr>
<tr>
<td>Diclofenac 50 mg</td>
<td>50 tabs</td>
</tr>
<tr>
<td>Diazepam, rectal solution 10 mg</td>
<td>3 tubes</td>
</tr>
<tr>
<td>Tramadol 100 mg iv</td>
<td>5 vials</td>
</tr>
<tr>
<td>Tramadol 50 mg po</td>
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</tr>
<tr>
<td>Zopiclone 3.75 mg</td>
<td>20 tabs</td>
</tr>
<tr>
<td>Temazepam 10 mg po</td>
<td>28 tabs</td>
</tr>
<tr>
<td>Salbutamol inhaler</td>
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<tr>
<td>Prochlorperazine</td>
<td>40 tabs</td>
</tr>
<tr>
<td>Cetirizine 10 mg</td>
<td>10 tabs</td>
</tr>
<tr>
<td>Epipen</td>
<td>1</td>
</tr>
<tr>
<td>Adrenaline 1/100000 10 ml</td>
<td>1 vial</td>
</tr>
<tr>
<td>Hydrocortisone 100 mg iv</td>
<td>2 vials</td>
</tr>
<tr>
<td>Loperamide 2 mg</td>
<td>24 tabs</td>
</tr>
<tr>
<td>Anusol HC suppository</td>
<td>6 sups</td>
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<tr>
<td>Ondansetron 8 mg iv</td>
<td>4 vials</td>
</tr>
<tr>
<td>Omeprazole 20 mg</td>
<td>20 tabs</td>
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</tbody>
</table>
Equipment


<table>
<thead>
<tr>
<th>Drug</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide 250 mg</td>
<td>180 tabs</td>
</tr>
<tr>
<td>Dexamethasone 2 mg</td>
<td>30 tabs</td>
</tr>
<tr>
<td>Dexamethasone 4 mg IV</td>
<td>5 vials</td>
</tr>
<tr>
<td>Nifedipine MR 20 mg</td>
<td>14 tabs</td>
</tr>
<tr>
<td>Chloramphenicol eye ointment 1%</td>
<td>2 x 4 g tube</td>
</tr>
<tr>
<td>Cefuroxime 750 mg iv</td>
<td>3 vials</td>
</tr>
<tr>
<td>Clarythromycin 250 mg</td>
<td>14 tabs</td>
</tr>
<tr>
<td>Ciprofloxacin 500 mg</td>
<td>40 tabs</td>
</tr>
<tr>
<td>Co-Amoxiclav 500/125</td>
<td>42 tabs</td>
</tr>
<tr>
<td>Metronidazole 400 mg</td>
<td>21 tabs</td>
</tr>
<tr>
<td>Aciclovir cream 1%</td>
<td>2 g x 2 tubes</td>
</tr>
<tr>
<td>Clotrimazole 1% cream</td>
<td>20 g x 1 tube</td>
</tr>
<tr>
<td>Betadine spray</td>
<td>1 can</td>
</tr>
<tr>
<td>N. Saline 0.9% 1 L</td>
<td>2 bags</td>
</tr>
<tr>
<td>N. Saline 10 ml flushes</td>
<td>10 vials</td>
</tr>
<tr>
<td>Dioralyte sachets</td>
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</tr>
<tr>
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<td>5 vials</td>
</tr>
<tr>
<td>Flamazine cream</td>
<td>1 tube</td>
</tr>
<tr>
<td>SPF 50 sunscreen</td>
<td>1 tube</td>
</tr>
</tbody>
</table>

References


Websites

12. The British Mountaineering Council www.thebmc.co.uk.
13. Expedition Medicine Courses www.expeditionmedicine.co.uk.
REVIEW

Hazards of topical ophthalmic drug administration

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Keywords:
Drug administration, topical
Ophthalmic surgery
Pharmacology
Drug side effects

SUMMARY

A wide range of topical ophthalmic drugs is available for use to provide a complete eye examination or a decrease in intraocular pressure or optimum conditions for many surgical procedures, but administration of these drugs is not free from the risks of serious adverse events. Most of the ophthalmic topical drugs show their effects via adrenergic or cholinergic receptors and systemic side effects of these drugs generally occur due to systemic absorption and overdose/toxicity. There are also other contributing factors such as age and related physiology of the patients or co-morbidities or previously prescribed medications. Therefore, one should be aware of the possible adverse reactions to topical ocular drugs and question the accompanying disorders and current medications of the patients inclusively to prevent and manage deleterious effects observed due to concomitant disorders and interaction between drugs.

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1. Introduction

A wide range of topical ophthalmic drugs is available for use to provide a complete eye examination or a decrease in intraocular pressure or optimum conditions for many surgical procedures, but administration of these drugs is not free from the risks of serious systemic adverse events. Such events are usually underestimated by both anaesthesiologists and ophthalmologists. Many side or adverse effects occur due to systemic absorption and overdose/toxicity of these drugs. However, hazards of topical ocular drugs are not necessarily a consequence of a particular property of drugs. There are other contributing factors such as age and related physiology of the patients or co-morbidities (cardiovascular, pulmonary or endocrine diseases) or previously prescribed medications that may interfere with these drugs (Table 1).

2. Concerns related to pharmacologic effects of topical ophthalmic agents

Most of the ophthalmic topical drugs show their effects via adrenergic or cholinergic receptors (Table 2). There is a rich supply of adrenergic receptors in the iris. β-receptors mostly spread in ciliary, retinal and choroidal vasculature whereas contraction of iris radial muscle takes place via α-1 receptors. Muscarinic receptors are present both in the iris and ciliary muscle and epithelium. Consequently, topical application of cholinergic, adrenergic drugs, and local anaesthetics may present with the systemic effects of the drug itself. Therefore, the potential hazards of topically used ophthalmic drugs are mainly related to the mechanism of action of the agent and possible interaction with local or general anaesthetics.

3. Expected undesired systemic effects of the topical ophthalmic agents

Systemic absorption of the ophthalmic eye drops via conjunctival sac or nasolacrimal mucosa remains as a potential cause of the undesired systemic effects of topical agents and 99% of every drop is considered to be absorbed systemically. Several approaches have been advocated for reducing systemic absorption and the associated side effects. These include eyelid closure, digital occlusion of nasolacrimal duct for several minutes and wiping away excess drops during and after drug instillation and proper dilution or reduced volume of eye drops for use in children.

3.1. Cholinergic drugs

The cholinergic ophthalmic drugs provide miosis by the contraction of iris sphincter muscle via M3 receptors and a decrease in intraocular pressure (IOP) by increasing trabecular aqueous humour outflow. Systemic effects of cholinergic agents (e.g. pilocarpine) are bradycardia which need reversal with i.v. Atropine treatment, increased salivation, hypotension, bronchospasm, pulmonary edema. Side effects of cholinesterase inhibitors are notably more severe than cholinergic receptor agonists. Echothiophate, a long acting miotic agent, is an indirect cholinergic
agonist with its feature to be an irreversible cholinesterase inhibitor and rarely used today for glaucoma treatment. Ecthopithecophane can cause prolonged apnoea and bronchospasm after succinylcholine administration used for facilitation of endotracheal intubation.6 Newer volatile agents like sevoflurane or desflurane are currently preferred instead of halothane for maintenance of general anaesthesia since vagotonic anaesthetics like halothane can accentuate the effects of all cholinergic drugs.7

3.2. Anticholinergic drugs

Anticholinergic drugs (atropine, cyclopentolate, tropicamide, homatropine, scopolamine, etc) produce mydriasis and cycloplegia by relaxing the ciliary body and iris.8 However, they also manifest cardiovascular, respiratory, cerebral and gastrointestinal effects when absorbed in the systemic circulation such as tachycardia, atrial dysrhythmias, fever and flush, bronchodilatation, prolonged gastric emptying time and alterations in mental status ranging from sedation or excitement and restlessness to acute psychotic reaction.9,10 Myasthenia gravis-like syndrome has also been reported after topical administration of these drugs.11

3.3. Adrenergic agonists

3.3.1. Adrenaline (epinephrine)

Adrenaline is a non-selective sympathetic agonist, which acts at α-1,2 and β-1,2 receptors. Topical form of this drug is used for conjunctival decongestion, mydriasis and reducing IOP in ophthalmology. Its systemic absorption may cause significant symptoms like hypertension, tachycardia and headache. Therefore, caution should be taken in patients anaesthetized with halogenated hydrocarbons, which sensitize the myocardium to sympathomimetics leading to dysrhythmias.7,12

3.3.2. Phenylephrine

Phenylephrine is a direct acting adrenergic agonist at the α1 receptor and dilates the pupil and produces capillary decongestion for ophthalmologic purposes in its topical form. Significant absorption after topical administration may result in hypertensive crisis, tachycardia, reflex bradycardia, ventricular arrhythmias, myocardial infarction, and cardiac arrest.12 Children and the elderly are more vulnerable for these side effects.

Several adult and paediatric case reports involving phenylephrine eye drops and plegyds have been presented. An eight year-old boy scheduled for retinal detachment surgery under sevoflurane anaesthesia, developed profound reflex bradycardia after instillation of 2–5 drops of 10% aequous phenylephrine for pupil dilatation and required treatment with glycopyrrolate. Then, the ECG displayed multifocal atrial and ventricular ectopic beats. The increased systolic blood pressure and heart rate were treated with labetalol.13 An episode of angina and myocardial infarction leading to septicoma and anteomeral hypokinesia was reported in a 77-year-old patient with diabetic retinopathy.14 In a case series including children and adults, adverse systemic reactions like severe headache, light headedness, hypertension, subarachnoid haemorrhage, cerebrovascular accident, convulsion, ventricular fibrillation, and cardiac arrest have been reported after topical ocular phenylephrine 1% in the pledget form.15 Contrary to these case reports, in a randomized, double-blind study phenylephrine 1% was reported to be safe for topical ocular application in adults.16 It is strongly recommended that blood pressure and heart rate should be closely monitored after phenylephrine administration in the susceptible population throughout surgery under anaesthesia.17

3.3.3. Clonidine

Clonidine (e.g. apraclonidine, brimonidine, etc), a selective α2 adrenergic agonist, effectively reduces IOP at low topical doses with minimal effect on systemic blood pressure.18 Clonidine also has a potential for sedation.

