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Managing Iatrogenic Opioid Dependence with Methadone

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As advances in critical care medicine have made possible the management of more severely ill children, the need for long-term sedation and analgesia has increased. In many of these patients, prolonged administration of opioids is necessary to provide comfort, but may result in the development of tolerance and physiologic dependence.[1-6] After dependence has developed, abrupt discontinuation will produce symptoms of withdrawal. To avoid withdrawal, opioid exposure must be slowly decreased to allow for physiologic readjustment.

Mechanisms of Opioid Dependence

The mechanisms by which opioids cause tolerance and physiologic dependence have not been firmly established. Several mechanisms have been proposed, involving changes in opioid receptor number, structure, or binding affinity. These adaptations may be associated with negative feedback inhibition of endogenous opioid production, changes in neurotransmitter or second messenger concentrations, or alteration in neurotransmitter function.[1,6-8]

One theory suggests that neuronal firing from the locus coeruleus increases during dependence, and that withdrawal symptoms are a manifestation of excessive norepinephrine release from that region of the brain. Recently, Cuellar and colleagues have shown in a murine model that morphine dependence produces changes in both the number and intensity of nitric oxide synthase immunoreactive neurons throughout several regions of the brain. The authors postulate that nitric oxide up-regulation at N-methyl-D-aspartate receptors may lead to the excessive noradrenergic hyperactivity seen in the locus coeruleus during withdrawal.[9]

Opioid Withdrawal

The signs and symptoms of withdrawal have been well described in the pediatric population (Table).[1,6,10,11] The classic withdrawal triad includes neurologic excitability, gastrointestinal dysfunction, and autonomic dysfunction.

Table. Signs and symptoms of withdrawal

Neurologic Excitability	
Agitation	Inability to sleep
Irritability	Yawning
Crying/inconsolability	Tremors
Increased tone	Hyperactive reflexes
Tachypnea	Seizures
Sneezing	Uncoordinated suck
Gastrointestinal dysfunction	
Vomiting	Abdominal pain
Diarrhea	Dehydration
Feeding intolerance	Poor weight gain
Autonomic dysfunction	
Tachycardia	Pupillary dilatation
Fever	Sweating
Itching	

While iatrogenic opioid dependence has been recognized in critically ill children for more than 20 years, the scope of this phenomenon in neonatal and pediatric intensive care units has yet to be fully understood.[6,12] In 1994, Katz et al found that of 23 infants and children given fentanyl by continuous infusion while mechanically ventilated, 57% developed physiologic dependence.[8] Dose and duration were both positive predictors of dependence.

In 1995, Scott and colleagues surveyed 244 nurses, pharmacists, and physicians regarding the frequency and management of dependence in their intensive care units.[13] Preventing and managing withdrawal was seen as a problem by 74% of the respondents. Sixty-eight percent reported caring for at least one patient experiencing withdrawal in the month prior to completing the survey.

Management of iatrogenic opioid dependence has taken many forms, ranging from gradual tapering of opioid therapy to substitution of other

agents to control symptoms. The most widely used method is a gradual reduction in opioid dose. For ease of administration, patients tolerating oral therapy can be converted to a long-acting agent, allowing the tapering process to continue outside of the intensive care unit. Methadone has gained considerable popularity over the past decade for this purpose. It offers several advantages for opioid tapering, including a relatively high oral bioavailability, a long elimination half-life, and the availability of an oral liquid dosage form.[2-6]

Methadone Pharmacology

Methadone is a synthetic opioid, first produced during the second World War. It is an agonist at both mu_1 and mu_2, as well as kappa opioid receptors. Methadone may also affect the release of several other endogenous neurotransmitters, including acetylcholine, norepinephrine, dopamine, and substance P. Methadone provides a level of analgesia and sedation similar to that of morphine, when given in a comparable dose.

