REVIEW

Multimodal analgesia in children

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Acute and chronic pain management in children is increasingly characterized by either a multimodal or a preventive analgesia approach, in which smaller doses of opioid and nonopioid analgesics, such as nonsteroidal anti-inflammatory drugs, local anaesthetics, *N*-methyl-D-aspartate antagonists, α_2-adrenergic agonists, and voltage-gated calcium channel α-2 δ-proteins, are combined alone and in combination with opioids to maximize pain control and minimize drug-induced adverse side effects. A multimodal approach uses nonpharmacological complementary and alternative medicine therapies too. These include distraction, guided imagery, hypnosis, relaxation techniques, biofeedback, transcutaneous electrical nerve stimulation, and acupuncture. Using the neurophysiology of pain as a blueprint, the molecular targets and strategies used in multimodal pain management are described. Finally, weight-based dosage guidelines for commonly used opioid and nonopioid analgesics are provided to facilitate therapy.

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Introduction

The treatment and alleviation of pain is a basic human right regardless of age.[1,2] The old 'wisdom' that young children neither respond to, nor remember, painful experiences to the same degree that adults do is simply untrue.[3] Many, if not all, of the nerve pathways essential for the transmission and perception of pain are present and functioning by 24 weeks' gestation.[4,5] Recent research in newborn animals has revealed that failure to treat pain leads to 'rewiring' of the nerve pathways responsible for pain transmission in the dorsal horn of the spinal cord and results in increased pain perception in the future.[6,7] This confirms human newborn research in which failure to provide anaesthesia or analgesia for newborn circumcision resulted not only in short-term physiological perturbations but also in longer term behavioural changes, particularly during immunization.[3,8–10]

As pain physicians we champion the benefits of analgesia and often minimize or even deny the negative effects of therapy. Indeed, some opioid-induced side effects such as nausea, vomiting, itching and constipation are so common and severe that many patients choose to experience the pain rather than the treatment. Because of this, acute and chronic pain management in both children and adults is increasingly characterized by a multimodal or 'preventive analgesia' approach in which smaller doses of opioid and nonopioid analgesics, such nonsteroidal anti-inflammatory drugs (NSAIDs), local anaesthetics, *N*-methyl-D-aspartate (NMDA) antagonists, and α_2-adrenergic agonists, are combined to maximize pain control and minimize adverse side effects. In the next sections, we will review some of the drugs used in multimodal–modal pain treatment, but in order to understand these therapeutic strategies, a basic review of pain physiology is required.

Neurophysiology of pain

Pain is more than simply the physiological transmission of nociceptive input from a site of injury to the brain, and its subsequent modulation within the central nervous system. Rather, it is a complex sensation that is integrated and given value at higher, conscious brain centres. Like symphonic music, no two people experience it the same way. Despite the fact that the physiology of sound transmission is the same in all of us, symphonic music to some is simply awful and to others it is glorious. As we integrate neural transmissions, we give them subjective value based on our age, culture, genes, previous experience and education, values, and state of mind. The same is true for pain.

Many, if not all, of the nerve pathways essential for the transmission, perception, and modulation of pain are present and functioning by 24 weeks of gestation.[4,5] Although neural transmission in peripheral nerves is slower in neonates because myelination is incomplete at birth, the major nociceptive neurons in neonates as well as in adults are either unmyelinated C fibres or thinly myelinated Aδ fibres. Following an acute injury such as surgical or accidental trauma, inflammatory mediators are released which lower the pain threshold at the site of injury (primary hyperalgesia) and in the surrounding uninjured tissue (secondary hyperalgesia). These inflammatory mediators, which include hydrogen and potassium ions, histamine, leukotrienes, prostaglandins, cytokines, serotonin, bradykinins, and nerve growth factors, make a 'sensitizing soup', which together with repeated stimuli of the nociceptive fibres cause decreased excitatory thresholds and result in peripheral sensitization. They are also targets of therapeutic intervention. Secondary effects of peripheral sensitization include

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hyperalgesia, an increased response to a noxious stimulus, and allodynia, whereby nonnociceptive fibres transmit noxious stimuli resulting in the sensation of pain from nonnoxious stimuli.

