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Use of Etomidate for Pediatric Procedural Sedation

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Development of the ideal drug for procedural sedation in children remains an elusive goal. Etomidate has many of the desired characteristics for a sedative agent, including a rapid onset of action, a short duration of action, and a relatively mild adverse effect profile. Approved by the Food and Drug Administration (FDA) in 1982 for induction of anesthesia in adults, it has become a frequent choice for pediatric sedation and rapid sequence intubation (RSI) over the past decade.[1,2] In a recent retrospective study of pediatric procedures conducted in community emergency departments, etomidate was used in 16% of patients.[3] This issue of *Pediatric Pharmacotherapy* will provide an overview of recent studies conducted with etomidate in children and review its mechanism of action, pharmacokinetics, and adverse effects.

Mechanism of Action

Etomidate is a carboxylated imidazole sedative/hypnotic agent with no analgesic properties. Although the exact mechanism by which etomidate produces sedation is not fully understood, it is believed to enhance gamma-aminobutyric acid (GABA) neurotransmission. Etomidate has an onset of action within 1 minute and a duration of action ranging from 4 to 15 minutes.[4,5] Like most anesthetic agents, etomidate produces a transient reduction in cerebral blood flow with a resultant reduction in cerebral oxygen utilization.[6] It also produces a moderate reduction in intraocular pressure. Etomidate has little effect on cardiovascular or respiratory function, producing only a slight increase in arterial carbon dioxide tension with recommended dosing.[4,5]

Pharmacokinetics

After intravenous (IV) administration, etomidate is widely distributed, then undergoes rapid redistribution out of the central nervous system, producing a short duration of effect. It is metabolized in the liver, primarily to R-(+)-1-(1-pheynylethyl)-1H-imidazole-5-carboxylic acid, an inactive compound which is excreted in the urine. The average elimination half-life in adults is approximately 75 minutes. The elimination half-life is significantly prolonged in patients with hepatic dysfunction.[4,5]

Retrospective Studies

Several retrospective studies have assessed the efficacy and safety of etomidate in children. In 1995, McDowall and colleagues at Memorial Sloan-Kettering Cancer Center conducted an evaluation of their experience with etomidate, ketamine, and propofol for procedural sedation in children.[7] The authors evaluated 971 pediatric oncology patients (newborn to 19 years of age) treated during a one year period. The average dose of etomidate was 0.3 mg/kg given IV with fentanyl or sufentanil. The authors did not include information on efficacy, but evaluated the frequency of adverse effects. Etomidate produced vomiting in 10% of patients and hypoxemia in 2%, which was no different than the frequencies observed with ketamine and propofol. Etomidate produced less tachycardia and agitation (in 2% and 4% of patients, respectively) than the other sedatives, but was the only agent to produce myoclonus (in 18% of patients). Based on their experience, the authors concluded that etomidate was a safe alternative for children requiring brief procedural sedation.

Dickinson, Singer, and Carrion published a similar chart review in 2001.[8] They evaluated 53 children (mean age 9.7 years) who were undergoing fracture reduction. The mean total etomidate dose was 0.24 mg/kg, with a range of 0.13-0.52 mg/kg. In most cases, reduction was successful on the first attempt. Sixty-four percent of the patients were discharged from the ED after an average observation period of 94 minutes (range 35 to 255 minutes). The authors reported no major adverse effects and concluded that etomidate was a safe and effective choice in this setting.

Among the more recent papers, in 2006 Zuckerbraun and colleagues published a review

of 77 children given etomidate for RSI in a pediatric emergency department.[9] The mean age of the patients was 8.2±6.2 years. The mean etomidate dose was 0.31±0.07 mg/kg, with a range of 0.05 to 0.64 mg/kg. Adjunctive medications included lidocaine and atropine. Rocuronium was used to provide neuromuscular blockade in 76 of the children. Intubating conditions were judged to be good in 68 of the 69 patients who had documentation of assessment. Etomidate produced a 10% mean decline in systolic blood pressure. A decline in blood pressure of 20% or greater was noted in only 12 of the patients (17.4%) Based on their results, the authors suggested that etomidate may be a useful agent for RSI in children, but requires further study.