Several case series and small scale studies have demonstrated the efficacy of methadone in treating pain in children.[7,14-16] Berde and colleagues conducted a double-blinded, randomized study to compare 0.2 mg/kg intravenous doses of either morphine or methadone.[14] The opioids were given for postoperative pain to 35 children, between 3 and 17 years of age, over a 36 hour period. Although both groups responded well, the methadone group required fewer supplemental doses and had lower pain scores overall. No significant adverse effects were noted in either treatment group. The authors concluded that methadone provides a similar degree of analgesia to morphine, but offers the benefit of a longer duration of effect.

Pharmacokinetics

Methadone is well absorbed from the oral route, with a bioavailability of 70-80% and an onset of 30 to 60 minutes. It has a relatively high degree of lipid solubility and is highly protein bound to α_1-acidglycoprotein. Elimination half-life increases with repeated dosing, reaching an average of 19 hours in children. Like other opioids, methadone is highly metabolized. The primary pathway for metabolism is N-demethylation, producing inactive 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine.[17-19]

Adverse Effects

The adverse effects associated with methadone are similar to those of other mu-receptor agonists. Respiratory depression can occur with methadone use, and may last for a longer period than that seen with morphine.[20] Other adverse effects associated with this therapeutic class include: dysphoria, sedation, hallucinations, cardiovascular instability, nausea, vomiting, constipation, urinary hesitancy or spasm, choreic movements, and hypersensitivity reactions.[17]

Availability

Methadone, as an analgesic, may be prescribed by a physician and dispensed by a pharmacist as any other Schedule II drug under the Controlled Substances Act in the United States. When used for the management of addiction to heroin or other illicit drugs, its use is restricted to a limited number of clinicians and centers licensed by the Food and Drug Administration to ensure the necessary patient follow-up.[2]

Methadone is available in 5, 10, and 40 mg tablets, as well as 1 mg/ml, 2 mg/ml, and 10 mg/ml oral solutions and a 10 mg/ml injectable dosage form.[17] Oral methadone doses are approximately twice the intravenous dose, to account for decreased bioavailability.

Developing a Tapering Regimen

The process of discontinuing an opioid used for more than 5 to 7 days typically begins with a reduction of the total daily dose by approximately 10% every 12 to 24 hours. Tapering may be conducted more rapidly or slowly, depending on the patient's condition. If the patient exhibits symptoms of withdrawal, the dose is increased to the previous amount at which the patient was comfortable and the tapering process is stopped for 24 hours.

When substitution with an oral agent is desired, methadone may be initiated at an oral dose of 0.05 to 0.1 mg/kg. Administration every 6 hours for the first 24 to 48 hours is needed to provide accumulation of drug. After this initial period, the dosing interval should be lengthened to every 12 to 24 hours. During this time, the intravenous agent should be gradually discontinued. Once the patient is stable, the methadone dose may then be tapered by 5 to 10% every 24 to 48 hours, as tolerated.[1,3,4]

Calculation of an oral methadone dose equivalent to the patient's original opioid dose, using equipotency charts, is not advised. While many references give intravenous methadone equal potency to morphine, these mathematical

determinations do not take into consideration the differences in methadone pharmacokinetics with repeated dosing and the likelihood for incomplete cross-tolerance.[7] Many patients on high dose fentanyl or morphine will be adequately treated with only moderate doses of methadone. In a study of 38 adult cancer patients, the equianalgesic dose ratios for morphine to methadone ranged from 2.5:1 to 14.3:1, suggesting that after repeated use, methadone was significantly more potent than previously reported.[21]

Patient Assessment

Ongoing assessment of the patient for withdrawal is necessary during the tapering process. Several scoring systems are available which convert withdrawal symptoms into a numeric value for comparison.[1,10,11] One of the earliest and most widely used systems, the Neonatal Abstinence Scale developed by Finnegan and colleagues[10], has demonstrated a high degree of inter-rater reliability. Like many of the pediatric scoring systems, it was originally designed for the evaluation of neonates born to drug-addicted mothers. These scoring systems have now been adapted for use in patients of all ages with iatrogenic dependence.