As the primary afferent neurons enter the spinal cord they segregate and occupy a lateral position in the dorsal horn. These afferent neurons release one or more excitatory amino acids (glutamate and aspartate) or peptide neurotransmitters (substance P, neurokinin A, calcitonin gene-related peptide, cholecystokinin, and somatostatin). 'Second-order' neurons that receive these chemical signals integrate the afferent input with facilitatory and inhibitory influences of interneurons and descending neuronal projections. It is this convergence within the dorsal horn that is responsible for much of the processing, amplification, and modulation of pain. Nociceptive activity in the spinal cord and the ascending spinothalamic, spinoreticular, and spinomesencephalic tracts carry messages to supraspinal centres (periaqueductal grey, locus caeruleus, hypothalamus, thalamus and cerebral cortex) where they are modulated and integrated with autonomic, homeostatic, and arousal processes. This modulation, particularly by the endogenous opioids gamma aminobutyric acid (GABA) and norepinephrine, can either facilitate pain transmission or inhibit it. Modulating pain at peripheral, spinal, and supraspinal sites helps to achieve better pain management than targeting only one site, and is the underlying principle of multimodal treatment.

Preemptive analgesia, preventive analgesia and multimodal analgesia

The possibility that pain after surgery might be preemptively prevented or ameliorated by the use of opioids, local anaesthetics given preoperatively, or both has been one of the most cherished beliefs held by this generation of anaesthesiologists.[11,12] Whether this actually occurs in adults is not so clear.[11,13,14] There is no evidence to either validate or disprove this notion in children at all. Rather than discarding it altogether, over the last few years the concept of preemptive analgesia has expanded and evolved to include the reduction of nociceptive inputs before, during, and after surgery. This expanded conceptual framework, which includes preoperative, intraoperative and postoperative analgesia, targets multiple sites along the pain pathway, and is referred to as 'preventive' or 'multimodal' analgesia.[1,3] Indeed, acute paediatric (and adult) pain management is increasingly characterized by a multimodal or 'balanced' approach in which smaller doses of opioid and nonopioid analgesics, such as NSAIDs, local anaesthetics, NMDA antagonists, and α-2 adrenergic agonists, are combined to maximize pain control and minimize drug-induced adverse side effects.[15] Additionally, a multimodal approach includes nonpharmacological complementary and alternative medicine therapies too. These include distraction, guided imagery, hypnosis, relaxation techniques, biofeedback, transcutaneous electrical nerve stimulation, and acupuncture.[16] Taking this approach, activation of peripheral nociceptors can be attenuated by providing NSAIDs, antihistamines, serotonin antagonists, and local anaesthetics. Within the dorsal horn, nociceptive transmission and processing can be affected by the administration of local anaesthetics, neuraxial opioids, α-2 adrenergic agonists (clonidine and dexmedetomidine), and NMDA receptor antagonists (ketamine and methadone). Within the central nervous system, pain can be ameliorated by systemic opioids, α-2 adrenergic agonists, voltage-gated calcium channel α-2 δ (Ca_v-α_2-δ) proteins (the anticonvulsants gabapentin and pregabalin), and pharmacological (benzodiazepines and α-2 agonists) and nonpharmacological (hypnosis and acupuncture) therapies that are thought to reduce anxiety and induce rest and sleep.

Weaker nonopioid analgesics with antipyretic activity

The 'weaker' or 'milder' analgesics with antipyretic activity constitute a heterogeneous group of nonopioid analgesics. The most common are paracetamol, classic NSAIDs (ibuprofen, naproxen, ketoprofen, and diclofenac), and the selective cyclooxygenase (COX-2) inhibitors (celebrex) (Table 1).[17–20] They produce various degrees of analgesia, anti-inflammatory, antiplatelet, and antipyretic effects primarily by blocking peripheral and central prostaglandin and thromboxane production through inhibition of cyclooxygenase types 1, 2, and 3. Prostaglandin and thromboxane sensitize peripheral

Table 1 Dosage guidelines for commonly used nonopioid analgesics with antipyretic effects