3.4. Adrenergic antagonists

β-blockers have been the mainstay as a first line drug therapy in glaucoma treatment to decrease IOP by reducing aqueous humour production.5 After ocular instillation to the conjunctival epithelium, β-adrenergic antagonist drugs rapidly drain via the lacrimal channels, nasal mucosa and gastrointestinal tract to reach the systemic circulation. Then, systemic effects of β-receptor antagonism occur mainly on the heart19,20 vasculature, lungs and kidneys. All β-blockers mask to tachycardia associated with hypoglycemia, which is the earliest physiologic response hypoglycemia.

3.4.1. Timolol maleate (timoptic/timoptol ophthalmic solution)

Timolol maleate, a non-selective β-adrenergic antagonist (β1 and 2) used to be a popular antiglaucoma drug, and reaches therapeutic plasma levels approximately 1 h after topical administration because an estimated 80% of the eye drop is absorbed systemically.4 Eventually, β 1 blockade produces negative inotropy and chronotropy and decreases renin secretion, while β 2 blockade causes bronchoconstriction, peripheral constriction and inhibition of glycogenesis.5 Symptoms associated with a slow or irregular heart beat and difficulty in breathing may be observed. The bradycardia initiated by timolol may be atropine-resistant.
Moreover, exacerbation of myasthenia gravis and development of postoperative apnoea in neonates and young infants have been reported. When compared with aqueous solution, the use of hydrogel form of timolol reduced systemic absorption without affecting ocular efficacy. Since β-blockers are metabolized by cytochrome P450, particularly with CYP2D6 genotype which based on 4 types as poor, intermediate, extensive and ultra rapid metabolizers, when 0.5% aqueous solution of ophthalmic timolol is used, poor metabolizers may be more prone to bradycardia than extensive metabolizers. Therefore, routine genotyping is becoming more readily available in many clinical centers.

3.4.2. Betaxolol HCl (Betoptic ophthalmic solution)

Betaxolol HCl with cardioselective β-1 blocking properties has minimal systemic effects, however it is well known that even cardioselective β-blockers would block β-2 receptors at higher doses. Betaxolol is contraindicated in sinus bradycardia, congestive heart failure, heart block greater than 1st degree, cardiogenic shock and overt myocardial failure. It has been reported to exacerbate asthma and fall in spirometry in elderly patients. Also, it should be used with caution as well because catecholamines utilize β-2 receptor to promote glycogenolysis and glucose mobilization.

3.5. Local anaesthetics

Topical local anaesthetics currently used in ophthalmology -proparacaine, oxybuprocaine, lidocaine- are almost free of complications. Tetracaine can produce corneal epithelial erosion. No systemic side effects have been documented with them. However, inappropriate use by patients might cause corneal ulcerations and perforations. Known hypersensitivity to a local anaesthetic drug itself or its preservative is a contraindication for topical local anaesthetic use.

4. Overdose/toxicity due to topical administration

One of the primary reasons for systemic toxicity is the use of high concentrations because of the low ocular bioavailability resulting in high systemic absorption, since only 1% is absorbed by the eye and the remaining 99% is considered to be systemically absorbed via the vessels of conjunctival sac and more rapidly by the highly vascular nasolacrimal duct mucosa avoiding first-pass hepatic metabolism. Additionally, dosage of these drugs can be rarely measured or recorded and as far as the local anaesthetics are concerned, mucous membranes do not have adequate buffer capacity providing a route for diffusion of the base form of local anaesthetics. Second cause of the toxicity is the use of non-selective drugs.

Overdose of atropine, the centrally acting cholinergic drug, given as 1% eye drop may cause central anticholinergic syndrome which manifests with dry mouth, tachycardia, flushing, fever and mental status ranging from unconsciousness to delirium. The specific treatment should include centrally acting cholinesterase inhibitors, particularly physostigmine which penetrates blood–brain barrier. Similarly, excessive systemic absorption of cyclopentolate may also cause toxic effects like disorientation, psychosis and convulsions similar to those associated with atropine overdose. Central nervous system dysfunction is more likely with a 2% than 1% solution of cyclopentolate and 0.5–1% solutions are recommended in children since convulsions may occur in children. Young and elderly patients are particularly susceptible to the systemic effects of this drug.

Guidelines on the topical use of phenylephrine in the operating room have been developed because phenylephrine has been reported to cause catastrophic effects when applied inappropriately in patients, especially paediatrics. According to these guidelines, the initial topical phenylephrine dose should not exceed 0.5 mg for adults and 20 μg/kg for children up to 25 kg.

5. Allergic reactions against topical ophthalmic drugs and anaphylaxis

Allergic reactions or anaphylaxis have been reported with topical ophthalmic drugs, particularly against topical antibiotics or fluorescein. However topical β-blocker therapy is also associated with an increase in the severity and incidence of acute anaphylaxis, which may be protracted and resistant to conventional treatment because of the β-adrenergic blockade. Although these are probably infrequent, the need for aggressive and prolonged support in patients who experience anaphylaxis while receiving β-blocker therapy should be kept in mind. Also, allergy skin testing or immunotherapy is inadvisable in patients taking a β-blocker in the form of ophthalmic eye drop.

6. Concerns related to patients

6.1. Age

Patients’ age, related body weight and immaturation or impairment of physiologic functions is of special concern during topical ophthalmic drug administration. Since ocular dosing of the topical drugs isn’t weight-adjusted, paediatric patients are at greater risk for systemic side effects. Because of their inability for efficient metabolism of the drugs and increased permeability of brain–blood barrier, infants are more prone to undesired effects of the drugs. Especially phenylephrine and cyclopentolate are related with higher incidence of serious side effects in children. In the elderly, tachycardia initiated by anticholinergic drugs can lead to adverse events such as angina, whereas geriatric patients are particularly susceptible to the systemic effects of cyclopentolate. Additionally, systemic side effects of timolol are increased in the elderly who often have lax distensible conjunctival fornices that permit greater retention of the drug.

6.2. Co-morbidities and medications

Many drugs used by the patients have potential for interaction with topical ophthalmic drugs. Because of the antimuscarinic features of antihistaminic drugs, tricyclic antidepressants (TCA), antipsychotics, patients using these drugs may be prone to developing central anticholinergic syndrome after administration of anticholinergic eye drops. One should avoid administering phenylephrine, if possible, in patients using monoamine oxidase (MAO) inhibitor drugs, since dangerous interaction may develop with MAO inhibitors, which are one of the responsible enzymes for the breakdown of catecholamines. The similar risk also exists with clonidine. The effect of clonidine also alters with concomitant use of TCA. Since the risk for a drug interaction with a topical β-adrenergic receptor antagonist is considered to be similar to that of its oral form, these agents should be used with caution in patients who are already using angiotensin-converting enzyme inhibitors, diuretics, calcium channel blockers, hypoglycemics, thyroid supplements since these patients may develop potent hypotension, severe bradycardia and hypoglycemia. Patients receiving oral β-blocker therapy should be observed for potential additive effects.

Moreover co-morbidities of the patients may worsen or lead to life-threatening situations after topical administration of ophthalmic drugs. Topical use of phenylephrine in patients with arterial changes, aneurysms, or insulin dependent diabetes requires close monitoring of the patients. Serious cardiovascular system disease is also a risk factor for topical clonidine use. Adrenergic
antagonists, especially timolol, should be cautiously used in patients with chronic obstructive airway diseases, congestive heart failure, 2° or 3° heart blocks (risk of prolongation in QT interval exists) and diabetes.

7. Conclusion

In conclusion, one should be aware of the possible adverse reactions to topical ocular drugs and question the accompanying disorders and current medications of the patients inclusively to prevent deleterious effects observed due to concomitant disorders and interaction between drugs. Whatever the reason for using a topical ocular drug is, either for treatment or diagnosis, it is important to appreciate that some of these drugs have the potential for developing catastrophic problems. Awareness of the possibility is key to good management.

Conflict of interest

None.

References

REVIEW

Viral Hepatitis

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SUMMARY

This commentary aims to provide Anaesthetists and Intensivists with an understanding of the viral hepatitides and their impact on clinical practice. This will include the modes and risks of transmission, clinical features and new options for disease treatment. Peri-operative management, safe clinical practice and needlestick injury will also be discussed.

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1. Introduction

Viral hepatitis is common worldwide. Anaesthetists and Intensivists may encounter infected patients in a variety of clinical scenarios. This article aims to improve the understanding of this disease spectrum, to allow effective management and safe clinical practice.

2. Hepatitis – an overview

Hepatitis may be due to non-infective or infective causes. Non-infective causes include metabolic (e.g. Wilson's disease), alcohol, drugs and ischaemia. However, a significant number of cases result from infection due to viruses. Such viruses may include cytomegalovirus (CMV), Epstein Barr virus (EBV) and Herpes Simplex Virus (HSV). These infections mainly affect other organs.

There also exist a number of hepatotropic viruses that have a propensity to cause liver dysfunction. These 'Hepatitis Viruses' can be classified either on the basis of their genome (DNA or RNA) or more typically on their route of transmission. Hepatitis A and E are spread by the faecal-oral route, whereas Hepatitis B, C, D and G are spread parenterally (Table 1).

Clinically, viral hepatitis comprises a number of distinct clinical entities. Acute hepatitis develops initially. This usually resolves, but occasionally progresses and may cause death by liver failure. Patients may also develop a chronic viral carrier status following resolution of this acute phase (which may be asymptomatic). Chronic hepatitis may also ensue, with further risk of progression to cirrhosis and chronic liver failure or hepatocellular carcinoma. For patients with acute (fulminant) or end-stage chronic liver decompensation, transplantation is the only option for treatment. For patients with chronic viral hepatitis, new drug treatments may reduce risks of disease progression. The course of viral hepatitis varies according to the virus, with B and C viruses more likely to cause chronic disease (which does not happen with hepatitis A infection).

