Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit

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Objective: To describe the consequences of the prolonged administration of sedative and analgesic agents to the pediatric intensive care unit (PICU) patient. The problems to be investigated include tolerance, physical dependency, and withdrawal.

Data Sources: A MEDLINE search was performed of literature published in the English language. Cross-reference searches were performed using the following terms: sedation, analgesia with PICU, children, physical dependency, withdrawal; tolerance with sedative, analgesics, benzodiazepines, opioids, inhalational anesthetic agents, nitrous oxide, ketamine, barbiturates, propofol, pentobarbital, phenobarbital.

Study Selection: Studies dealing with the problems of tolerance, physical dependency, and withdrawal in children in the PICU population were selected.

Data Extraction: All of the above-mentioned studies were reviewed in the current manuscript.

Data Synthesis: A case by case review is presented, outlining the reported problems of tolerance, physical dependency, and withdrawal after the use of sedative/analgesic agents in the PICU population. This is followed up by a review of the literature discussing current treatment options for these problems.

Conclusions: Tolerance, physical dependency, and withdrawal can occur after the prolonged administration of any agent used for sedation and analgesia in the PICU population. Important components in the care of such patients include careful observation to identify the occurrence of withdrawal signs and symptoms. Treatment options after prolonged administration of sedative/analgesic agents include slowly tapering the intravenous administration of these agents or, depending on the drug, switching to subcutaneous or oral administration. (Crit Care Med 2000; 28:2122–2132)

Key Words: tolerance; physical dependency; withdrawal; sedation; pediatric intensive care unit; sedation; children; opioids; benzodiazepines; propofol; barbiturates

During recent years, there has been an increased awareness of the need to ensure adequate sedation and analgesia in critically ill patients. Although the major impetus for improvements in providing comfort measures to critically ill infants and children may be related to the humanitarian issues of such care, the implications of effective pain management are much broader. Anand and colleagues (1, 2) demonstrated that the level of intraoperative and postoperative analgesia may impact on postoperative morbidity and even mortality. The importance of such initiatives has led to the development of formal policy statements concerning intensive care unit (ICU) sedation (3). This heightened awareness followed by the increased use of sedative and analgesic agents has led to new consequences, including physical dependency, tolerance, and withdrawal, that require definition and effective treatment strategies. Effective management schemes to treat these problems as well as methods to delay or prevent their occurrence are needed so that these newly recognized issues do not limit the much needed use of sedative and analgesics in the pediatric intensive care unit (PICU) patient. This article reviews the initial studies describing tolerance, physical dependency, and withdrawal after the prolonged use of sedative and analgesic agents, identifies with which agents these problems occur, investigates the cellular mechanisms of tolerance and physical dependency, and suggests treatment strategies aimed at limiting their incidence as well as treating these problems.

Definitions

An effective approach to the patient with tolerance and physical dependency begins with an appropriate understanding and the correct use of terminology (4). Without these, communication between healthcare providers becomes more difficult. Tolerance is a decrease in a drug’s effect over time or the need to increase the dose to achieve the same effect. Tolerance is related to changes at or distal to the receptor, generally at the cellular level. For the purpose of this article, the term tolerance will not be used to refer to issues related to altered metabolism or clearance of the drug. Other authors (5) have divided tolerance into various subcategories, including innate tolerance referring to a genetically predetermined lack of sensitivity to a drug, pharmacokinetic or dispositional tolerance referring to changes in a drug’s effect because of alterations in distribution or metabolism, learned tolerance or a reduction in a drug’s effect as a result of learned or compensatory mechanisms (learning to walk a straight line while intoxicated by repeated practice at the task), and pharmacodynamic tolerance. The latter is the most appropriate definition for this article because it refers to alterations at or distal to the receptor.

For pharmacodynamic tolerance to occur, the plasma concentration of the drug remains constant but results in a decreased effect (sedation or analgesia). The magnitude of tolerance is illustrated...
by my previous report of a 16-yr-old, 52-kg boy who required mechanical ventilation for 5 wks (6). Sedation was provided by continuous infusions of lorazepam and fentanyl. Progressive tolerance resulted in the need to intermittently increase the fentanyl infusion up to a maximum of 3500 μg/hr (67.3 μg/kg/hr), which required the administration of 70 mL/hr fentanyl, at a concentration of 50 μg/mL. Because of the large volume of fluid required to administer the fentanyl, the sedation regimen was changed to sufentanil. The patient eventually made a full recovery and was discharged home on an oral methadone taper.

Withdrawal includes the physical signs and symptoms that manifest when the administration of a sedative or analgesic agent is abruptly discontinued in a patient who is physically tolerant. The symptomatology of withdrawal varies from patient to patient and may be affected by several factors, including the agent involved, the patient’s age, cognitive state, and associated medical conditions. Physiologic (physical) dependence is the need to continue a sedative or analgesic agent to prevent withdrawal. Psychological dependence is the need for a substance because of its euphoric effects. Addiction is a complex pattern of behaviors characterized by the repetitive, compulsive use of a substance, antisocial or criminal behavior to obtain the drug, and a high incidence of relapse after treatment. Psychological dependency and addiction are extremely rare after the appropriate use of sedative/analgies agents (to treat pain or to relieve anxiety in the ICU setting). The rare occurrence of psychological dependency/addiction and concerns regarding the development of tolerance, physical dependency, and withdrawal should not limit the use of sedative/analgies agents in the PICU population. The latter consequences can be effectively controlled and dealt with through the use of appropriate weaning schedules and patient monitoring.

Initial Clinical Reports

The problems of opioid dependency and withdrawal in neonates and infants were first encountered in the 1970s and 1980s in infants of drug-addicted mothers (7–9). Despite the difference in the origin of the problem, these initial studies provide valuable information for dealing with today’s PICU population. The studies from the 1970s and 1980s have provided various pharmacologic treatment regimens as well as scoring systems that may be used to quantitate the severity of withdrawal and to evaluate the efficacy of the treatment regimens.