Comparison Trials

Etomidate has been compared to pentobarbital in two studies of children undergoing computed tomography (CT). In 2004, Kienstra and colleagues performed a prospective, randomized, double-blind trial of etomidate and pentobarbital in 61 children (6 months to 6 years of age) undergoing a head and neck CT.[10] Initially, patients were randomized to receive either 0.1 mg/kg etomidate or 1.25 mg/kg pentobarbital IV for up to 3 doses. After encountering a number of treatment failures (inadequate sedation) in the etomidate group, the dosing regimen was changed to an initial dose of 0.2 mg/kg followed by up to 2 doses of 0.1 mg/kg (total dose 0.4 mg/kg). The success rate for etomidate was 57% in the original group (0.3 mg/kg total dose) and 76% in the higher dose (0.4 mg/kg total dose) group (p=0.04). In contrast, the success rate in the pentobarbital group was significantly higher, at 97%. Etomidate, however, produced a shorter induction time (difference of the means 3.1 min, p=0.02) and a shorter duration of sedation (difference of the means 31.3 minutes, p<0.001). More parents of the children receiving etomidate reported that their children were at baseline at the time of discharge, and fewer parents in this group had concerns over their child's behavior after discharge.[10]

In 2007, Baxter and colleagues, working as the Pediatric Sedation Research Consortium, conducted a chart review in 26 institutions to compare patients who received etomidate and pentobarbital for sedation during CT.[11] A total of 842 patients between 6 and 83 months of age were evaluated. The median doses were 0.33 mg/kg etomidate (range 0.3-0.44 mg/kg) and 4 mg/kg pentobarbital (range 3.2-4.8 mg/kg). Sedation was classified as "not ideal" in 11 of the 396 pentobarbital patients and only one of the 446 etomidate patients. Duration of sedation was significantly shorter in the etomidate group (mean 32 minutes) than in the pentobarbital group (mean 144 minutes). Adverse effects, including oxygen desaturations, apnea, and prolonged recovery, were more common in the children receiving pentobarbital (4.5% versus 0.9%, p=0.005).

Etomidate has also been compared to midazolam for procedural sedation in children. In 2006, Di Liddo and colleagues published the results of a randomized, double-blind trial of 100 children between 2 and 8 years of age with displaced extremity fractures.[12] The children received 1 mcg/kg fentanyl and either 0.2 mg/kg etomidate or 0.1 mg/kg midazolam IV. Sedation was evaluated with the Ramsey Sedation Scale, with a score of 4 or more considered adequate sedation. Forty-six of the 50 children (92%) given etomidate achieved adequate sedation compared to only 18 of the 50 children (36%) given midazolam. Both time to induction and recovery were shorter in the etomidate group. Adverse effects were similar, except for more reports of injection site pain in the etomidate group, 46% versus 12% in the midazolam group, and myoclonus, reported in 22% of etomidate patients and in none of the midazolam patients.

Adverse Effects

Etomidate is generally well tolerated. In clinical trials, the most frequently reported adverse effects have been injection site pain and transient skeletal muscle movement. Pain at the injection site has been reported in approximately 20% of patients. It is generally self-limited and is less common when larger veins are used. Transient muscle movement, including myoclonus, has been in up to 30% of adult patients. The incidence of these movements is reduced by concomitant administration of an opioid or benzodiazepine.[4,5] Studies conducted in children have reported an incidence of myoclonus varying from 0 to 22%.[7-13]

In patients with a history of focal seizures, administration of etomidate may lower the seizure threshold.[4,5] In a review of 105 children (average age 3±2.9 years) who received etomidate for RSI, Guldner and colleagues identified four patients who had seizures after treatment.[13] All four had a known seizure disorder and presented to the emergency department with seizures. There were no cases of myoclonus, status epilepticus, or new-onset seizures after etomidate administration. Similar results were published in the Zuckerbraun paper, with brief seizure activity reported in 3 of the 77 children evaluated. All had a previous seizure

history and/or other potential sources for their seizure actuvity.[9]