In the acute phase, the viral hepatitides may present suddenly or more insidiously. A ‘flu-like illness may develop, with mild fever, fatigue and gastrointestinal disturbance (nausea, vomiting and abdominal discomfort or right upper quadrant pain). Anorexia, weight loss and dehydration may follow. In addition to jaundice, cholestatic symptoms associated with dark urine and pale stools can develop (after 2 weeks), as can myalgia, joint pains and itchiness. The jaundice that develops can remain for up to 6 weeks. Liver tenderness may be present and splenomegaly occurs in 10% of cases.

2.1. Blood tests

7–14 days prior to the onset of jaundice, liver transaminase levels often rise to above 1000 IU, falling as jaundice develops. Transaminase recovery usually takes from 6 to 10 weeks. If transaminases remain high one should suspect the development of chronic hepatitis.

Finally, severe acute hepatitis may lead to poor synthetic function, causing a high prothrombin time and low albumin level.

2.2. Prognosis

The majority of patients with acute viral hepatitis gain complete recovery in 2–8 weeks. Some patients will develop a chronic carrier status. Others develop fulminant liver failure (encephalopathy, cerebral oedema and coma) or sub-fulminant disease (progressive ascites and encephalopathy). Only around one-fifth of such patients will survive without transplantation.
3. Hepatitis A virus (HAV)

HAV is very common in the developing World and in areas of civil unrest. It is spread by the faecal-oral route in areas of the world with poor sanitation. HAV is a 27 nm RNA virus. It is generally a mild disease. Symptoms commence a fortnight after infection, coinciding with rising transaminase levels and faecal viral shedding. IgM and IgG anti-HAV antibody titres rise. The former indicates acute infection and disappears within 3–12 months. The latter remains for life. Diagnosis of the disease is made clinically together with rising transaminase levels and faecal viral shedding. Full recovery from disease is the norm, it being rare to progress to fulminant hepatitis.

Passive immunity to HAV is provided to individuals travelling to high-risk areas by injection of immunoglobulin. Active immunity (by an inactivated viral vaccine) can be provided to adults, pregnant women and children above the age of 2.

4. Hepatitis B virus (HBV)

HBV is a 42 nm DNA virus. It consists of an outer lipid coat and an inner nucleo-capid of DNA and protein. An outer and inner protein layer covers the genome and DNA polymerase enzyme. These protein layers contain surface antigen (HBsAg), core antigen (HBCAg) and HBeAg. There is a fourth protein, HBxAg whose function is incompletely understood.

HBV is spread by percutaneous exposure, vertical transmission and sexually. In contrast to HAV, there are a much higher proportion of patients (10–25%) who develop a chronic carrier state and its associated complications. Vaccination has been effective at reducing the burden of disease.

In acute HBV infection symptoms develop after approximately two months. Hepatitis is shown by the rise in ALT (alanine aminotransferase) levels. Fig. 1 demonstrates the changes in antigen/antibody levels over time. HBV DNA, HBsAg and HBeAg are measurable in the blood prior to symptom onset. IgM and IgG anti-HBC antibodies develop, followed a month later by anti-HBe antibodies. These clear the HBeAg. Over the next few months, HBsAg is cleared from the blood and anti-HBsAg antibodies develop. The presence of anti-HBe antibodies indicates hepatitis resolution. Overall, IgM anti-HBc indicates acute infection. The continued presence of HBV DNA indicates ongoing viral replication. If HBeAg and HBsAg are also present in patients with a chronic carrier state, there is an associated high level of infectivity. This is particularly true for vertical transmission risk. It should be noted that a variable number of patients have a precore mutation that prevents HBeAg production and are consequently HBeAg negative. However this mutation is still associated with high infectivity and a higher risk of cirrhotic progression.

Approximately 5% of patients will develop chronic liver disease following acute HBV infection, with a higher risk if infected at a young age. Of these, 10–15% develop cirrhosis and 10% hepatocellular carcinoma. As previously stated, vaccination may prevent acute disease and therefore also the development of the complications. Interestingly, HBsAg has multiple genetic variants that should be targeted by polyvalent vaccines to ensure its effectiveness. A number of antiviral treatments have been employed in the management of chronic hepatitis B. PEG Interferon-2 can be targeted by polyvalent vaccines to ensure its effectiveness. A number of antiviral treatments have been employed in the management of chronic hepatitis B. PEG Interferon-2α causes viral suppression, as do the nucleoside and nucleotide analogues tenofovir, lamivudine and entecavir. Some authorities recommend the use of combination therapy to reduce the risk of drug resistance, though there is no current evidence to support this.

With regards to vertical transmission, Caesarean section does not appear to reduce the risks from Hepatitis B. However, the neonate should be given immunoglobulin and vaccinated to prevent infection.

5. Hepatitis D virus (HDV)

HDV (delta virus) is an RNA virus that requires the presence of HBV (helper virus) for infection. Thus it may occur as co-infection.
with simultaneous transmission with HBV, or as a super-infection in patients with HBV carrier status. In either circumstance, there is a potential for greater disease severity. With co-infection, fulminating acute disease may develop. In super-infection, a greater proportion of patients develop the complications of cirrhosis and hepatocellular carcinoma. All these are associated with an increase in mortality. Overall, HDV infects 15 million patients worldwide.

Vaccination against HBV renders HDV infection impossible. Interferon therapy for HDV has been tried with limited success. Future treatment options may utilise the ribozymic property of the HDV RNA, which enables it to catalyse chemical reactions (ribozyme, ribozyme).

6. Hepatitis C virus (HCV)

This RNA virus exists as 6 main genotypes and infects approximately 170 million people worldwide by parenteral spread. It was initially known as the 'non-A non-B virus.' This acute hepatitis rarely progresses to a severe fulminating disease. However, there is a high (75–80%) risk of developing chronic hepatitis. Leading on from this, 20% develop cirrhotic disease and 1–5% hepatocellular carcinoma. The genotype 1 variant is the most common in the USA and Western Europe.

The parenteral transmission may occur as a result of blood transfusion or via needlestick (intravenous drug abuse or occupational exposure in healthcare workers). It may also spread via the sexual route, though the risks of this are low: 1–3% in a stable heterosexual relationship. Perinatal transmission occurs in 4% of cases and does not appear to vary with the method of delivery.

Serologically, HCV RNA appears in the serum around a month after initial exposure. A week or two later, a transaminis develops to coincide with symptoms. Jaundice may not always be a feature of the mild illness. 1–6 months later, anti-HCV antibodies develop.

Prevention; currently there is no available vaccine. If one were to be produced, it would have to be polyvalent, to target the variety of antigens produced by the different genotypes. Treatment options are therefore directed at the acute and chronic stages of the disease. Post-exposure prophylaxis is not efficacious, but hyper-immune immunoglobulin has been used to prevent hepatitis developing in HCV infected patients post liver transplant. Interferon therapy during the acute hepatitis phase may lead to a 75% rate of viral clearance. With regards to chronic hepatitis, combination treatments of interferon and ribavirin are used. Virus is cleared in 80% of patients with genotype 2 and 3 HCV and 40–50% of patients with genotype 1. Future therapies may target blockade of cell entry by virus or prevention of its replication.

7. Hepatitis E virus (HEV)

This RNA virus is spread mainly by the faecal-oral route (like HAV), but can also be transmitted from animals (pigs in particular). It causes fatal hepatitis in pregnant women with a 20% mortality risk in the third trimester. It can cause chronic infection in immunosuppressed patients, such as those post-transplant. Diagnosis is clinical, together with anti-HEV antibody measurement and exclusion of other hepatitides. A vaccine is currently not available as the virus cannot be presently cultured.

8. Hepatitis G virus (HGV)

This is also known as GB virus C (GBV-C). The GBV-A and –B do not cause disease in humans. Although included in this review, it is uncertain as to whether even GBV-C causes hepatitis or other disease in humans either. It is present in healthy blood donors (up to 2% in the USA). Of interest, if patients with HIV are simultaneously infected with GBV-C (due to similar routes of transmission), there are reports of an increase in life expectancy and slower HIV disease progression.

9. Implications for anaesthesia and intensive care

Intensivists may encounter patients with acute or chronic hepatitis as their primary problem, or as a co-morbid condition. Anaesthesia and invasive procedures may also be required for such patients, including pregnant women during delivery. The following section will discuss this further. The management of acute and end-stage chronic liver disease is complex and may require liver transplantation. The management of this multi-organ dysfunction is beyond the scope of this review.

10. Anaesthesia

Studies are limited and involve small numbers of patients. Surgical risk for patients with chronic hepatitis depends on its severity and its impact on liver function, hence is safe in mild disease. Chronic liver disease with altered liver function affects drug handling, with significant changes in drug pharmacokinetics and pharmacodynamics.

Acute viral hepatitis does pose risk for surgery. A mortality rate of 9.5% (and 11.9% significant morbidity) associated with laparotomy has been reported.1 Hence elective surgery is contra-indicated and emergency surgery should only performed if essential. The specific potential ill effects of anaesthesia include a reported 30–50% fall in hepatic blood flow and this can be caused by both general and neuraxial anaesthesia. This increases the risk of hepatic ischaemia. However, propofol and ketamine infusions have been successfully employed for anaesthesia maintenance in patients with acute hepatitis. In addition, isoflurane minimally affects hepatic blood flow and may therefore be used.

Coagulopathy contraindicates neuraxial techniques. The prothrombin time, an indicator of synthetic function, should be measured and if elevated, neuraxial techniques cannot be performed. The prothrombin time may be corrected (prothrombin complex concentrate, PCC, is preferred to fresh frozen plasma) if there is risk of bleeding. However, this prevents further use of the prothrombin time / International Normalised Ratio as a marker of synthetic function and disease severity. It is a source of contention as to the importance of the prothrombin time in many procedures and clear evidence of risk is hard to find. In the absence of disseminated intravascular coagulation, a number of invasive procedures can be conducted without clotting correction, in the authors' experience.