Arnold and colleagues (10) were among the first to recognize the problems of dependency and withdrawal after prolonged opioid administration in the PICU population. In a retrospective review of 37 neonates who required extracorporeal membrane oxygenation (ECMO) for respiratory failure and who had received intravenous fentanyl for sedation, they sought to identify the signs and symptoms of the neonatal abstinence syndrome (NAS) and risk factors for its occurrence. They noted an increase in the fentanyl infusion requirements to achieve the desired level of sedation (“sedated but arouseable”) from 11.6 ± 6.9 μg/kg/hr on day 1 to 52.5 ± 19.4 μg/kg/hr on day 8. Plasma fentanyl concentrations were measured in five neonates. Over time, there was an increase in the plasma fentanyl concentration required to achieve the same level of sedation, thereby demonstrating that the tolerance was pharmacodynamic and not pharmacokinetic (related to increased metabolism of the opioid). A subsequent study by the same investigators (11) demonstrated a similar phenomenon with the development of tolerance in neonates and infants sedated with fentanyl during mechanical ventilation, but not placed on ECMO. Risk factors for the development of tolerance and physical dependency were identified (10). NAS developed in 21 or 57% of neonates. The total fentanyl dose and the duration of the infusion were significantly greater in infants who developed NAS as opposed to those who did not. A cumulative fentanyl dose >1.6 mg/kg or an ECMO duration of >5 days were risk factors for the development of NAS (odds ratio, 7 and 13.9, respectively). The reports from Arnold et al. (10) provide several important insights into opioid dependency and tolerance: a) NAS can occur after the prolonged administration of sedative/analgies agents in the PICU population; b) its incidence can be significant, 57% in the ECMO study; c) over time, there is an increase in the plasma fentanyl concentration required to achieve the desired level of sedation (pharmacodynamic tolerance is occurring). Additionally, they used a standard scoring system described by Finnegan et al. to grade the severity of the NAS and to assess the response to therapy; they worked out a treatment regimen and demonstrated certain risk factors to identify the at-risk population.

In 1990, we (12) reported for the first time a protocol using oral methadone to treat or prevent opioid withdrawal after the prolonged administration of fentanyl in the PICU patient. Although the report was intended to outline the use of oral methadone, the three infants reported demonstrated the problem of opioid tolerance, dependency, and withdrawal in a PICU population that was older, with different medical/surgical problems (post-cardiovascular surgery patients) from those reported by Arnold et al. Before our report and that of Arnold et al., there had been limited data concerning opioid withdrawal syndromes in the PICU.

Tolerance and Abstinence Syndromes with Other Agents

The bulk of the information available concerning withdrawal syndromes comes from the adult literature as it relates to opioid-addicted patients and the neonatal literature as it relates to infants of drug-addicted mothers. This information is supplemented by the more recent information concerning problems after the prolonged administration of opioids for sedation in the PICU patient. From this data, it is known that tolerance, physical dependency, and withdrawal occur after the prolonged administration of opioids. The signs and symptoms of opioid withdrawal are well described, at least in the neonatal and adult populations.

However, in the PICU population, many agents in addition to opioids are used for sedation. Do tolerance, physical dependency, and withdrawal occur with these agents? If so, are the signs and symptoms similar? Although less common than opioid-related problems, benzodiazepine addiction and dependency are well-recognized problems in the drug abuse population. Benzodiazepine withdrawal has been reported in the adult psychiatric and drug-addicted population (13, 14).

Benzodiazepine withdrawal has been previously reported in the adult ICU population. Freda et al. (15) reported a 72-yr-old man, chronically receiving alprazolam as an outpatient, who was admitted to the ICU after aortic aneurysm surgery. Forty-eight hours after the last dose of alprazolam, while in the ICU, the patient developed agitation, delirium, and signs of sympathetic hyperactivity, in-
cluding tachycardia, hypertension, and tachypnea. The signs and symptoms responded to the intravenous administration of diazepam. Although the report deals with an adult ICU patient, it demonstrates some of the signs and symptoms of benzodiazepine withdrawal as well as demonstrating the importance of considering what medications the patient had been previously receiving when admitted to the ICU. Although we generally consider physical dependency and withdrawal to result from what has been administered in the PICU, it may also result from medications that the patient received before admission. The latter may become a more common problem as technology increases, and more patients are receiving outpatient medications to treat chronic health issues.

Benzodiazepine withdrawal has also been reported in the PICU population. Sury et al. (16) described benzodiazepine withdrawal in three children (ages, 4, 11, and 12 yrs) after prolonged sedation with a continuous infusion of midazolam. The patients had received midazolam for 7, 14, and 17 days for sedation during mechanical ventilation. Mean infusion rates were 0.17, 0.22, and 0.56 mg/kg/hr in the three patients. The midazolam infusions were stopped without tapering the infusion rate, and within 24 hrs, withdrawal symptoms were noted, including visual hallucinations, combative behavior, and seizures. The problems resolved once a benzodiazepine was administered.

van Engelen et al. (17) reported similar problems after the prolonged administration of midazolam to two pediatric patients (ages, 15 months and 14 days). The midazolam infusion rates reached maximum values of 0.14 and 0.57 mg/kg/hr with durations of infusion of 12 and 29 days. After discontinuation of the midazolam infusion, both patients demonstrated agitation, tachycardia, hyperpyrexia, and gastrointestinal (GI) symptoms, including aerophagia and emesis. The latter was attributed to the aerophagia. Symptoms disappeared with reinstitution of the midazolam infusion.

Additional information concerning benzodiazepine withdrawal is provided by a retrospective review of Fonsmark et al. (18) concerning 40 children who received sedation during mechanical ventilation. Sedation was provided by midazolam, pentobarbital, or a combination of the two. Withdrawal symptoms occurred in 14 of 40 patients (35%). Of those manifesting withdrawal symptoms, eight received both midazolam and pentobarbital, three received only midazolam, and three received only pentobarbital. The authors noted that the cumulative midazolam dose (≥60 mg/kg) was significantly associated with withdrawal, whereas the duration of the infusion was not. Sedation was gradually tapered in only one of 14 patients who experienced withdrawal.

Withdrawal has also been reported after prolonged administration of pentobarbital for sedation during mechanical ventilation (18, 19). The study of Fonsmark et al. (18) reports the occurrence of withdrawal in 11 children who received pentobarbital (eight received pentobarbital and midazolam, whereas three received only pentobarbital). A cumulative pentobarbital dose of ≥25 mg/kg was associated with an increased probability of withdrawal.

Experience with pentobarbital withdrawal in a 17-month-old infant has previously been reported (19). When sedation was inadequate, despite escalating doses of fentanyl and midazolam, a pentobarbital infusion was started at 2 mg/kg/hr. The pentobarbital infusion was increased to a maximum of 4 mg/kg/hr at the end of 8 days. After extubation, 6–8 hrs after discontinuing the pentobarbital infusion, the child become irritable and inconsolable, with an increase in heart rate and blood pressure. The symptoms resolved after the administration of pentobarbital (2 mg/kg bolus over 10 mins) and restarting the infusion at 2 mg/kg/hr. The patient was subsequently switched to oral pentobarbital, and a taper schedule was started.

The relative rarity of reports of withdrawal after pentobarbital may relate to the infrequent use of barbiturates for ICU sedation (20). However, with the increased use of pentobarbital in the author’s practice as a second-line agent when the usual combination of opioids and benzodiazepines is ineffective, additional cases have been noted when the infusion is weaned too rapidly or abruptly discontinued. The possibility of the development of tolerance to barbiturates is supported by animal studies demonstrating the rapid development of tolerance after repeated administration (21), as well as an increased susceptibility to pentyleneetetrazol-induced seizures as a manifestation of barbiturate withdrawal (22).