At the University of Virginia Children's Medical Center, the method developed by Lipsitz is used.[11] First published in 1975, this method has been validated with neonatal controls and patients exposed to opioids prenatally. In the Lipsitz system, 11 categories are given scores of 0 to 1, 2, or 3 depending on severity. The highest possible score, 20, reflects severe withdrawal. Our goal is to maintain a score no greater than 4 during the tapering process. The timing of patient evaluation is individualized, with more frequent assessment early in the taper and during conversion to an oral agent.

Adjunctive Therapies

Clonidine, an alpha$_2$-agonist, has been used successfully for many years to control the symptoms of opioid withdrawal. It is believed to block the symptoms of withdrawal by decreasing the amount of norepinephrine released into the synaptic cleft and reducing the firing rate of noradrenergic neurons within the locus coeruleus. As described earlier, neuronal hyperactivity in this area may be associated with the development of withdrawal.[22,23] Like other agents substituted for opioids to control symptoms of withdrawal, such as barbiturates and benzodiazepines, clonidine may not completely ameliorate all symptoms of withdrawal. If used for iatrogenic opioid dependence, these agents are most appropriately used as adjuncts to an opioid tapering regimen.

Summary

Iatrogenic opioid dependency has become a frequently encountered issue in neonatal and pediatric intensive care units. Slowly decreasing the patient's exposure to opioids is the single best method to prevent or control symptoms of withdrawal. In children able to tolerate oral medications, methadone, a long-acting synthetic opioid, is a useful alternative for tapering regimens.

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Literature Review

Doxepin toxicity after topical use

While it is known primarily as an antidepressant, doxepin is also useful for its antihistaminic and antipruritic properties. Doxepin is available in the United States as a 5% topical cream. In this case report, topical doxepin was prescribed for a 5 year old girl with an eczematous rash. The child's caregivers mistakenly applied the entire 30 gram tube during the first 24 hours of therapy. The patient became obtunded after significant systemic absorption, but experienced a full recovery with supportive care. Zell-Kanter M, Toerne TS, Spiegel K, et al. Doxepin toxicity in a child following topical administration. **Ann Pharmacother 2000;34:328-9.**

d-Penicillamine dosing

In this retrospective study, the authors describe the efficacy and safety of a reduced dosage regimen of d-penicillamine for lead chelation. The results from 55 children were examined. A dose of 15 mg/kg/day was administered until a target concentration $\leq$ 15 mcg/dl was achieved. Mean length of therapy until reaching goal was 77$\pm$44 days, not significantly different than values reported previously with a higher dose. Shannon MW, Townsend MK. Adverse effects of reduced-dose d-penicillamine in children with mild-to-moderate lead poisoning. **Ann Pharmacother 2000;34:15-8.**

Efficacy of epoetin alfa in premature infants

A retrospective review of 44 patients was conducted to identify those factors associated with effective use of epoetin alfa for anemia of prematurity. Linear regression analysis revealed that postnatal age at onset of therapy and length of therapy were the most significant factors affecting success. An inverse relationship was also observed between reticulocyte count and number of transfusions required. Reiter PD, Rosenberg AA, Valuck RJ. Factors associated with successful epoetin alfa therapy in premature infants. **Ann Pharmacother 2000;34:433-9.**

Sinusitis review

This brief review covers the management of acute sinusitis in children. The authors provide an overview of the diagnosis and common causes of sinusitis, then devote the remainder of the article to the results of clinical trials comparing antibiotics. A comparison of average wholesale prices is included. Temple ME, Nahata MC. Pharmacotherapy of acute sinusitis in children. **Am J Health-Syst Pharm 2000;57:664-8.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 6/23/00:

1. Levetiracetam (Keppra®) was added to the Formulary as adjunctive therapy in the treatment of partial onset seizures in adults.
2. Entacapone (Comtan®) was also added to the Formulary. It is a reversible inhibitor of catechol-o-methyltransferase (COMT) used as adjunctive therapy for Parkinson's disease. Tolcapone (Tasmar®) was removed.
3. Cilostazol (Pletal®) was added for the management of intermittent claudication.
4. The restriction of rapacuronium (Raplon®) to the OR and VASC was amended to include use for intubation of patients in status epilepticus.
5. Dolasetron (Anzemet®), a $5HT_3$ antagonist, was rejected.

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