11. Reduction in transmission risk

Virus may be transmitted from staff to patient, patient to patient and patient to staff. Vaccination of healthcare staff is effective for hepatitis B, but as previously stated there is no vaccine for HCV. Interferon and lamivudine have been used to reduce HBV viral load in affected medical staff. Universal precautions should be employed in ICU and theatres. Overfilling of sharps containers and sharing of drugs from one ampoule to multiple patients increases transmission risk. Re-use of single use devices should be avoided. Interestingly, a study found a third of theatre surfaces were contaminated with blood after surgery. Such surfaces included pulse oximeters, laryngoscopes and ventilators. It should be noted that HBV can survive in dry blood for up to 1 week. Placing infected patients at the end of the list should allow adequate time to thoroughly clean the theatre environment afterwards.
12. Needlestick injury

Despite universal precautions, needlestick injuries occur and pose a risk for HBV, HCV and HIV. The risk of seroconversion depends on the size of the inoculum and viral load. 1 ml of infected HBV blood contains up to $10^{13}$ viral particles compared with $10^{1}–10^{4}$ in HIV. For HBV (especially HBeAg positive) the seroconversion risk has been estimated at 30% for unvaccinated individuals and 3% for HCV (0.3% for HIV). Healthcare workers should be vaccinated against HBV prior to any exposure. However, there is up to a 12% failure rate. When vaccinated, the protective titre may last up to 9 years, but boosters are recommended more often than this.

Following assessment of type and size of injury, unvaccinated individuals exposed to a high risk of HBV can be given Hepatitis B immunoglobulin and vaccination performed as soon as practicable (within 7 days). There is no post-exposure prophylaxis for HCV. If a patient seroconverts due to HBV or HCV then specialist hepatology referral should be made for treatment as previously outlined. The Health Protection Agency publication ‘Eye of the Needle’ (2005) provides information on the surveillance of occupational exposure to blood-borne viruses.2

13. Blood transfusion

The risks of hepatitis transmission from patient to patient by blood transfusion have diminished over time due to an increase in screening tests. Donors with HIV risk factors and those with raised transaminase levels are excluded and blood is tested for HBV, HCV, HIV, HTLV1 and sometimes CMV. However, the risk of hepatitis remains. For hepatitis B this is estimated at 2.2 per 1 million units of blood transfused. For HCV this is 0.03 per million.

14. Staff to patient transmission

There have been a number of instances where hepatitis (and HIV) have been transmitted from staff to patients, via ‘exposure-prone activities’ (EPA). These occur when a healthcare professional carrying the virus performs a procedure and is injured. There is then spillage of blood into a patient’s cavity with the attendant risk of seroconversion. Policies and procedures have therefore been created to minimise this risk, which applies to staff with Hepatitis B and C (and HIV). These are likely to be updated as further treatments for hepatitis emerge.

In understanding these policies, it is necessary to know how the definition of EPA applies to Anaesthetists and Intensivists. The Department of Health guidance suggests that the vast majority of procedures undertaken by these specialties are not exposure-prone as fingers and hands are visible at all times. Laryngoscopy, intubation, arterial line insertion and peripheral and temporary venous cannulation are not EPA. If a tunnelled Hickman line is inserted with a finger used to create a pouch, then this is exposure-prone. The issue of intercostal drain insertion is complicated. For Selinger-type techniques where the operator’s hands are constantly visible, this is not exposure-prone. However, formal drain insertion in a patient with rib fractures, where a finger sweep is used, may potentially be exposure prone. Overall, Anaesthesia and Intensive Care professionals pose a minimal risk to patients if they harbour virus. However, our work is related to surgeons and other specialties, who perform exposure-prone activities. An awareness of the policies can help ensure that these other staff adhere to them, in order to protect patients.

Hepatitis B carriage has significantly reduced following vaccination, which is mandatory for healthcare workers. For those Hepatitis B positive staff who are HBeAg positive, no EPA is allowed. For those HBeAg negative, the viral load is used to guide permissible activity. Staff with a baseline of above $10^{3}$ genome equivalents per ml blood (geq/ml), no EPA is allowed. If virus in these staff developed resistance, the viral load would be sufficient to place patients at risk of transmission. Healthcare workers who are on treatment (HBeAg negative) and have viral loads below $10^{3}$ geq/ml may be permitted to perform EPA but with a number of provisos. The first is that they are under the care of one of several nominated national Hepatologists. The second is that they have identified validated samples of blood checked every three months. These samples are taken in the Occupational Health Department with photographic identification. There is then a validated chain of processing to ensure that the sample has not been interfered with en route to the laboratory. If the viral load rises to above the threshold (10³ geq/ml), then staff must abstain from EPA once again. It is interesting to note that in patients with hepatitis B who do not have active hepatitis, treatment may not be instigated with a viral load of $10^{6}$ geq/ml. There is therefore a possibility that staff commence treatment purely to be able to perform duties at work.

For healthcare workers with hepatitis C (for which there is no vaccine), EPA is not permitted if they are positive for Hep C RNA. In addition to this, the Department of Health advice regarding junior doctors carrying Hep C (and B) virus is that they should not commence training in a specialty with EPA until such time as they are safe. When staff are negative for Hep C RNA for six months after cessation of treatment EPA may be allowed, but a re-assessment is made in a further six months.

Overall therefore, policies and procedures exist to protect patients from accidental transmission of hepatitis B and C. Further information is also available on patient notification in the event of potential exposure.

15. Concluding remarks

The clinical spectrum of disease caused by the viral hepatitides ranges from acute to chronic hepatitis and the development of cirrhosis and hepatocellular carcinoma. This review has described the currently identified viral agents and outlined the management of disease and prevention of transmission. Future work to identify a HCV vaccine and improve chronic hepatitis treatment would help reduce the morbidity and mortality associated with hepatitis.

Conflict of interest statement

None.

References

REVIEW

Dengue fever

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Keywords: Dengue Fever in returning traveller

SUMMARY

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. Infection may be subclinical or may lead to severe disease with vascular leakage, shock and death. Management of severe disease relies on prompt fluid resuscitation and frequent re-evaluation. In non-endemic countries the diagnosis is usually not confirmed during the acute illness. Dengue should be considered in any unwell traveller presenting within 2 weeks of leaving an endemic area.

1. Introduction

Dengue fever is a tropical disease which infects more than 50 million individuals every year and the incidence is increasing. More than 2 billion people live in areas where transmission is possible. It is estimated that there are half a million cases per year of severe disease resulting in around 22,000 deaths, mainly in children.3 The countries with the highest disease burden are in the Asia–Pacific region, South and Central America and the Caribbean. Dengue is found in Africa but is less common. In 2009, dengue re-emerged in Florida after a 75-year absence and in 2010 epidemics have been declared in the Philippines, the Caribbean, Central America and Sri Lanka.2 Transmission tends to occur mainly in urban rather than rural areas, related to behaviour of the vector, although the number of outbreaks detected in rural areas has risen in recent years.

Dengue infection is recognised increasingly as a cause of fever in returned travelers. In the UK there are approximately 200 laboratory-confirmed cases notified to the Health Protection Agency each year; however this is probably an underestimate since notification is not compulsory and the broad range of disease presentations means the diagnosis is often not confirmed. The incidence in travelers is likely to rise with international arrivals forecasted to reach almost 1.6 billion by the year 2020.4 Dengue-endemic regions feature prominently in the top three tourist destinations which are Europe (717 million), East Asia and the Pacific (397 million) and the Americas (282 million), followed by Africa, the Middle East and South Asia.

2. The virus and the disease

The dengue virus is an RNA flavivirus which has 4 serotypes numbered DENV1—DENV4. The Aedes aegypti mosquito is the most important vector. Immunity post infection is type-specific although there is short-lived protection against all serotypes. Worldwide children are most affected reflecting the age of acquisition of infection rather than increased susceptibility. There is no evidence that pregnant women are more susceptible to infection; however they may be more at risk of bleeding complications.4 Infection is often asymptomatic or the clinical presentation may range from a mild flu-like illness to severe disease complicated by vascular leakage, haemorrhage, shock and death. The mortality rate for shock associated with dengue is quoted as being around 1–5%.1 Severe dengue with shock is extremely uncommon in returned travellers but the projected increase in international travel coupled with frequent epidemics and an increase in vector numbers means this is likely to change.

Dengue has an incubation period of around 4–7 days but should be suspected in any patient presenting with fever within 2 weeks of returning from an endemic area, in whom malaria has been excluded. Apart from malaria the differential diagnosis includes bacterial infections e.g. typhoid or meningococcal infection, and other viral infections associated with a rash such as Chikungunya, HIV (acute seroconversion), rubella and infectious mononucleosis. Severe dengue can also mimic non-infectious diseases such as an acute abdomen.

Dengue was previously categorized using the World Health Organisation classification into dengue, dengue haemorrhagic fever and dengue shock syndrome. The case definitions did not always identify patients at risk of severe illness and the classification is under review with a move towards classifying patients simply as having either uncomplicated or severe disease.
Typical symptoms, apart from fever, which suggest the diagnosis are severe headache, arthralgia, myalgia, retro-orbital pain and rash which may be generalised and macular, maculopapular or petechial in appearance. There may be nausea and vomiting. Patients should be asked about any bleeding e.g. from the gums. The duration of symptoms may be as long as 10 days and a ‘saddleback’ fever pattern has been described in some patients with defervescence occurring temporarily for about 48 h midway through the illness before relapse. A very low white blood cell count may be a very useful clue that the patient has dengue infection.\(^5\)

Thrombocytopenia is another common observation. A tourniquet test is sometimes performed to corroborate the diagnosis which involves inflating a blood pressure cuff on the upper arm to a point midway between the systolic and diastolic pressures for 5 min. The test is positive if there are \(>20\) petechiae per 2.5 cm\(^2\). This tends not to provide much additional useful information in patients requiring hospitalization.

A proportion of patients will progress to severe disease on day 3–5 of the illness. Retrospective analyses have not been able to identify any predictors of who is likely to progress. Severe infection is characterized by vascular leakage which, if incorrectly managed will result in hypovolaemic shock with a possible fatal outcome. This may be associated with haemorrhage and organ failure e.g. renal failure, hepatitis and rarely encephalitis. A rising haematocrit or thrombomodulin, tissue and plasminogen activator inhibitor type 1 concentration may activate fibrinolysis leading to subsequent procoagulant activation.\(^7\)

### 4. Diagnosis

In non-endemic countries the diagnosis is usually confirmed retrospectively by serological testing. PCR methods have also been developed. The major nonstructural dengue virus protein NS1 is the target of a number of commercial ELISAs, including point of care tests; however these are not widely available.