As with barbiturates, such as pentobarbital, ketamine is not a commonly used agent for sedation in the PICU patient (23). As such, there is limited information concerning the adverse effects related to its prolonged administration. To date, there are no reports that demonstrate withdrawal after the prolonged administration of ketamine. However, tolerance to the anesthetic effects of ketamine has been reported (24–26). Because of its relative lack of deleterious effects on cardiorespiratory function, ketamine is frequently used to provide sedation and anesthesia in the “outside the operating room” environment (during radiation therapy or diagnostic imaging). Because many of these patients require repeated procedures, an opportunity exists to determine whether tolerance develops and if there is an increase in the dose required to achieve the desired effect. Several reports (24–26) demonstrated an increased dose requirement and/or decreased sleep time with the same dose of ketamine after repeated exposure to the medication.

More recently, propofol has been added to the list of agents used for sedation of children and adults during mechanical ventilation (27, 28). Cammarano et al. (29) recently retrospectively investigated the problem of acute withdrawal after prolonged sedation in the adult ICU patient. They noted a correlation of the incidence of withdrawal behavior in patients with both the use of propofol and the dose administered. Withdrawal behavior was more likely in patients who received propofol for >1 day (p = .026) and more likely in patients who received prolonged infusions of propofol (p = .046). Because all of the patients had also received benzodiazepines and opioids, the authors were unable to prove that the withdrawal was related to the use of propofol.

Au et al. (30) reported a withdrawal syndrome after the administration of propofol for 5 days (dose unspecified) during mechanical ventilation after repair of an ascending aortic aneurysm in a 41-yr-old man. After 5 days of propofol infusion, the patient was successfully weaned from mechanical ventilation, the propofol infusion was discontinued, and the patient’s trachea was extubated. The patient became increasingly confused, tremulous, hallucinated, and had a generalized tonic-clonic seizure. Before extubation, the patient was also receiving a papaveretum infusion (dose not specified). Both the propofol and papaveretum infusions were restarted and gradually tapered over a 48-hr period. The patient

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had no other signs or symptoms of withdrawal. The authors suggested that the clinical features of the patient’s withdrawal were more compatible with that of a withdrawal syndrome from a general depressant agent rather than from an opioid and, therefore, attributed the problem to the propofol. However, the impact of the opioid withdrawal and central nervous system problems related to cardiovascular bypass and circulatory arrest during repair of the aortic aneurysm cannot be excluded.

Imray and Hay (31) reported propofol withdrawal in an 10-month-old girl who required mechanical ventilatory support for 2 wks after an inhalation smoke injury. Propofol was administered for 2 wks (dose not specified) to provide sedation during mechanical ventilation. When the drug was discontinued, the patient exhibited “generalized twitching and jitteriness.” No treatment was administered, and the problem subsided over a 3-day period. The authors noted that there was no suspicion of cerebral hypoxia as the cause of the problem, and the child made an uneventful recovery.

The paucity of reports of propofol withdrawal may be related to some unique property of the drug or more likely, as suggested by Cammarano et al. (29), may be related to the limited clinical experience with prolonged propofol sedation in the ICU population. Although propofol has gained popularity for short-term sedation, clinical experience is limited with its use for prolonged periods of time, especially in children.

As the search for the perfect agent for ICU sedation continues, several drugs and routes of administration have been tried. One of the more novel approaches for sedation during mechanical ventilation is the administration of inhalational anesthetic agents, such as isoflurane. Although a relatively common practice in Europe and Great Britain, this technique has not gained widespread application in this country. Arnold and colleagues (35) reported their experience with ten patients who had received isoflurane for sedation during mechanical ventilation. The patients, who ranged in age from 3 wks to 19 yrs, received isoflurane for sedation during mechanical ventilation. When the usual combination of opioids and benzodiazepines proved to be ineffective. The duration of isoflurane administration varied from 29 to 769 hrs (mean, 245 hrs). The minimum alveolar concentration (MAC)-hours ranged from 13 to 497, with a mean of 131 MAC-hrs.

During the administration of isoflurane, the opioid and benzodiazepine infusions were gradually tapered and discontinued. Although the inhalational agent proved effective in providing sedation, agitation and nonpurposeful movements occurred in five of the ten patients within 2 hrs of discontinuation of isoflurane. These five patients had received >70 MAC-hrs of isoflurane. The symptoms were thought to be related to withdrawal from the isoflurane and responded to the administration of benzodiazepines and/or opioids. The authors were surprised at the occurrence of an abstinence syndrome after isoflurane because previous studies in laboratory animals had suggested that tolerance and dependency did not occur after the prolonged administration of inhalational anesthetic agents (33). A recent study in the adult population (34) did not identify withdrawal phenomena with the administration of up to 30 MAC-hrs, although all the patients in this study were also receiving intravenous morphine infusions.

Arnold and colleagues (35) subsequently reported tolerance and withdrawal phenomena after the prolonged administration of isoflurane to a 4-yr-old boy for sedation during mechanical ventilation. After 19 days of administration, with end-tidal concentrations of isoflurane of 0.8% to 1.2%, the patient was awake and able to follow commands. The expected MAC-awake of isoflurane, as with all inhalation anesthetic agents, is 0.3–0.4 MAC. Because the MAC of isoflurane is 1.3%, the MAC-awake is expected to be 0.4% to 0.5%. After 32 days of administration, mechanical ventilation and the isoflurane were discontinued. Shortly after discontinuing the isoflurane, the patient developed agitation, diaphoresis tachycardia, hypertension, and profuse diarrhea. The symptoms were eventually controlled with pentobarbital and midazolam infusions.

Hughes et al. (36) reported hallucinations and seizures after the prolonged administration of isoflurane for sedation to a 7-yr-old boy. Isoflurane, in an unspecified concentration, was administered for 4 days. After its discontinuation, the patient became agitated, experienced visual and auditory hallucinations, and had a generalized tonic-clonic seizure. He was treated with rectal diazepam and within 5 days, had returned to his baseline status.

Nitrous oxide is no longer recommended for prolonged administration because of its effects on vitamin B12 metabolism, which can result in megaloblastic anemia and, more importantly, neurotoxicity. However, there are laboratory and clinical data to suggest that tolerance also develops to nitrous oxide. In 1972, Kripke and Hechtman (37) reported the use of nitrous oxide to treat chronic pain from an esophageal stricture (from a caustic ingestion as a child) in a 38-yr-old woman. Before using nitrous oxide, the pain had been controlled with increasing doses of pentazocine (700–1000 mg/day) administered by intermittent subcutaneous injections. Significant adverse effects on gastrointestinal motility as well as multiple abscess sites from repeated subcutaneous injections necessitated changing the analgesic regimen. Initially, 15% nitrous oxide was required to alleviate the pain and to allow for ambulation. A nasal cannula apparatus was devised to allow the continuous delivery of 15% nitrous oxide. The pentazocine was weaned over a 7-day period. Twenty-two days after discharge from the hospital, the nitrous oxide no longer provided adequate analgesia, and the patient was readmitted. At this time, retesting with nitrous oxide delivered via an anesthesia machine revealed that a concentration of 30% to 35% was required to provide adequate analgesia.