Name	Dose ($mg\,kg^{-1}$) frequency	Comments
Ibuprofen	4–10 q 6–8 h	Available as an oral suspension Maximum adult dose $2400\,mg\,kg^{-1}$
Ketorolac	i.v. or i.m. 0.5 q 6 h	Maximum dose $30\,mg\,kg^{-1}$ or $90–120\,mg\,kg^{-1}\,day^{-1}$ (adult)
Paracetamol	10–15 p.o. q 4 h 30 p.r. q 6–8 h	Lacks anti-inflammatory activity The daily maximum paracetamol dose in the preterm, term, and older child is 60, 80, $90\,mg\,kg^{-1}$, respectively
Salicylates	10–15 q 4 h	Permanently inhibits platelet aggregation and adhesion Gastrointestinal irritability Reye syndrome precludes routine use in children

i.m., intramuscular; i.v., intravenous; p.o., orally; p.r., rectally; q, every.

nerve endings and vasodilate blood vessels causing pain, erythema, and inflammation.

These analgesic agents are administered enterally via the oral or, on occasion, the rectal route and are particularly useful for inflammatory, bony, or rheumatic pain. Parenterally administered agents, such as ketorolac and paracetamol, are available for use in children in whom the oral or rectal routes of administration are not possible.[21] Unfortunately, regardless of dose, the nonopioid analgesics are limited by a 'ceiling effect' above which pain cannot be relieved by these drugs alone. Because of this, the weaker analgesics are often administered in oral combination with opioids such as codeine, oxycodone, or hydrocodone.

Only a few trials have compared their efficacy in head-to-head competition, and, in general, these studies have shown that there are no major differences in their analgesic effects when appropriate doses of each drug are used. The commonly used classic NSAIDs have reversible antiplatelet adhesion and aggregation effects, which are attributable to the inhibition of thromboxane synthesis.[22,23] As a result, bleeding times are usually slightly increased but, in most instances, they remain within normal limits in children with normal coagulation systems. Nevertheless, this side effect is of such great concern, particularly in surgical procedures in which even a small amount of bleeding can be catastrophic (e.g. tonsillectomy and neurosurgery), that few clinicians prescribe them even though the evidence supporting increased bleeding is equivocal at best.[24,25] Finally, many orthopaedic surgeons are also concerned about the negative influence of all NSAIDs, both selective and nonselective COX inhibitors, on bone growth and healing,[26–28] and consequently they are reluctant to use them.

The discovery of at least three COX isoenzymes, referred to as COX-1, COX-2, and COX-3, has enhanced our knowledge of NSAIDs.[29,30] The COX isoenzymes share structural and enzymatic similarities, but are specifically regulated at the molecular level and may be distinguished by their functions. Protective prostaglandins, which preserve the integrity of the stomach lining and maintain normal renal function in a compromised kidney, are synthesized by COX-1.[25,29,31] The COX-2 isoenzyme is inducible by proinflammatory cytokines and growth factors, implying a role for COX-2 in both inflammation and control of cell growth; in addition, it is found in the brain and spinal cord, where it may be involved in nerve transmission, particularly for pain and fever. Prostaglandins made by COX-2 are also important in ovulation and in the birth process.[25,29,31] The discovery of COX-2 has made it possible to design drugs that reduce inflammation without removing protective prostaglandins in the stomach and kidney made by COX-1. In fact, developing a more specific COX-2 inhibitor was a 'holy grail' of drug research because this class of drug was postulated to have all of the desirable anti-inflammatory and analgesic properties without the gastrointestinal and antiplatelet side effects. Unfortunately, the increased risk of myocardial infarction in adult patients receiving COX-2 inhibitors has dampened much of the enthusiasm for these drugs and has led to the removal of some of them (rofecoxib) from the marketplace.[31,32]