### 5. Management

There is no specific antiviral therapy so treatment of dengue is supportive. Patients with signs of shock should ideally be managed in the intensive care unit. Intra-arterial blood pressure monitoring is desirable. Prompt, effective fluid resuscitation with frequent reassessment is the cornerstone of the management of severe dengue. The optimum choice of fluid has been investigated in 3 randomised controlled trials in children.\(^5\)–\(^10\) The fluids studied were 2 crystallloid solutions: Ringer’s Lactate and 0.9% normal saline and 2 colloid solutions: Dextran 70 and 6 percent hydroxyethyl starch. The studies concluded that in all but very severe cases there is no advantage to giving colloid over crystallloid solutions. Dextran 70 and 6 percent hydroxyethyl starch performed similarly in children with severe shock, but there were more adverse allergic-type reactions associated with the use of dextran. Use of colloids was not associated with increased coagulopathy. More research is needed to investigate whether early intervention with colloid solutions improves outcome in more advanced shock. If major bleeding occurs it is usually from the gastrointestinal tract and transfusion may be indicated. There is no evidence that adjuvant therapies such as steroids, intravenous immunoglobulins or recombinant Activated Factor VII are useful in the management of severe dengue. The increased vascular permeability resolves spontaneously within days and recovery is usually rapid and unremarkable.

### 6. Control

At the moment a number of candidate vaccines are under development, with some in Phase 2 clinical trials, but control of dengue relies primarily on control of the vector. Aedes aegypti, the principal vector, flourishes in urban environments, especially where inhabitants have an unreliable water supply and need to store water since the mosquitoes breed in the water storage vessels. The other important vector is Aedes albopictus. This was originally viewed as an Asian mosquito but in the 1980s was discovered to have become established in the Americas and subsequently in parts of Africa, its dispersion in part due to importation of used car tyres containing the mosquito eggs. A. albopictus is also found in Albania and in many parts of Italy although it is thought that all cases of dengue in Italy to date have been imported.

### 7. Summary

Imported infections leading to critical illness are still uncommon; however delays in diagnosis and failure to recognise complications will lead to worse outcomes. In the case of severe dengue infection prompt effective fluid resuscitation with frequent...
re-evaluation is the key to successful management. Dengue is the most rapidly spreading mosquito-borne viral disease in the world. The diagnosis should be considered in any unwell traveller presenting within 2 weeks of leaving an endemic area.

**Table**

<table>
<thead>
<tr>
<th>Summary points.</th>
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<tbody>
<tr>
<td>• Suspect dengue in patients presenting with fever within 2 weeks of travelling to an endemic area (typically Asia-Pacific, South America, the Caribbean), in whom malaria has been excluded.</td>
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<tr>
<td>• Retro-orbital pain and skin rash suggest the diagnosis.</td>
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<td>• Low white blood cell count and platelet count may be a useful clue.</td>
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<tr>
<td>• Rising haematocrit may signify vascular leakage and incipient shock.</td>
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<tr>
<td>• Effective fluid resuscitation is the key to managing severe disease.</td>
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**Conflict of interest**

None declared.

**Acknowledgment**

Thanks to Dr Neil Soni for helpful comments on the manuscript.

**References**

2. Promed website http://www.promedmail.org/. [Accessed 05.08.10].
FOCUS REVIEW

Emergency, anaesthetic and intensive care management of a case of eventration of diaphragm, Bochdalek hernia and an intra-thoracic gastric rupture with gastric gangrene

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Keywords:
Eventration of diaphragm
Bochdalek hernia
Intra-thoracic gastric rupture
Gastric gangrene
Emergency surgery
Anaesthetic management

SUMMARY

A combination of eventration of diaphragm, Bochdalek hernia and an iatrogenic intra-thoracic gastric rupture with gastric gangrene is rare and poses various challenges which require urgent and efficient management with close co-ordination between various specialities. We describe a 23-year-old female admitted with a history of pain in abdomen, chest pain, breathlessness and profound circulatory shock. Our patient suffered an iatrogenic gastric perforation induced by inadvertent insertion of the intercostal drain. Successful management of this challenging patient required quick decision making, skilled peri-operative care, good communication and close cooperation between the Anaesthesiologist, General Surgeon, Cardiothoracic Surgeon and Radiologist.

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1. Introduction

Diaphragmatic hernia may be congenital, traumatic, or iatrogenic following thoracic and abdominal surgery.1 Bochdalek herniae are the most common type of congenital diaphragmatic hernia (CDH) and in adulthood, they are diagnosed incidentally or when they become symptomatic.2 Eventration of diaphragm is seldom symptomatic and often requires no treatment, but may be confused with a traumatic rupture of the diaphragm.3 Various abdominal viscera may herniate through the defect leading to a wide spectrum of presentations and complications. Gastric herniation with intra-thoracic gastric rupture spontaneously,4 and months after thoraco-abdominal trauma have been described.5 A combination of eventration of diaphragm, Bochdalek hernia and an iatrogenic intra-thoracic gastric rupture with gastric gangrene is rare and poses various challenges which require urgent and efficient management with close co-ordination between various specialties. We describe the successful management of such a rare case in a young adult.

2. Report of a case

A 23-year-old female (weight = 54 kg) was admitted with a history of pain in abdomen for 3 days, and chest pain and breathlessness for 1 day. There was no history of trauma. She was being treated as a case of acid-peptic disease (for on and off epigastric pain) for the past 3 years. She was admitted to a private hospital and the treating physician referred her to our institute after making a diagnosis of left sided hydro-pneumothorax based on chest radiograph.

On examination in the emergency department, she was conscious, drowsy, tachypneic and peripheral pulses were not palpable. She was in profound circulatory shock with a heart rate = 180 b/min, unrecordable blood pressure and cold peripheries. Respiratory system examination revealed a respiratory rate = 45/min and grossly reduced air entry on left hemithorax without any added sounds. She was administered oxygen and intravenous fluid (1 L normal saline) was infused rapidly. The resident in the emergency department made the diagnosis of left hydrothorax on the basis of chest radiograph (Fig. 1A) and inserted (by blunt dissection) an intercostal drain (ICD) in the left 5th intercostal space in mid-axillary line which drained 1.2 L of brownish thick fluid with particulate matter. The fluid was sent for urgent biochemical and pathological analysis, and culture and
sensitivity testing. Chest radiograph post-ICD insertion showed a massively dilated stomach in the left hemithorax and collapsed left lung with a further shift of mediastinum to the right without an identifiable left hemidiaphragm (Fig. 1B).

A triple lumen right subclavian central venous catheter was secured and the central venous pressure (CVP) was 22 mmHg (consistent with high intra-thoracic pressure). Blood samples were drawn and arterial blood gas showed pH = 7.02, PaO2 = 71 mmHg, PaCO2 = 59.4 mmHg, HCO3 = 15, base deficit = −16.4, and oxygen saturation = 80.2%. The blood pressure was still not recordable and ionotrope infusion (Dopamine 10 µg kg\(^{-1}\) min\(^{-1}\) and Adrenaline 0.2 µg kg\(^{-1}\) min\(^{-1}\)) was started. Sodium bicarbonate (8.4%) 100 meq was administered intravenously. She did not respond to high-dose ionotropes. As the condition of the patient did not improve, trachea was intubated following administration of Ketamine 80 mg and succinylcholine 100 mg and put on mechanical ventilation. Her initial airway pressures were 28–30 cmH\(_2\)O.

Hydrocortisone 200 mg was administered intravenously and Vasopressin infusion was started suspecting refractory septic shock. The left femoral artery was cannulated and invasive blood pressure (initial BP 68/40 mmHg) monitoring initiated. The clinical situation was discussed with the General Surgeon, Cardiothoracic Surgeon and Radiologist. The patient’s attendants were explained about the condition and patient was shifted to Computed Tomography (CT) scan room. The CT-scan performed after instillation of about 50cc iodinated ionic contrast via the nasogastric tube clearly outlined the herniated stomach into the left hemithorax through a small defect posteriorly. There was associated eventration of the stomach with greater omentum was seen to herniate into the left hemithorax through a defect in the posterolateral part of the left hemidiaphragm (a Bochdalek hernia, Fig. 2A). The hernia was gently reduced which showed a gastric perforation and gangrenous changes along the greater curvature (Fig. 2B). The blood pressure rose to 138/80 mmHg along with a drop in CVP (from 24 mmHg to 10 mmHg) and airway pressure (from 30 cmH\(_2\)O to 15–16 cmH\(_2\)O) soon after the hernia was reduced allowing the infusion of Dopamine and Adrenaline to be reduced to 15 µg kg\(^{-1}\) min\(^{-1}\) and 0.3 µg kg\(^{-1}\) min\(^{-1}\), respectively. A sleeve gastrectomy including the gangrenous part and the perforation was performed, and the abdomen closed.

The patient was placed in the right lateral position from supine and a left posterolateral thoracotomy performed via the 7th intercostal space. The intercostal muscles around the ICD were partially digested by the gastric contents and the left lung surface was “angry looking”. The hernia was repaired and the evisceration was plicated with prolene. A thorough lavage was performed and the thorax closed after placing two pleural drains. The patient was transferred to the surgical intensive care unit (SICU) and ventilated with a lung protective strategy (tidal volume 8 ml/kg and respiratory rate 14/min) in Synchronized Intermittent Mandatory Ventilation (SIMV)-volume control mode. She required continued ionotrope support for the next three days which was tapered off gradually. She was successfully weaned and extubated on the 3rd day.