After the report of Kripke and Hechtman (37), more precise clinical and laboratory studies have demonstrated tolerance to the amnestic and analgesic effects of nitrous oxide in adult patients and volunteers (38–40). The mechanism of tolerance to nitrous oxide-induced analgesia has not been clearly identified; however, exposure to nitrous oxide increases opioid receptor density (41), and tolerance to its analgesic effects can be partially prevented by the inhibition of enkephalinases (42). This information implicates the opioid system in the analgesic properties of nitrous oxide as well as suggesting alterations in receptor density or function as a mechanism for the development of tolerance. Studies in laboratory animals have demonstrated that once tolerance has developed, withdrawal symptoms including seizures occur when nitrous oxide is discontinued (43). The development of tolerance and the occurrence of withdrawal phenomena such as seizures are related to both the duration of exposure and the concentration of nitrous oxide that is administered.
Clinical Signs and Symptoms of Withdrawal

The development of strategies to provide effective treatment of physical dependency and related problems requires the accurate identification and recognition of withdrawal symptoms. Ongoing or associated conditions that can manifest similar clinical signs and symptoms as withdrawal must be investigated and ruled out before concluding that the patient’s symptoms are the result of withdrawal. In the PICU patient, these associated conditions may include central nervous system insults or infections, ICU psychosis, metabolic abnormalities, hypoxia, hypercarbia, and cerebral hypoperfusion from alterations in cardiac output or cerebral vascular disease.

Although many of the signs and symptoms of withdrawal are the same regardless of the agent, there may be subtle differences depending on the specific agent. The time to the onset of withdrawal symptoms may vary depending on the half-life of the agent and the half-life of active metabolites, which may be several times longer than the parent compound. The signs and symptoms of sedative/analgesic agent withdrawal include the following: a) central nervous system activation; b) GI disturbances; and c) sympathetic hyperactivity. The central nervous system manifestations include irritability, increased wakefulness, tremulousness, hyperactive deep tendon reflexes, clonus, inability to concentrate, frequent yawning, sneezing, delirium, and hypertonicity. In neonates and infants, additional signs of central nervous system stimulation include a high-pitched cry and an exaggerated Moro reflex. Seizures have been reported with withdrawal from opioids, benzodiazepines, barbiturates, propofol, and inhalational anesthetic agents (16, 22, 30, 36). Visual and auditory hallucinations have been described with opioid, benzodiazepine, barbiturate, and inhalational anesthetic withdrawal. Prolonged tinnitus, lasting 6–8 months, has been anecdotally associated with benzodiazepine withdrawal (44).

GI manifestations of withdrawal may be especially prominent in neonates and infants. The only manifestation of opioid/sedative agent withdrawal may be feeding intolerance, with vomiting, diarrhea, uncoordinated suck and swallow, or persistent residuals with tube feedings (19). These GI disturbances are often attributed to other problems and not withdrawal.

Activation of the sympathetic nervous system is a prominent finding with withdrawal from sedative/analgesic agents. Signs and symptoms may include tachycardia, hypertension, and tachypnea. Additional signs and symptoms of sympathetic hyperactivity include nasal stuffiness, sweating, and fever. The latter may be particularly troublesome in the PICU patient with multiple indwelling central catheters, in whom temperature instability requires immediate investigation and, at times, treatment with broad-spectrum antibiotics.

The manifestations of withdrawal vary according to the agent used for sedation, manifesting shortly after discontinuation of the drug if the agent has a short half-life (propofol, fentanyl) or days later if the agent or its metabolites have long half-lives (diazepam). Delayed clearance of active metabolites or the parent compound in patients with underlying renal or hepatic dysfunction may also delay the onset of withdrawal symptoms. Although the complete withdrawal syndrome is easily recognized, many patients have relatively subtle clinical findings that are easily confused with other problems encountered in the PICU patient. The signs and symptoms vary from patient to patient in number, severity, and presentation. Equally important, especially in the PICU patient, withdrawal syndromes should not be overdiagnosed. Withdrawal remains a diagnosis of exclusion. Fever or vomiting should never be attributed to withdrawal until other possible causes are excluded.

Unique clinical scenarios that may represent the withdrawal phenomena have recently appeared in the literature. I previously cared for and subsequently reported on two patients who developed signs and symptoms of upper airway obstruction with stridor, which was later thought to be a manifestation of opioid withdrawal (45). Upper airway obstruction with stridor developed shortly after tracheal extubation and discontinuation of the opioid infusion. Direct laryngoscopy and airway examination in the operating room revealed no anatomical cause for the stridor. Upper airway obstruction and stridor resolved after reinstituting the opioid infusions. Although the only readily apparent manifestation of opioid withdrawal was airway compromise, the two patients had closed head injuries and altered mental status, with Glasgow Coma Scale scores of 10–11, which may have influenced the manifestations of opioid withdrawal. On retrospective analysis, both patients also demonstrated sympathetic hyperactivity with tachycardia and hypertension, which may have been signs of opioid withdrawal but were initially attributed to respiratory distress.

Lane et al. (46) reported choreoathetoid movements and myoclonus in five children after fentanyl infusions for sedation during mechanical ventilation. In addition to the more usual manifestations of opioid withdrawal, such as tremor, irritability, and insomnia, the patients developed myoclonus, ataxia, and choreoathetosis. Autonomic manifestations of opioid withdrawal were absent. No treatment was instituted, and all patients made a complete recovery without permanent neurologic sequelae. When comparing the five symptomatic patients with other patients sedated with fentanyl who did not develop the syndrome, the authors noted no differences between the two groups other than the group that did not develop problems had received other opioids after the fentanyl was discontinued. The authors concluded that this unusual movement disorder was a manifestation of opioid withdrawal.

Bergman et al. (47) described a similar syndrome in infants sedated with a combination of fentanyl and midazolam. The infants manifested choreoathetoid movements, with poor social interactions, decreased visual attentiveness, and dystonic posturing. As in the previous report of Lane et al. (46), all patients eventually made a full recovery, although some were symptomatic for up to 4 wks. Retrospective analysis revealed risk factors for the disorder, including the combination of a continuous infusion of midazolam and fentanyl, young age, female gender, low serum albumin, and concomitant administration of aminophylline. Although the authors offered several suggestions as to the cause and pathogenesis of this disorder, their impressions were only speculative and no clear-cut evidence was provided for the cause. They were unable to determine whether this was a true withdrawal syndrome or a toxic adverse effect related to the sedative agents, perhaps in combination with other medications.