Paracetamol

One of the most commonly used nonopioid analgesics in paediatric practice remains paracetamol, although its analgesic effectiveness in the neonate is unclear.[33,34] Unlike aspirin and other NSAIDs, paracetamol produces analgesia centrally as a COX-3 inhibitor and via activation of descending serotonergic pathways.[34,35] It is also thought to produce analgesia as a cannabinoid agonist and by antagonizing NMDA and substance P in the spinal cord.[36] Paracetamol is an antipyretic analgesic with minimal, if any, anti-inflammatory and antiplatelet activity and takes about 30 min to provide effective analgesia. When administered orally (p.o.) in standard doses, 10–15 mg kg^{-1}, paracetamol is extremely well tolerated, effective, and has very few serious side effects. When administered rectally, higher doses, 25–40 mg kg^{-1}, are required.[37,38] Because of its known association with fulminant hepatic necrosis, the daily maximum paracetamol dose, regardless of formulation or route of delivery, in the preterm, term, and older child is 60, 80, 90 mg kg^{-1}, respectively. Thus, when administering it rectally, it should be given every 8 h rather than every 4 h. Finally, an intravenous (i.v.) formulation of paracetamol is now available in Europe and can be used in patients in whom the enteral route is unavailable. This formulation has been associated with better analgesia than oral paracetamol in clinical trials in adult patients and in children is equally effective and less painful than the 'prodrug' formulation.[21]

Opioids

Over the past 30 years, multiple opioid receptors and subtypes have been identified and classified. There are three primary opioid receptor types, designated mu (μ) (for morphine), kappa (κ), and delta (δ). These receptors are primarily located in the brain and spinal cord, but also exist on peripheral nerve cells, immune cells, and some other cells (e.g. oocytes).[39–41] The μ receptor is further subdivided into several subtypes, which determine the different pharmacological profiles of the opioids. These are the μ1 (supraspinal analgesia), μ2 (respiratory depression and inhibition of gastrointestinal motility), and μ3 (anti-inflammation and leucocytes).[42–44] Both endogenous and exogenous agonists and antagonists bind to various opioid receptors.

Opioid receptors, which are found anchored to the plasma membrane both presynaptically and postsynaptically, decrease the release of excitatory neurotransmitters from terminals carrying nociceptive stimuli. These receptors

belong to the steroid superfamily of G protein-coupled receptors. Their protein structure contains seven transmembrane regions with extracellular loops that confer subtype specificity and intracellular loops that mediate subreceptor phenomena.[41] These receptors are coupled to guanine nucleotide (GTP)-binding regulatory proteins (G proteins) and control transmembrane signalling by regulating adenylate cyclase [cyclic AMP (cAMP)], various ion (K^+, Ca^{2+}, and Na^+) channels and transport proteins, neuronal nitric oxide synthetase, and phospholipase C and A2.[42,45,46] Signal transduction from opioid receptors occurs via bonding to inhibitory G proteins (Gi and Go). Analgesic effects are mediated by decreased neuronal excitability from an inwardly rectifying K^+ current, which hyperpolarizes the neuronal membrane, decreases cAMP production, increases nitric oxide synthesis, and increases the production of 12-lipoxygenase metabolites. Indeed, synergism between opioids and NSAIDs occurs as a result of the greater availability of arachidonic acid for metabolism by the 12-lipoxygenase pathway, after blockade of prostaglandin production by NSAIDs.[47] Some of the unwanted side effects of opioids, such as pruritus, may be the result of opioid binding to stimulatory G proteins (Gs) and may be antagonized by low-dose infusions of naloxone.[46,48,49] The most commonly used opioids in paediatric practice are listed in Table 2.

Analgesic adjuvants

Adjuvant pain medications are drugs whose primary indication is not to treat pain, but they may have analgesic properties in specific circumstances. Many of the drugs which will be discussed below were initially used to treat neuropathic and chronic pain, but are now increasingly being used to treat acute pain as part of a multimodal therapeutic regimen.

Antidepressants

Because serotonin and norepinephrine mediate descending inhibition of ascending pain pathways in the brain and spinal cord, antidepressant medications, which inhibit their reuptake, may have efficacy in relieving pain.[50] Antidepressants that enhance norepinephrine action are more effective analgesics than those, such as many of the newer antidepressants, that predominantly enhance serotonin action.[50] Older antidepressants, particularly the tricyclics, amitriptyline, doxepin, and nortriptyline, have been the most thoroughly studied and are thought to cause analgesia by norepinephrine and serotonin reuptake inhibition.[51] They also have other pharmacological properties that may contribute to analgesia such as reducing sympathetic activity, NMDA receptor antagonism, anticholinergic activity, and sodium channel blockade. Newer, nontricyclic antidepressants seem to be less efficacious analgesics but have not been studied for this use in children.