The pleural drain output on day-1, day-2 and day-3 in SICU was 1425 ml, 625 and 415 ml, respectively. She developed severe hypocalcemia (Ca\(^{2+}\) = 7.9 mg/dl) with hypoproteinemia (serum total protein = 2.7 g/dl and albumin = 1.5 g/dl). She was administered human albumin every day for 5 days till the serum albumin was 3 g/dl along with 2 g calcium gluconate/day. Parenteral nutrition was started with amino acids and dextrose on the 3rd day, and lipids included on 5th day. Oral feeds were started on day-10 which she tolerated well. Aggressive physiotherapy was begun after

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(A) An air fluid level and elevated left hemidiaphragm with mediastinal shift to right.
(B) Massively dilated stomach in the left hemithorax and collapsed left lung with a further shift of mediastinum to right without an identifiable left hemidiaphragm.

Fig. 1. Chest radiographs (A) An air fluid level and elevated left hemidiaphragm with mediastinal shift to right. (B) Massively dilated stomach in the left hemithorax and collapsed left lung with a further shift of mediastinum to right without an identifiable left hemidiaphragm.
extubation. The patient recovered well, she was transferred to the ward on the 17th day and discharged home 1 month later. She is currently being followed up in our institute. She had lost ≈20 kg when she came for the follow-up one month after discharge.

3. Discussion

In 1848, Victor Alexander Bochdalek first described both right and left posterolateral CDH. The major problem in Bochdalek herniae is the posterolateral defect of the diaphragm.6 The incidence of CDH is 1:2000–1:5000 live births with equal gender preference2,7,8 and Bochdalek hernia accounts for 78–90% cases.2,8 The prevalence of Bochdalek hernia in adults has variously been reported to be 0.17%–12.7%.9–11 If CDH does not present acutely in the neonatal period, diagnosis of the defect is more difficult as the signs and symptoms become chronic, vague and inconsistent. Symptoms can be either cardiorespiratory or gastrointestinal, with the latter becoming more prominent as the age of onset of symptoms increases.2,8 These herniae are one of the causes of secondary gastric volvulus. Surgical repair is indicated in all symptomatic adults12 to prevent incarceration and strangulation of abdominal viscera. Currently, many reports have demonstrated the safety and efficacy of using open (laparotomy/thoracotomy or both) or minimally invasive repair techniques,6 with or without mesh reinforcement.

Eventration of diaphragm is a condition where the muscle is permanently elevated, but retains its continuity and attachments to the costal margins.13,14 This condition may be confused with a traumatic rupture of the diaphragm in a patient with trauma.5 Traumatic diaphragmatic hernia may manifest immediately or several months/years after the original event (as late as 30 years).15 Eventration is conservatively managed if asymptomatic.

Multiple imaging modalities are available for the diagnosis of diaphragmatic injury. Chest radiographs are the most commonly performed and initial imaging modality to evaluate the diaphragm. Chest radiograph may be confusing and may lead to inadvertent insertion of the chest tube3 as occurred in our patient. When chest radiographs are indeterminate, spiral CT with thin sections and reformatted images is the next study of choice. Magnetic resonance imaging is used to evaluate the diaphragm for patients with clinical suspicion but an indeterminate diagnosis after chest radiography and spiral CT.16 Diagnostic laparoscopy should be considered in difficult cases where imaging is inconclusive.17

Fig. 2. Bochdalek hernia (A) and gastric gangrene with perforation (B).

Our patient suffered an iatrogenic gastric perforation induced by inadvertent insertion of the ICD. Our case highlights an important aspect of the management of such patients, i.e. do not insert a chest tube without confirming the diagnosis, as it can be very dangerous for these patients. It was extremely challenging to obtain the CT-scan of our patient preoperatively as she was in refractory hypotension. The fact that she was conscious (slightly drowsy though) gave us the reassurance to go ahead with the preoperative CT evaluation. In case of extreme haemodynamic instability (as in our patient), a difficult decision of preoperative diagnostic CT-scan vs directly taking the patient for surgery and per-operative evaluation has to be made as it could prove life-saving. Preoperative evaluation with a definite diagnosis helps in proper planning of the surgical management although an urgent per-operative surgical evaluation may be the only option in case of an unstable patient.

Lung isolation techniques are useful in the anaesthetic management of repair of diaphragmatic hernia.18 The mass effect of the intra-thoracic viscera causes cardiovascular impairment by direct compression of the heart and mediastinal shift, which can kink the vena cavae and pulmonary veins, impair venous return to the heart, and reduce cardiac output.18 Any re-expansion of the collapsed lung may exacerbate the mass effect with rapid worsening of the circulation. The collapsed lung should therefore be isolated and the normal lung ventilated with small tidal volumes and pressures, until the affected hemithorax has been decompressed. If effective lung isolation is not possible as occurs with difficult airway,18 technical problems or non-availability of appropriate gadgets, priority should be given to rapidly decompress the thorax which may have dramatic beneficial haemodynamic effects as observed in this case.

Intentional right endo-bronchial positioning of the endotracheal tube in the emergency department could have had favourable effects on the haemodynamics. We did not resort to any lung isolation technique in the operation theatre because of the extreme haemodynamic instability and the surgical exposure was satisfactory during thoracotomy. A low tidal volume (6 ml/kg) with slightly higher respiratory rate (18–20/min) ventilation strategy facilitated the surgical exposure.

Lung protective ventilator strategy was continued post-operatively as there was severe inflammation of the pleurae. Early initiation of the parenteral nutrition may enhance the recovery as a major surgery such as this leads to extreme catabolism associated with a delayed initiation of enteral nutrition. We considered the insertion of a naso-jejunal feeding tube per-operatively for early initiation of
the enteral nutrition; this was not performed because of the doubtful viability of the stomach. To our knowledge, this is the first report of an eventration of diaphragm, Bochdalek hernia and an intra-thoracic gastric rupture with gastric gangrene secondary to an ICD insertion.

4. Conclusion

Successful management of this challenging patient required quick decision making, skilled peri-operative care, good communication and close cooperation between the Anaesthesiologist, General Surgeon, Cardiothoracic Surgeon and Radiologist.

Conflicts of interest

There are no conflicts of interests involved in this report.

References

FOCUS REVIEW

TURP syndrome☆

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Keywords:
Glycine
Hyponatraemia
Cardiac arrest
Prostatectomy transurethral

SUMMARY

A 70 year old man with underlying cardiac disease presented for elective transurethral prostate resection. General anaesthesia was administered uneventfully until the patient presented with an asystolic cardiac arrest only 33 min into the procedure. The patient was resuscitated and the cardiac output restored after 7 min of cardiopulmonary resuscitation. Subsequent tests revealed a serum sodium of 102 mmol/litre and transurethral resection of the prostate syndrome as cause for the arrest. This unusual but dangerous complication presenting during transurethral resection of the prostate illustrates how regional anaesthesia, better communication and earlier use of the alcometer can lead to earlier diagnosis and better management of this complication. The use of normal saline as irrigation fluid, with bipolar diathermy, may signal the end of the life threatening complications associated with glycine and hyponatraemia.

1. Pre-operative history

A 70 year old man with a 6 month history of prostatism presented for a prostate resection procedure. Past medical history included ischaemic heart disease with previous coronary bypass grafting. He was known to be hypertensive but well controlled. Preoperative echocardiography showed mild aortic and mitral regurgitation, mild aortic stenosis and mild left ventricular hypertrophy with good left ventricular function. His electrocardiogram showed sinus rhythm with heart rate of 64/min but he also had first degree heart block and left bundle branch block. The chest X ray was unremarkable. Other preoperative measurements included a plasma sodium of 138 mmol/L, potassium 4.1 mmol/L, and haemoglobin of 13.3 gm/dl. The options of regional or general anaesthesia were discussed with the patient and the patient preference was general anaesthesia. General anaesthesia was induced intravenously with fentanyl and propofol and maintained with spontaneous ventilation using a mixture of oxygen, air and sevoflurane delivered via laryngeal mask airway. During the procedure the bladder was irrigated with a total of 21 L of 1.5% glycine with 1% ethanol at a pressure of up to 70 cm water. After about 30 min the surgeon announced that the capsule of the prostate has been perforated. An alcometer was being sought to assess the amount of irrigating fluid absorbed when the patient suddenly lost his pulse and became asystolic. Cardiopulmonary resuscitation was commenced, the patient intubated and then ventilated with 100% oxygen. The advanced life support arrest algorithm was followed and cardiac output was restored within 5 min. A provisional diagnosis of TURP syndrome was made and furosemide 40 mg IV administered immediately. Bradycardia and hypotension was treated with an adrenaline infusion at rate of 0.05 mcg/kg/min. The serum sodium is measured at 102 mmol/L. The patient was transferred to the intensive care unit. The patient was ventilated relatively easily. The hyponatraemia was slowly corrected to 132 mmol/L by diuresis and fluid restriction. Although the patient continued to experience rhythm problems including a supraventricular tachycardia and then atrial flutter, he did well and was transferred to the coronary care unit for further management.

2. Pathophysiology

TURP syndrome is due to absorption of irrigation fluid via open prostatic venous sinuses in sufficient quantities to cause hyper-volaemia, hyponatraemia and hyperglycinaemia (if glycine is being used) leading to encephalopathy and cardiac, respiratory and renal failure. TURP is still the standard surgical procedure for treatment of benign prostate hyperplasia. This operation remains associated with significant morbidity and the occurrence of TURP syndrome. The syndrome has a reported incidence of 1–8%1–3 and can be fatal.4,5

☆ TURP (transurethral resection of the prostate) syndrome refers to the symptoms and signs that occur as a result of the absorption of large amounts of irrigating fluid. It can present either intra or postoperatively. Prompt recognition and treatment is essential to limit morbidity and mortality associated with this condition.

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2.1. Signs and symptoms

When under regional anaesthesia, the patient characteristically complains of:

- Nausea
- Tight feeling in the chest
- Shortness of breath
- Dizziness
- Restlessness
- Confusion
- Retching
- Abdominal pain
- Blurring of vision

Both systolic and diastolic blood pressures rise and the heart rate decreases. The patient may become hypotensive and even suffer cardiac arrest. Frequently the presentation is neurological with symptoms of drowsiness progressing to unconsciousness with or without short episodes of tonic-clonic seizures. Early signs may include pupillary dilatation with sluggish reaction to light.