Factors Affecting the Development of Tolerance

Sedative and analgesic drugs exert their effects through agent-specific cell
surface receptors. The majority of information concerning the cellular mechanisms of tolerance and dependence involves opioids and related compounds, with limited information concerning other agents. In the central nervous system, four major opioid receptor systems have been identified: mu, kappa, delta, and sigma receptors. The mu receptor is further subclassified into mu1 and mu2 subtypes. The mu, delta, and kappa receptors produce analgesia through a similar mechanism, the end result of which involves the inhibition of synaptic transmission in the central nervous system. Binding of the opioid to the receptor results in a conformational change in the receptor, leading to interactions with the G protein system and alterations in intracellular concentrations of cyclic adenosine monophosphate (cAMP), various ions (K$^+$, Ca$^{2+}$, Na$^+$), and phospholipases A$_2$ and C. The end result is a decrease in the release of excitatory neurotransmitters with the hyperpolarization of neural pathways involved in nociception.

The key factors determining tolerance and dependence are occupancy of the receptor by an agonist and the specificity or degree of binding of the agonist at the receptor. Despite the obvious development of clinical tolerance, the exact cellular mechanisms responsible for tolerance and dependence remain poorly defined. The mechanism may not be a decrease in the receptor number or binding affinity (48) but rather alterations of the interactions between the receptor, the regulatory G proteins, and intracellular enzyme systems such as phospholipase and adenylyl cyclase. Abrupt discontinuation of the opioid with decreased receptor occupancy results in increased afferent activity to the central nervous system, with activation of the reticular activating system as well as sympathetic centers, such as the locus ceruleus, with increased efferent sympathetic activity resulting in autonomic effects, including tachycardia and hypertension.

Like the opioids, benzodiazepines and barbiturates act through specific cell surface receptors. Although the receptors are specific for the individual agent, the end result is the same, alteration of chloride conductance in the central nervous system. Similar mechanisms of action are suggested for propofol and the inhalation anesthetic agents. Benzodiazepines increase the affinity of the inhibitory neurotransmitter, $\gamma$-aminobutyric acid, for cell surface receptors located on postsynaptic neurons, leading to increased chloride conductance and hyperpolarization. During chronic benzodiazepine administration in laboratory animals, Miller et al. (49) noted receptor down-regulation with decreased function as indicated by chloride uptake. Abrupt discontinuation of the benzodiazepine leads to decreased pharmacologic efficacy of the same concentration of $\gamma$-aminobutyric acid, with a resultant disinhibition of the central nervous system.

The majority of information concerning factors affecting the development of tolerance and ways to prevent or delay it is based on information obtained from laboratory and clinical studies with opioids, with limited information concerning other sedative agents. Duration of opioid receptor occupancy is the key factor in determining the development of tolerance (50). It has been suggested that tolerance develops more rapidly with the continuous vs. the intermittent administration of sedative and analgesic agents (11, 50). Because of their increased affinity for the opioid receptor, synthetic opioids, such as fentanyl, may result in tolerance more rapidly than nonsynthetic opioids, such as morphine. This effect must be weighed against the potential benefit of improved analgesia with continuous vs. intermittent administration and more effective control of the stress response and vasomotor tone of the pulmonary vasculature with synthetic opioids vs. other agents (1, 2).

Regardless of the agent(s) chosen, the amount of the drug required can be lessened and tolerance can be delayed with the use of pain or sedation scales to allow for appropriate titration of the infusion. The use of scoring systems allows the drip to be adjusted according the patients' needs so that the minimal amount of drug is administered. Katz and Kelly (51) demonstrated significant interpatient variability in fentanyl clearance in the PICU patient with a ten-fold variability in the infusion requirement to achieve the same degree of sedation. In their recent retrospective review, Cammarano et al. (29) reported that a risk factor for the development of tolerance and withdrawal was the concomitant use of neuromuscular blocking agents. The authors speculated that when caring for patients receiving neuromuscular blocking agents, many of the usual clues used to titrate the sedative and analgesic agents are lacking. Furthermore, these patients may have received higher doses of sedative and analgesic agents than patients not receiving neuromuscular blocking agents in an attempt to avoid undetected awareness and pain.

As tolerance develops related to receptor occupancy, it is theoretically possible to delay its development by rotating sedation regimens at specific intervals. Another option is to switch to another agent when an obvious dose escalation above specific predetermined doses is noted (20). Prospective evaluations are needed to determine the efficacy of these maneuvers in preventing or delaying the occurrence of tolerance and physical dependency.

Basic science research has provided some insight into what the future may hold to prevent or delay the development of tolerance. Interactions between opioid receptor subtypes may be involved in the development of tolerance. In laboratory animals, blockade of delta receptors prevents the development of acute and chronic tolerance to mu receptor agonists (52). The administration of mu antagonists increases the analgesic effects of kappa agonists (53), whereas the activation of spinal kappa receptors attenuates the development of tolerance to morphine (54).

The n-methyl-D-aspartate (NMDA) receptor system is also closely involved in nociception and the development of tolerance. Antagonism of central NMDA receptors slows the development of opioid tolerance (55) and attenuates certain withdrawal behaviors (56). Although the current experience with NMDA receptor antagonists is limited to laboratory studies with agents such as MK-801 and LY274614, which are not available for clinical use; ketamine possesses specific NMDA receptor antagonistic properties, which theoretically suggests that it may play a role in sedation in the PICU patient as a means of delaying the development of opioid tolerance.

More recently, magnesium has shown some promise as an agent to slow the development of tolerance. NMDA receptor ion channels are blocked by magnesium in a voltage-dependent manner at a location deep within the ion channel. McCarthey et al. (57) demonstrated that the coadministration of intrathecal magnesium with morphine delayed the development of tolerance to the antinociceptive effects of morphine.
**Treatment Options**

For the future, prospective studies are needed to better address the efficacy of rotating sedation regimens, intermittent vs. continuous infusions of sedative/analgesic agents, and the role of other pharmacologic agents such as NMDA receptor antagonists and magnesium in preventing tolerance and dependency. Until further investigations provide additional insight into the factors controlling opioid dependency and ways of preventing or delaying it, PICU physicians will be faced with a group of patients who require specific actions to prevent the development of withdrawal symptoms. Treatment strategies and protocols are necessary so that the problems associated with tolerance, physical dependency, and withdrawal do not limit the administration of these agents in the PICU population.