Antiepileptic agents

Like the tricyclic antidepressants, antiepileptic adjuvant analgesics are burdened with an unfortunate name. Most families and physicians who are unaware of their analgesic properties question the use of an antiepileptic drug in a child who does not have seizures. Gabapentin and pregabalin have been most widely studied and used for the treatment of chronic pain conditions such as postherpetic neuralgia, diabetic neuropathy, and complex regional pain

Table 2 Commonly used μ-opioid agonists

Agonist	Equipotent i.v. dose ($mg\,kg^{-1}$)	Comments
Morphine	0.1	'Gold standard', very inexpensive, seizures in newborns Histamine release (? use in asthma and hypotension) Oral bioavailability 20–30% (give three times the i.v. dose p.o. or $0.3\,mg\,kg^{-1}$) Extended duration tablet and sprinkles available Liquid preparation formulated in concentrations of $2–20\,mg\,ml^{-1}$
Hydromorphone	0.02	Less itching and nausea than morphine Useful i.v., p.o., and epidural
Fentanyl	0.001	Ideal for short painful procedures; may be administered i.v., epidural, intranasal, transmucosal, and transdermal Bradycardia; minimal haemodynamic effects Chest wall rigidity Oral transmucosal dose of $10–15\,\mu g\,kg^{-1}$, transdermal for chronic pain only, intranasal dose ($1–3\,\mu g\,kg^{-1}$) useful when no i.v. access is available
Methadone	0.02–0.1	Liquid preparation available (70+% bioavailability) (useful when i.v. access unavailable) Long duration of action makes it ideal for cancer pain, prolonged pain (limb trauma), and weaning dependent patients; morphine equivalence is reduced in dependent patients NMDA antagonist, suggesting role in neuropathic pain
Codeine	1.2	'Prodrug' must be metabolized (10% of administered dose) into morphine by cytochrome P450 2D6 isoenzyme in liver; poor metabolizers get no analgesia, rapid metabolizers may produce toxic amounts of morphine Liquid preparation available (70+% bioavailability)
Oxycodone and hydrocodone	0.1	p.o. only (60% bioavailability) Less nausea than codeine Sustained release oxycodone tablet cannot be crushed or given via a gastric tube and has high diversion and abuse potential

i.v., intravenous; NMDA, *N*-methyl-D-aspartate; p.o., orally.

syndromes. Interestingly, despite their names, gabapentin and pregabalin are not GABAergic and produce analgesia by binding to Ca_v-α_2-δ proteins in the spinal cord and central nervous system.[52] Increasingly, they are being used in the perioperative period as a component of multimodal pain therapy.[53–55] Adult studies have demonstrated their effectiveness (1200 mg gabapentin and 300 mg pregabalin p.o.) at enhancing postoperative analgesia and preoperative anxiolysis, preventing chronic postsurgical pain, attenuating the haemodynamic responses to laryngoscopy and intubation, and reducing postoperative delirium.[56] The main side effect of both drugs is somnolence. Paediatric studies are lacking at this time.

Alpha-2 adrenergic agonists: clonidine, tizanidine, and dexmedetomidine

Norepinephrine is involved in the control of pain by modulating pain-related responses through various pathways. Alpha-2 adrenergic agonists, such as clonidine, tizanidine, and dexmedetomidine, have well established analgesic and sedative profiles and wide application in perioperative multimodal pain management. Clonidine is the prototype and most widely studied of this class of drugs. It can be administered via the epidural, i.v., subcutaneous, p.o., and transdermal routes. It is traditionally used as an antihypertensive and to minimize the symptoms of opioid withdrawal.[57] However, when administered p.o., i.v., or transdermally, clonidine may reduce opioid requirements and improve analgesia. Similarly, the addition of clonidine to local anaesthetic solutions for neuraxial or peripheral nerve blocks may enhance and prolong analgesia. Clonidine can be a useful antineuropathic agent, especially in children who cannot tolerate oral medications or who have coexisting problems such as steroid-induced hypertension.[58] However, the analgesic benefits remain controversial and its use is limited by side effects, which include bradycardia, hypotension, and excessive sedation.[54,55]