Under general anaesthesia, the neurological manifestations are masked and so the diagnosis of TURP Syndrome is difficult and often delayed. The cardiovascular signs predominate. An unexplained rise in BP followed by a fall often associated with refractory bradycardia. ECG changes such as nodal rhythm, ST changes, U waves and widening of QRS complexes may be observed.

2.2. Irrigation fluid

The irrigation fluids used during endo-urolological procedures are essential to the procedure. An ideal irrigation fluid must be isotonic, non-haemolytic, non-toxic, electrically neutral and inexpensive. A solution with all these ideal properties is yet to be available for clinical use. Electrolyte solutions like normal saline and Hartmann's solution do not cause much harm when absorbed into the circulation but can dissipate electrical current from the resectoscope and cause injury to the patient. Commonly used irrigation fluids used for TURP procedures include sterile water, glycine 1.2%, 1.5%, 2.2%, glucose, mannitol 3%, and urea. Glycine is a popular irrigating fluid because of its good optical properties. It is non-electrolytic and hence does not disperse the high frequency current. Furthermore, it is non-haemolytic above 1% concentration. However, it has been shown that glycine may be toxic to the cardiovascular system and central nervous system if infused in large amounts. Glycine is also an inhibitory transmitter in the retina and excess amount slows down the transmission of impulses from the retina to the cerebral cortex.

3. Complications

3.1. Glycine toxicity and visual disturbance

Glycine is known to be a major inhibitory neurotransmitter in the spinal cord and in the brain stem, probably acting in the same manner as gamma amino butyric acid on the chloride ion channel. The normal value of serum glycine in man is 13–17 mg/l. Absorbed into circulation glycine is potentially toxic to the heart. In vitro glycine can be shown to be harmful to the myocardial histoskeleton causing swelling of isolated cardiomyocytes. Clinically, glycine 1.5% has also been associated with myocardial effects, manifested as depression or inversion of the T wave on the electrocardiogram 24 h after surgery. Glycine absorption seems to depress myocardial function, particularly when the operative duration exceeds 1 h which may be a feature of effective absorption dosage. 0.5% of patients develop acute myocardial infarction during TURP, though transient myocardial ischemia has been detected during 20% of TURPs. This may be one of the reasons for the higher long-term mortality after transurethral versus open prostatectomy. The signs of glycine toxicity are nausea, vomiting, slow respiration, seizures, spells of apnoea and cyanosis, hypotension, oliguria, anuria and then death. Other effects include toxicity to the retina and hyperammonaemia. Ammonia is a major by-product of glycine metabolism and high concentrations suppresses noradrenaline and dopamine release in the brain which causes the encephalopathy of TURP syndrome. Fortunately this is a rare phenomenon. Characteristically the toxicity occurs within 1 h after surgery. The patient develops nausea and vomiting and then lapses into coma.

3.2. Circulatory overload

The average rate of fluid absorption during TURP is 20 ml/min. Therefore an estimated uptake of 1 L of fluid per hour which corresponds to an acute decrease in the serum sodium concentration of 5–8 mmol/l. With the fluid absorption, the blood volume increases, systolic and diastolic pressures increase. This may jeopardise cardiac contractility and the heart may fail. The absorbed fluid dilutes the serum proteins and decreases the oncotic pressure of blood. Combined changes in hydrostatic and oncotic pressures tend to drive fluid from the vascular to the interstitial compartment potentially causing pulmonary and cerebral oedema. In addition to direct absorption into the circulation, a significant volume (up to 70%) of the irrigation solution has been found to accumulate interstitially, in the peri-prostatic and retroperitoneal spaces. For every 100 ml of fluid entering the interstitial compartment, 10–15 mmol of sodium also moves with it.

3.3. Capsular perforation

Absorption of 1–2 L of irrigation fluid during transurethral resection of the prostate causes a mild TURP syndrome. More severe events are associated with absorption of more than 3 L of fluid. The amount of fluid absorption depends mainly on the number and size of venous sinuses opened, perforation of prostatic capsule, duration of exposure and the hydrostatic pressure of the irrigating fluid. With prolonged procedures, where resection becomes increasingly extensive, fluid absorption increases. In order to limit the likelihood of a serious reaction developing, it is advocated that resection times should be limited to 1 h. However, it has been reported that water intoxication can occur within 15 min of the start of procedure. Damage to a venous sinus or perforation of the capsule of the prostate during resection increases the incidence of TURP syndrome. The driving force for fluid absorption is the fluid pressure which needs to be higher than the venous pressure of 1.5 KiloPascals when a vein is severed during electrosurgery. Instrumental perforation of the prostatic capsule can cause catastrophic absorption of large amounts of irrigation fluid in a very short time and this occurs in at least 10% of TURP cases. With a perforation the fluid pressure only needs to exceed the intraabdominal pressure of around 0.5 KPa for extravasation of large amounts of irrigation fluid into the peri-prostatic space. It is important to emphasise that the anaesthetist is rarely cognisant of intracystic pressure during these procedures and that absorption is invariably occult.

3.4. Water intoxication and hyponatraemia

Part of the TURP syndrome is due to water intoxication, a neurological disorder caused by increased water content of the brain. The patient becomes incoherent and restless. Seizures may also develop...
leading on to coma in decerebrate position. Papilloedema, with dilated, sluggishly reacting pupils can occur. The EEG will show low voltage, bilaterally. The symptoms of water intoxication appear when serum sodium level falls below 15–20 mmol/l below normal level.

Sodium is essential for proper function of excitatory cells, particularly those of heart and brain. Several mechanisms proposed for hyponatraemia in TURP patients include

- Dilution of serum sodium through excessive fluid absorption.
- Loss of sodium into the stream of the irrigation fluid from the prostatic resection site.
- Loss of sodium into pockets of irrigation solution accumulated in the periprostatic and retroperitoneal spaces.
- Larger amounts of glycine stimulate the release of atrial natriuretic peptide in excess of that expected by the volume load, which further promote natriuresis.

When serum sodium falls below 120 meq/l, hypotension and reduced myocardial contractility occur. Below 115 meq/l, ECG changes including T wave inversion, bradycardia, widening of QRS complex, ventricular ectopics, ventricular Tachycardia, Ventricular fibrillation and cardiac arrest occur. Below 100 meq/l generalised seizures, coma and respiratory arrest can occur.

### 3.5. Hypovolemia and hypotension

The classical hemodynamic signs of the TURP syndrome, when glycine is used as irrigating fluid, consist of a transient arterial hypertension, that may be hidden if the bleeding is profuse and there are therefore other causes for hypotension. This is usually followed by more prolonged hypotension. Release of prostatic tissue substances and endotoxins into the circulation and associated metabolic acidosis might contribute to this hypotension. Blood loss correlates with the size of prostatic gland resected, duration of surgery and skill of the surgeon. The average blood loss during TURP is 10 ml/gram of prostate resected. Sometimes the procedure is associated with bladder perforation and retroperitoneal haematoma which may be the cause for hypotension and can present very late. Bladder perforation should be actively looked for if there is a decrease in return of the irrigating fluid.

### 3.6. Hypothermia

Hypothermia is a frequent observation in patients undergoing TURP. This results in shivering and markedly increases oxygen consumption. Bladder irrigation is an important source of heat loss and the use of irrigating fluids at room temperature results in a decrease in body temperature of 1–2 °C. Moreover elderly patients are particularly susceptible to hypothermia because of possible autonomic dysfunction. The associated vasoconstriction and acidosis can adversely affect the heart and can contribute to CNS manifestations. Shivering can also enhance bleeding from the resection site and make the surgical procedure more difficult.

Other complications associated with this procedure include bacteremia, septicaemia and toxemia as 30% of all TURP patients have infected urine preoperatively. When prostatic venous sinuses are opened preoperatively and high pressure irrigation is used, bacteria enter the circulation. In about 6% of patients, the bacteremia is complicated by septicaemia. Be aware that the increasing range of ESBL gram negative organisms colonizing outpatients may be resistant to standard prophylaxis. Absorption of bacterial endotoxins and toxic byproducts of tissue coagulation may lead to a toxic state in some patients after the procedure. Disseminated intravascular coagulation (DIC) has also been noted with this procedure due to release of prostatic particles rich in tissue thromboplastins into the circulation causing secondary fibrinolysis. It is very difficult to estimate the exact blood loss with this procedure as it is complicated by the use of irrigation fluid and in some instances by bladder or prostatic capsule perforations leading to retroperitoneal accumulation of blood and irrigation fluid.

### 3.7. Measuring fluid absorption

Whatever the surgical and anaesthetic technique adopted we cannot avoid absorption of irrigation fluid during TURP. So it becomes necessary to devise a method to determine amount of fluid absorbed. The measurement of serum sodium at the end of the operation gives a rough indication of amount of fluid absorbed even though the correlation is poor. Other described methods include:

#### 3.7.1. Alcometers

The use of glycine solution with a tracer amount of ethanol for detecting and quantifying irrigating fluid absorption has been pioneered in Sweden. The volume of irrigant absorbed can be estimated using the nomogram developed by Hahn and his colleagues. A rising breath ethanol levels indicate absorption of irrigation fluid. If glycine is used as irrigation fluid, the routine use of alcometers is a useful aid in the early detection of irrigation fluid absorption.

#### 3.7.2. Volumetric method

This is based on the principle that the difference between the amounts of infused volume to the volume recovered is absorbed by the patient. But this is not an accurate method as values can be influenced by factors like spillage, blood loss and urinary excretion.

#### 3.7.3. Gravimetric method

This involves the patient to be operated on a bed-scale and increase in body weight means fluid absorption.

#### 3.7.4. Central venous pressure

Even though this is not a standard monitoring technique for this procedure, an increase in CVP reading roughly correlates with amount of fluid absorbed. This method is relatively insensitive because at least 500 ml of fluid should be absorbed within 10 min to increase the CVP by 2 mmHg.