The first steps in the treatment of patients with dependency and tolerance are identification of the “at risk” group and the development of appropriate tools (scoring systems) to identify and quantify the signs and symptoms of withdrawal. Identifying the risk factors associated with the development of withdrawal will allow PICU physicians to identify the at risk group and, thereby, institute appropriate therapy, such as slowly tapering infusions, thereby preventing withdrawal rather than treating it once it has occurred. Katz et al. (58) evaluated the factors that could be used to identify the at risk group in 23 infants and children, aged 1 wk to 22 months, who received continuous infusions of fentanyl for sedation. Once sedation was no longer required, the fentanyl infusion was decreased by 50% every 24 hr times two and then discontinued. Withdrawal was assessed using a neonatal scoring system originally described by Finnegan et al. (59). Withdrawal behavior was observed in 13 of 23 patients (57%). The total fentanyl dose and the duration of the infusion correlated with the risk of withdrawal, whereas the maximum fentanyl infusion rate did not. A total fentanyl dose of ≥1.5 mg/kg or a duration of infusion of ≥5 days was associated with a 50% incidence of withdrawal, whereas a total fentanyl dose of ≥2.5 mg/kg or a duration of infusion of ≥9 days was associated with a 100% incidence of withdrawal. Similar results were reported by Arnold et al. (10), who noted a correlation of both total dose (>1.6 mg/kg) and duration of administration (>5 days) with the incidence of withdrawal.

Arnold et al. (32) also noted that the total dose administered may be a risk factor for patients receiving sedation using an inhalation anesthetic agent, isoflurane. Withdrawal occurred only in patients who had received >70 MAC-hrs of isoflurane. There are limited data concerning the duration of administration and total dose of benzodiazepines and barbiturates that place patients at high risk for withdrawal symptoms. Although it is appealing to apply the same durations noted in the studies of Katz et al. and Arnold et al., this may not be appropriate. In their retrospective review, Fonsmark et al. (18) reported that an increased probability of withdrawal was noted with a total dose of midazolam of ≥60 mg/kg or a total dose of pentobarbital of ≥25 mg/kg.

Regardless of the agent(s) used for sedation, once the decision is made to start weaning the infusion, careful observation of the patient is mandatory to monitor for signs and symptoms of withdrawal. A scoring system is useful to provide a way to quantify the patient’s symptoms and to assess the need for treatment. Many of these scoring symptoms were developed to assess the severity of withdrawal in infants of drug addicted mothers, and therefore, two problems arise: a) they were developed to assess neonatal behavior; b) they were developed to assess opioid withdrawal. Despite such problems, with a lack of better tools, these scoring systems can provide useful information in the PICU patient.

Kahn et al. (9) introduced the first scoring system for withdrawal, using it when treating infants of heroin-addicted mothers. The scoring system was basic and divided withdrawal into three grades: grade I included mild, but abnormal behavior; grade II included marked symptoms that occurred when the infant was disturbed; whereas grade III included marked symptoms that occurred spontaneously. These initial scoring systems were followed by more detailed scoring systems (Finnegan et al. [59]), which assigned points to different types of abnormal behavior and allowed for an actual point system (Table 1). Total scores of >6–8 were suggested to indicate significant withdrawal and the need for treatment. Several different scoring systems have now been developed. These are outlined in the review of Anand and Arnold (60).

The mainstay of therapy to prevent withdrawal remains slowly weaning the sedative/analgesic infusions. This can be done rapidly (10% to 15% every 6–8 hrs) in patients who have been receiving these agents for brief periods of time (<3–5 days). However, after prolonged administration, the weaning process may take 2–4 wks to prevent withdrawal symptoms. It may not be possible to decrease the infusion rate in 10% increments when patients are receiving 50 μg/kg/hr. In such circumstances, it may be necessary to decrease the rate by as little as 1 μg/kg/hr every 12 hrs. Although the weaning process can be accomplished by slowly decreasing the intravenous infusion rate, this mandates the maintenance of intravenous access, ongoing hospitalization, and at times, continued monitoring in the ICU because, depending on hospital policies, certain medications such as fentanyl cannot be administered on the regular, inpatient ward. In this

### Table 1. Components of the Finnegan score

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cry</td>
<td>2</td>
</tr>
<tr>
<td>Continuous</td>
<td>3</td>
</tr>
<tr>
<td>Sleep (hr) after feeding</td>
<td>1 &lt; 1 hr</td>
</tr>
<tr>
<td>≤ 2 hrs</td>
<td>2</td>
</tr>
<tr>
<td>≤ 3 hrs</td>
<td>1</td>
</tr>
<tr>
<td>More reflex</td>
<td>2</td>
</tr>
<tr>
<td>Hypoactive</td>
<td>3</td>
</tr>
<tr>
<td>Markedly hypoactive</td>
<td>3</td>
</tr>
<tr>
<td>Tremors</td>
<td>1</td>
</tr>
<tr>
<td>Mild, disturbed</td>
<td>2</td>
</tr>
<tr>
<td>Moderate-severe, disturbed</td>
<td>3</td>
</tr>
<tr>
<td>Increased muscle tone</td>
<td>2</td>
</tr>
<tr>
<td>Prolonged yawning</td>
<td>2</td>
</tr>
<tr>
<td>Excitation</td>
<td>1</td>
</tr>
<tr>
<td>Seizures</td>
<td>1</td>
</tr>
<tr>
<td>Sweating</td>
<td>5</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
</tr>
<tr>
<td>100–101</td>
<td>2</td>
</tr>
<tr>
<td>&gt;101</td>
<td>1</td>
</tr>
<tr>
<td>Motting</td>
<td>1</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>1</td>
</tr>
<tr>
<td>Sneezing</td>
<td>1</td>
</tr>
<tr>
<td>Nasal flaring</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>1</td>
</tr>
<tr>
<td>&gt;60 breaths/min</td>
<td>1</td>
</tr>
<tr>
<td>&gt;60 with retractions</td>
<td>2</td>
</tr>
<tr>
<td>Excessive sucking</td>
<td>1</td>
</tr>
<tr>
<td>Poor feeding</td>
<td>2</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>2</td>
</tr>
<tr>
<td>Projectile vomiting</td>
<td>3</td>
</tr>
<tr>
<td>Stools</td>
<td>2</td>
</tr>
<tr>
<td>Loose</td>
<td>2</td>
</tr>
<tr>
<td>Watery</td>
<td>3</td>
</tr>
</tbody>
</table>

A score of 0–7 indicates mild symptoms of withdrawal, 8–11 indicates moderate withdrawal, and 12–15 indicates severe withdrawal.
setting, two options may be considered to facilitate patient care: subcutaneous or oral administration.