Compared with clonidine, dexmedetomidine is a more selective α-2 antagonist, has a shorter duration of action, and is noted in the perioperative period for its opioid-sparing and analgesic effects. Because dexmedetomidine does not cause respiratory depression, despite its potent sedative effects, it is increasingly being used in patients for deep procedural sedation, as a general anaesthetic adjuvant in the operating room, and for sedation of intubated patients in the ICU. As a sedative with analgesic properties, it may be particularly useful in patients at high risk of opioid-induced airway obstruction and respiratory depression (e.g. patients with obstructive sleep apnoea and morbid obesity). Initial studies recommended a loading dose of dexmedetomidine, $1\,\mu g\,kg^{-1}$, followed by an infusion of $0.4\,mg\,kg^{-1}\,h^{-1}$. However, this regimen may cause cardiovascular side effects (bradycardia and hypotension). Therefore, avoidance of a loading dose is preferred. Of note, most studies of dexmedetomidine have evaluated its use in the immediate perioperative period; therefore, any long-term benefits are not yet clear.

N-Methyl-D-aspartate receptor antagonists

NMDA receptor antagonists, such as ketamine and methadone, are important modulators of chronic pain and some studies show them to be useful in preventive analgesia. They reduce acute postoperative pain, analgesic consumption, or both, when they are added to more conventional means of providing analgesia, such as opioids and NSAIDs, in the perioperative period.[59] NMDA receptor antagonists may reduce pain by two nonmutually exclusive mechanisms; a reduction in central hypersensitivity and a reduction of opioid tolerance. Nevertheless, the effectiveness of NMDA antagonists in preventive analgesia has been equivocal at best.[59,60] Ketamine is well known as a dissociative general anaesthetic and may be an effective adjuvant in pain management when used in low doses ($0.05–0.2\,mg\,kg^{-1}\,h^{-1}$).[61] I cannot, however, recommend it in paediatric practice in general, and in newborn patients in particular, until more evidence to support its use emerges.[62]

Regional anaesthesia and analgesia

Over the past 30 years, the use of local anaesthetics and regional anaesthetic techniques in paediatric practice has increased dramatically. Unlike most drugs used in medical practice, local anaesthetics must be physically deposited at their site of action by direct application, requiring specialized needles and patient cooperation. Because of this, for decades, children were considered poor candidates for regional anaesthetic techniques. However, once it was recognized that regional anaesthesia could be used as an adjunct, and not a replacement for general anaesthesia, its use increased dramatically. Regional anaesthesia offers the anaesthesiologist and pain specialist many benefits. It modifies the neuroendocrine stress response, provides profound postoperative pain relief, ensures a more rapid recovery, and may shorten hospital stay with fewer opioid-induced side effects. Furthermore, as catheters placed in the epidural, pleural, femoral, sciatic, brachial plexus, and other spaces can be used for days or months, local anaesthetics are increasingly being used not only for postoperative pain relief but also for medical, neuropathic, and terminal pain.[63–69] Peripheral nerve blocks provide significant pain relief after many common paediatric procedures. Techniques range from simple infiltration of local anaesthetics to neuraxial blocks such as spinal and epidural analgesia. To be used safely, a working knowledge of the differences in local anaesthetic metabolism in infants and children is necessary.[65,70,71]

Conclusion

Using the neurophysiology of pain as a blueprint, I have highlighted some of the drugs and drug families used in

multimodal pain management. The underlying principle is to minimize opioid-induced adverse side effects by maximizing pain control with smaller doses of opioids supplemented with nonopioid analgesics such NSAIDs, local anaesthetics, NMDA antagonists, Ca_v-α_2-δ proteins, and α_2-adrenergic agonists.

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