### 4. Prevention

#### 4.1. Regional vs general anaesthesia

Regional anaesthesia is favoured for transurethral resection of the prostate surgery because it decreases blood loss, reduces the risk of pulmonary oedema, allows early detection of any change in mental status and permits early recognition of the typical syndrome. The commonest early sign of TURP syndrome is restlessness, followed by confusion, blurring of vision, headache, nausea and vomiting. This is associated with cardiovascular changes which typically include bradycardia and arterial hypotension or sometimes hypertension.

#### 4.2. Glycine vs saline

It has been shown that glycine may be toxic to the cardiovascular system and central nervous system if infused in large amounts. Normal saline is more physiological solution that can be...
given intravenous with minimal side effects. Studies comparing use of bipolar diathermy in normal saline with standard monopolar resection in glyce have shown advantages including shorter stay and less complication rates.30–33

4.3. Surgical time

It is recommended that the resection time should be kept to less than 1 h in order to prevent this problem. However, some case reports reveal development of this complication within 15 min of surgery.34

4.4. Alternative surgical techniques

With the advent of alternative surgical techniques like vaporization of the prostate, this problem can potentially be avoided.

4.5. Communication

The likelihood of TURP syndrome increases significantly with capsular perforation of the prostate or apparent damage to venous sinuses. Therefore good communication between the surgeon and anaesthetist is very important for the early recognition of TURP syndrome. It is vital that the surgeon communicates any surgical difficulties to the anaesthetist as soon as they occur.

5. Management

5.1. Surgical

As soon as a problem of TURP syndrome is suspected intraoperatively, everyone in the operating theatre should be alerted. Intravenous fluids should be stopped, bleeding points coagulated and surgery should be terminated as soon as possible.34

5.2. Medical management

Minor degrees of haemodilution will be corrected by spontaneous diuresis. If cerebral or circulatory signs indicate the need for active treatment, the concurrent administration of 3% hypertonic saline solution and a loop diuretic will both raise plasma sodium concentration and osmolality, and promote diuresis. Supplemental oxygen must be administered with intubation and ventilation if required. Intravenous anticonvulsants may be needed if the patient has a seizure. Both severe hyponatraemia and over rapid correction of chronic hyponatraemia and over rapid correction of chronic hyponatraemia can result in permanent neurological damage most commonly central pontine myelinolysis. The suggested treatment regime for use of 3% hypertonic saline is 1.2–2.4 ml/kg/h and this should produce a rise in serum sodium of 1–2 mmol/l.35 Correction of hyponatraemia should ideally not be faster than 1.5–2 mmol/L/h for 3–4 h then 1 mmol/L until symptomatic improvement or sodium greater than 125 mmol/L. Maximum rise of serum sodium should not exceed 12 mmol/L in 24 h.

6. Conclusion

TURP syndrome can be life threatening, so early recognition and prompt treatment is vital. The use of a regional anaesthetic technique and the use of alcometers can contribute to earlier recognition of this complication. Good communication between the surgical and anaesthetic teams is essential in order to alert the anaesthetist about complications such as capsular perforation and associated sudden absorption of irrigating fluid into the systemic circulation. The use of bipolar diathermy with saline can avoid the complications associated with glyce toxicity and hyponatraemia and may signal the end of TURP syndrome.36

Conflict of interest statement

None.

References

28. Starkman JS, Santucci RA. Comparison of bipolar transurethral resection of the prostate with standard transurethral prostatectomy: shorter stay, more...
Anaesthetic management of a patient with Eisenmenger syndrome for lower abdominal surgery

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1. Introduction

Eisenmenger syndrome after initial description by Victor Eisenmenger was redefined by Wood as the presence of high pulmonary vascular resistance associated with pulmonary hypertension at, or close to, systemic pressure and associated with a reversed or bi-directional shunt at the aortopulmonary, interatrial or interventricular level. This syndrome occurs in over 50% of adults with large ventricular or aortopulmonary communications, but in only 9% of those with a secundum atrial septal defect (ASD). It is rare and will be more so, as more of the patients with pre-disposing congenital cardiac lesions undergo corrective surgery. Survival beyond fifty years is unusual, but patients may lead relatively active and productive lives in early adulthood and will therefore present from time to time for non-cardiac surgical procedures. Though the theoretical risks of anaesthesia are considerable, these patients are known to do well with a variety of techniques, if the pathophysiology of the disease is well understood. We describe the anaesthetic management of a patient with Eisenmenger syndrome admitted in cardiac failure and undergone lower abdominal surgery after preoperative stabilization.

2. Case history

A 38-yr-old 40 kg nulliparous lady was admitted with a diagnosis of endometrial carcinoma of cervix. She was a diagnosed case of ASD and moderate mitral regurgitation. Her echocardiograph performed 12 years back showed a large ostium secundum ASD with a large main pulmonary artery. Cardiac catheterisation revealed pulmonary arterial pressures of 54/20 (mean 36) mm Hg and aortic pressure of 130/88 (mean 99) mm Hg. She had refused corrective surgery then and had no restriction of daily activity until now.

A week prior to presentation, she had developed oedema of feet and breathlessness after fractional curettage performed under local anaesthesia. On admission, she had bilateral pitting pedal oedema, orthopnoea, cyanosis and raised jugular venous pressure with a prominent v wave. Air entry was decreased in both the bases with scattered crepitations heard all over the chest. Her liver was palpable up to 10 cm below the costal margin. Chest X-ray showed severe cardiomegaly with bi-atrial enlargement and an aneurysmal pulmonary artery. She responded to digoxin and diuretics. Echocardiography after stabilization of her condition confirmed a large ASD with predominantly right-to-left shunt. Both, right atrium and ventricle were dilated, associated with severe tricuspid regurgitation and right ventricular systolic pressure more than 80 mm Hg. Contrast echocardiography showed visual ejection fraction of 45% and right-to-left shunt at atrial level. Her haemoglobin was 9.3 g%, coagulation profile were normal but liver enzymes (AST/ALT) were
An opioid-based premedication has been shown to be safe; we chose benzodiazepine to avoid the risk of preoperative respiratory depression, hypoventilation and hypoxemia, which might have precipitated a cyanotic crisis. On arrival to the OR, SpO2 was 86%; delivery of oxygen by a simple facemask with a flow of 5 L min⁻¹ improved this to 99%. Hypoxemia due to right-to-left shunt is usually not reversible by oxygen. The improvement in SpO2 may be explained by the vasodilator response of the pulmonary vasculature to oxygen with improvement in pulmonary arterial flow and decreased or no flow across the shunt. Pulmonary vascular resistance was previously believed to be fixed in these patients, but there is now evidence that high (80%) inspired oxygen concentrations may lower it. Besides, severe cardiomegaly might have produced some element of lung collapse resulting in some areas of ventilation perfusion mismatch. Bronchodilatation and oxygen inhalation might have improved the hypoxemia due to ventilation perfusion mismatch. Our patient responded both to nebulisation of bronchodilators and to oxygen therapy.

It has been suggested by Lumley et al. that a small pre-induction dose of metaraminol should be given to prevent fall in SVR. However Bird and Strunin reported severe reflex bradycardia and a worsening of intracardiac shunt after the administration of metaraminol in a patient of Eisenmenger syndrome. They advocated the use of powerful vasoactive drugs only when specifically indicated. Invasive blood pressure monitoring was instituted before induction to detect any abrupt change in blood pressure and control it with vasopressors if required. Fall in blood pressure was momentary and was not associated with any fall in saturation. Blood pressure returned to the pre-induction level after intubation without the use of any vasopressor agent.

Induction of anaesthesia has been successfully done with a variety of agents before. Inhalational anaesthetic agent has also been used for maintenance of anaesthesia without any event. However it has drawback of causing vasodilatation, myocardial depression in addition to theoretical risk of delayed uptake as blood is shunted past lung in these patients. We chose total intravenous anaesthesia (TIVA) with fentanyl and etomidate titrated to achieve BIS<60, because of their cardiovascular and short duration of action (adequate for the estimated duration of surgical procedure, i.e. 2 h). Others advantage of using TIVA were independence of pulmonary uptake and more predictable effect, avoiding hypotension and myocardial depression; as our patient had poor cardiovascular reserve. Tracheal intubation was facilitated by vecuronium, an intermediate acting cardiostable non-depolarising muscle relaxant with minimal cumulative effect. Epidural bupivacaine with fentanyl in low doses enabled us to provide good analgesia without causing clinically significant fall in SVR.

MacArthur et al. reported that the ventilatory function is abnormal with reduced lung and vital capacities, decreased FEV1 and peak expiratory flow rate in patients with Eisenmenger syndrome. Residual and closing lung volumes are increased and total lung compliance is reduced. Our patient was ventilated with a tidal volume of 7 ml kg⁻¹ body weight and a respiratory rate of 10 breaths min⁻¹ to keep end-tidal CO2 of about 3.9–4.3 kPa. The peak airway pressures rarely went above 25 cmH2O throughout the procedure.

Early tracheal extubation is preferable in these patients because of the deleterious effect of positive pressure ventilation and hence, intraoperative analgesia was provided with short acting opioid (fentanyl) intravenously and bupivacaine epidurally. Weber et al. discussed the role of low dose heparinisation to prevent thromboembolism and use of periproductive antibiotics to prevent infective endocarditis. The patient was given prophylactic antibiotics and low molecular weight heparin and encouraged to ambulate early, thereby preventing deep vein thrombosis.

In Eisenmenger syndrome, there is almost an irreversible pulmonary hypertension, producing a relatively fixed cardiac output, which does not respond to changes in systemic pressure. However, the systemic vascular resistance (SVR) remains responsive to physiological and pharmacological influences. A fall in SVR increases right-to-left shunting, leading to an increase in arterial hypoxemia which may be life-threatening. Conversely, increased SVR will cause increased left to right shunting, with a further increase in pulmonary pressure and right ventricular failure. Volume overload has the same effect. Thus, the anaesthetic agents and techniques used should maintain cardiac output and SVR. The factors to be avoided are myocardial depression, extreme changes of heart rate, decreased venous return, volume overload and vasodilation.
In conclusion, adequate pain relief, perioperative oxygen therapy and avoidance of factors that could potentially increase right-to-left shunt flow allow successful anaesthetic management of patients with Eisenmenger syndrome.

Conflict of interest statement

None.

References