When sedation/analgesia is no longer necessary, if it is decided that tapering the infusion can be accomplished within a reasonable period of time that will not delay hospital discharge and that switching to oral methadone will not expedite discharge home, the patient may be considered a candidate for subcutaneous administration of opioids/benzodiazepines (61). These patients usually are receiving moderate doses of fentanyl (5–10 μg/kg/hr), with or without midazolam (0.1–0.3 mg/kg/hr), to provide effective sedation. The switch to the subcutaneous route allows the removal of central venous access and eliminates the need for repeated needle sticks to maintain peripheral intravenous access. Both fentanyl and midazolam can be effectively administered via the subcutaneous route and the infusions slowly tapered to prevent symptoms of withdrawal.

Concentrated solutions of fentanyl (25–50 μg/mL) and midazolam (2.5–5 mg/mL) are used so that the maximum infusion rate of the agent(s) does not exceed 3 mL/hr. The subcutaneous infusions are started at the same dose that is currently being used for intravenous administration. EMLA cream (Eutectic Mixture of Local Anesthetics, Astra Pharmaceuticals, Westborough, MA) is placed over the site of anticipated subcutaneous cannulation. Several areas are suitable for subcutaneous administration, including the subclavicular region, abdomen, deltoid, or anterior aspect of the thigh. After 2 hrs, the site is cleaned with an iodine solution followed by alcohol. Either a standard 22-gauge intravenous cannula or a 23-gauge butterfly needle is inserted into the subcutaneous tissue. Before placement, the tubing and needle are flushed with the opioid/benzodiazepine solution. The insertion site is then covered with a transparent, bio-occlusive dressing. The site should be changed every 7 days or sooner if erythema develops. The same infusion pumps that are used for intravenous administration can be used for subcutaneous administration. The pressure limit may need to be adjusted to allow for subcutaneous administration. Alternatively, a syringe pump can be used. If symptoms of withdrawal develop, additional boluses can be administered subcutaneously if necessary. Several different opioids can be administered subcutaneously, including the synthetic opioids, morphine, hydromorphone, and meperidine. Longer acting agents such as methadone and levorphanol are not recommended because dose titration may be difficult because of the long half-lives of these agents. Tissue reaction and erythema has been noted with methadone. Although the use of subcutaneous infusions of opioids with or without benzodiazepines is a new technique to wean patients from opioids and prevent withdrawal, the subcutaneous route has been used to treat chronic cancer-related pain (62), as well as postoperative pain (63–65).

When prolonged administration of opioids or other sedative agents will be necessary, switching to oral administration of long-acting agents such as methadone may allow for earlier hospital discharge (66). In our PICU, patients who meet the criteria of Katz et al. (58) for a 50% incidence of withdrawal are considered candidates for oral methadone therapy. Although our initial report (12) concerning methadone use in the inpatient setting suggested a starting dose of 0.1 mg/kg every 12 hrs, the three patients reported in the study were receiving relatively low opioid doses and, therefore, higher doses of methadone were not needed. Our subsequent clinical experience has indicated that higher doses may be needed, depending on the dose of fentanyl (66). The switch from intravenous fentanyl to oral methadone should account for the difference of the potency of the two drugs (fentanyl:methadone = 100:1), the difference in the half-life (fentanyl:methadone = 1:75–100), and the oral bioavailability of methadone (75% to 80%). A 10-kg patient who is receiving 10 μg/kg/hr of fentanyl receives 2.4 mg/day of fentanyl. The conversion is relatively straightforward because the difference in potency (100:1) is offset by the difference in half-life (1:100), and therefore, the total daily dose of methadone should equal the total daily dose of fentanyl. Clinical experience suggests that increasing the dose to compensate for the decreased oral bioavailability of methadone (75% to 80%) is not needed to prevent withdrawal symptoms (66). Although the higher dose may be needed to provide sedation, it is not required to prevent withdrawal. Additionally, cross-tolerance of opioids is not 100%, so that switching from one opioid to another may result in a decrease in the total dose required when calculated on a standard potency ratio. Therefore, the starting oral methadone dose is equivalent to the total daily intravenous fentanyl dose (in this case, 2.4 mg/day). The conversion factors are illustrated in Table 2. The oral dosing of methadone is started with an every 12-hr dosing regimen. After the second oral dose of methadone, the fentanyl infusion is decreased by 50%, by 50% after the third dose, and then discontinued after the fourth dose. Symptoms of opioid withdrawal are graded according to the system proposed by Finnegan et al. (Table 1) and treated with “rescue doses” of morphine (0.05 mg/kg/dose). The total morphine requirement over a 24-hr period is added to the next day’s methadone dose. Further rescue doses of morphine are used as needed during the next 72-hr period, but no change is made in the subsequent methadone dose until 72 hrs have elapsed to allow for the attainment of a new steady-state serum concentration after the change in the methadone dose. If excessive sedation occurs, one methadone dose is held and the dose decreased by 10% to 20%. Once an appropriate dose is achieved, the patient is discharged to the inpatient ward and then discharged home once the physician staff is comfortable with the family’s ability to administer the medication at home. The oral methadone dose is then tapered once a week after a follow-up phone call to ensure that the infant or child is doing well. The dose is decreased by 20% of the initial dose so that the oral dose is gradually decreased and then discontinued after a 5–6-wk period.

There remain some stig mata concerning the use of methadone. Therefore, a thorough discussion with the parents is necessary to discuss why methadone is being used and to outline the differences between addiction and physical depen-

<table>
<thead>
<tr>
<th>Table 2. Conversion from intravenous fentanyl to oral methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency (fentanyl:methadone)</td>
</tr>
<tr>
<td>Half-life (fentanyl:methadone)</td>
</tr>
<tr>
<td>Oral bioavailability (methadone)</td>
</tr>
</tbody>
</table>

A 10 kg patient is receiving a fentanyl infusion of 10 μg/kg/hr. The total daily fentanyl dose = 2.4 mg/day.

Starting dose of methadone is 2.4 mg/day divided into an every 12-hr dose. After the second oral dose of methadone, the intravenous fentanyl infusion is decreased by 50% (to 5 μg/kg/hr). After the third oral dose, the intravenous fentanyl infusion is decreased by 50% (to 2.5 μg/kg/hr). After the fourth oral dose, the intravenous fentanyl infusion is discontinued.
dency. Because of these issues as well as familiarity with long-acting morphine preparations (MS Contin, Purdue Frederick, Norwalk, CT), which are used in the treatment of children with chronic cancer-related pain, some physicians prefer to use the latter agent. Based on potency and half-life, the dosing of methadone and MS Contin are similar. MS Contin is available only in tablets that cannot be crushed so that administration may be more difficult in younger patients. Methadone on the other hand is available in a liquid formulation.

Several other agents, both opioid and nonopioid, have been suggested for the treatment and prevention of opioid withdrawal. Mixtures of opioid alkaloids such as paregoric and tincture of opium were among the first agents used to treat opioid withdrawal in infants of drug-addicted mothers. Paregoric is no longer recommended in neonates and infants because of concerns of the toxicity of its other components, including central nervous system effects from camphor and cardiovascular manifestations of benzoic acid. Tincture of opium is still used to treat opioid withdrawal in neonates of drug-addicted mothers (67). However, because of its short half-life, repeated administration at 4-hr intervals may be necessary.

In addition to opioids, nonopioid agents have been used to treat opioid withdrawal. In the author’s opinion, this is less than optimal because it seems to make physiologic sense when dealing with the problems of tolerance and dependence to replace the missing agent rather than to treat the resulting symptoms. The benzodiazepine, diazepam, has been used to treat opioid withdrawal in both neonates and adults (74, 75). Diazepam receptors mediate part of the pharmacologic actions through the activation of the same potassium channel as opioid receptors. Because of its prolonged duration of action (12–18 hrs), once or twice a day dosing is possible. Starting doses range from 3 to 5 mg/kg/day. Adverse effects from clonidine include sedation, bradycardia, and hypotension. Although the use of clonidine is becoming more widespread in pediatric anesthesia as a premedicant for the operating room as well as for caudal/epidural anesthesia, to date, there is limited clinical experience with its use in the treatment of opioid withdrawal (76). Further information is needed to more clearly define the efficacy and safety of this agent as well as its role in treating opioid withdrawal in the PICU patient.

As with many other aspects of tolerance and dependency, most of our information concerning treatment strategies relates to opioids with less information and clinical experience with other agents, such as benzodiazepines and barbiturates. The subcutaneous administration of midazolam, as previously described, is a viable option (61), although it does require ongoing hospitalization and perhaps continued ICU admission. As with the opioids, longer acting equivalents are available for both the benzodiazepines and barbiturates with agents such as lorazepam and phenobarbital. For benzodiazepine tolerance, lorazepam may be preferred over diazepam because the latter agent has active metabolites with variable half-lives and durations of action. As with the conversion from fentanyl to methadone, the conversion from midazolam to lorazepam should account for differences in potency (1:2) and half-life (1:6) between midazolam and lorazepam, as well as the decrease in bioavailability (60% to 70%) with oral administration. The conversion from intravenous midazolam to oral lorazepam is outlined in Table 3. Although other agents have been evaluated in the adult population for the treatment of benzodiazepine withdrawal including propranolol, carbamazepine, and phenobarbital; to date, there is no information concerning the use of these agents in children.

Barbiturate tolerance presents similar problems as benzodiazepine tolerance in that there is limited information to suggest and evaluate treatment options. With the increased use of opioids and benzodiazepines, the use of barbiturates for prolonged sedation in the PICU patient has declined. Barbiturates are generally second- or third-line choices when the benzodiazepines and/or opioids fail (20). As with other agents, prolonged use can result in tolerance and withdrawal if these agents are abruptly discontinued (18, 19). The initial option we suggested was to switch to oral pentobarbital (19). However, because of its short half-life, an every 6 hr dosing regimen may be necessary. More recently, we have found that phenobarbital can be used instead of pentobarbital (unpublished data). This not only provides for easy oral administration because phenobarbital is available as an elixir and as tablets, but also allows for every 12 hr dosing. An effective means of switching from continuous intravenous pentobarbital to phenobarbital is to first use intravenous phenobarbital. This is usually best accomplished while the patient is still mechanically ventilated because the combination of the two agents may result

Table 3. Conversion from intravenous midazolam to oral lorazepam

<table>
<thead>
<tr>
<th>Potency (midazolam:lorazepam)</th>
<th>1:2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life (midazolam:lorazepam)</td>
<td>1:6</td>
</tr>
<tr>
<td>Oral bioavailability (lorazepam)</td>
<td>60% to 70%</td>
</tr>
</tbody>
</table>

A 10-kg patient is receiving a midazolam infusion of 0.3 mg/kg/hr. The total daily midazolam dose is 72 mg. An equivalent daily dose of lorazepam = 72 divided by 12 = 6 mg.

Starting dose of lorazepam is 6 mg/day or 1.5 mg every 6 hr. After the second oral dose of lorazepam, the intravenous midazolam infusion is decreased by 50% (to 0.15 mg/kg/hr). After the third oral dose, the intravenous midazolam infusion is decreased by 50% (to 0.075 mg/kg/hr). After the fourth oral dose, the intravenous midazolam infusion is discontinued.
The heightened awareness of the need for aggressive sedation and pain management for the PICU patient has resulted in new issues that must be dealt with by the PICU physician: tolerance, physical dependency, and withdrawal phenomena. Aggressive treatment strategies are needed so that these new problems do not limit our ability to provide much needed sedation and analgesia to our patients. Laboratory investigations are starting to unravel the cellular mechanisms of tolerance and dependency, with some insight into ways of delaying their development. Although the initial work is promising, the applications of these techniques into the clinical realm is not yet practical. For the applications of these techniques into ways of delaying their development.

The pentobarbital infusion is discontinued. Six hours later, half of the loading dose is infused over 1 hr, followed by the remaining half of the loading dose 6 hrs later. This is followed in 6 hrs by the first of the every 12-hr maintenance dose. The maintenance dose should equal one third of the initial loading dose. Once the patient is stabilized on the intravenous phenobarbital regimen, the same dose is administered orally and then weaned 10% to 20% every week.

in significant respiratory depression. Because of the long half-life of pentobarbital after prolonged administration, timing the increase in phenobarbital level to coincide with the fall in the pentobarbital concentration may not be possible. Therefore, a synergistic effect on respiratory drive may occur. The pentobarbital infusion is discontinued, followed 6 hrs later by half of the loading dose of phenobarbital. The total loading dose of phenobarbital is administered in two increments separated by 6 hrs, followed 6 hrs later by the maintenance dose. The loading dose and maintenance dose are based on the current pentobarbital infusion rates (Table 4). This is preliminary data, and future studies are needed to determine the efficacy of this regimen.

### Table 4. Conversion from intravenous pentobarbital to oral phenobarbital

<table>
<thead>
<tr>
<th>Pentobarbital Infusion (mg/kg/hr)</th>
<th>Phenobarbital Loading Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2</td>
<td>8</td>
</tr>
<tr>
<td>2–3</td>
<td>15</td>
</tr>
<tr>
<td>3–4</td>
<td>20</td>
</tr>
</tbody>
</table>

The pentobarbital infusion is discontinued. Six hours later, half of the loading dose is infused over 1 hr, followed by the remaining half of the loading dose 6 hrs later. This is followed in 6 hrs by the first of the every 12-hr maintenance dose. The maintenance dose should equal one third of the initial loading dose. Once the patient is stabilized on the intravenous phenobarbital regimen, the same dose is administered orally and then weaned 10% to 20% every week.

### References

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