Other adverse effects reported with etomidate administration include nausea, vomiting (in up to 10% of patients in pediatric studies), apnea and hypoxemia (in up to 2% of pediatric patients).[7-13] Etomidate may also produce changes in blood pressure or heart rate in up to 2% of pediatric patients. These effects tend to be associated with the administration of large doses or rapid injection.[2,4,5,11] With standard dosing, hemodynamic changes are uncommon. Sarkar and colleagues studied the cardiovascular changes after etomidate administration in 12 children undergoing cardiac catheterization.[14] The patients, ranging in age from 2 to 16 years, received a 0.3 mg/kg IV dose of etomidate. Compared to baseline, there were no significant differences after etomidate administration in right atrial, aortic, and pulmonary artery pressures, oxygen saturation, pulmonary artery pressure, or vascular resistance.

Effect on Cortisol Production

One of the most concerning adverse effects with etomidate is a reduction in plasma cortisol production resulting from blockade of 11-β-hydroxylation within the adrenal cortex. Impairment of adrenocortical function was initially reported in a study of critically ill adults by Ledingham and Watt in 1983.[15] Prolonged administration of etomidate or repeated dosing appears to increase the risk for adrenal suppression.

Studies conducted after a single etomidate dose have shown mixed results. In 1998, Donmez and colleagues evaluated plasma cortisol levels in children undergoing cardiac surgery.[16] Thirty children (ages 1 to 11 years) were randomized to receive either 0.3 mg/kg etomidate or 1 mg/kg ketamine for induction. All patients received 1 mcg/kg fentanyl. Plasma cortisol levels were measured at baseline, after induction, after cross-clamping, at the end of surgery, and 24 hours after surgery. Cortisol levels in the etomidate group were lower than baseline at all subsequent measurements. Levels were also significantly lower in the etomidate group than in the ketamine group at all points after treatment ($p < 0.05$). In these patients, where stimulation of the inflammatory response is often triggered by cardiopulmonary bypass, the authors concluded that the blunting of cortisol by etomidate may be a desirable effect.

Earlier this year, den Brinker and colleagues found a similar blunting of cortisol in children with meningococcal sepsis given a single dose of etomidate for RSI.[17] In this retrospective study, adrenocortical function was evaluated in 60 children with meningococcal sepsis treated between 1997 and 2004. Twenty-three of the children had received etomidate. The children given etomidate had significantly lower cortisol levels at 12 and 24 hours as well as higher ACTH and 11-deoxycortisol levels than the children who had not been treated. The authors concluded that a single dose of etomidate may suppress cortisol production for at least 24 hours in children, and potentially increase the risk for death in children with meningococcal sepsis.

While both of these studies demonstrated a reduction in cortisol levels, the clinical significance of this decrease remains controversial. In 2000, Sokolove and coworkers reviewed the records of 100 children under 10 years of age who received etomidate for RSI.[18] None of the children received corticosteroid replacement for suspected adrenal suppression during their hospitalization, supporting the authors' hypothesis that a single dose of etomidate would not routinely produce clinically significant adrenal insufficiency.

Dosing Recommendations

Etomidate is administered only intravenously. The usual dose for RSI is 0.1-0.3 mg/kg. For procedural sedation, a dose of 0.1-0.4 mg/kg may be administered.[4,5] In the pediatric studies published to date, the usual total dose for etomidate has ranged from 0.1 to 0.6 mg/kg.[7-13]

Availability and Cost

Etomidate is marketed as Amidate® (Hospira) and as a generic product. It is available as a 2 mg/mL injection in 10 and 20 mL single-use vials or ampules, and 20 mL pre-filled syringes. The average wholesale price (AWP) of a 10 or 20 mL vial or ampule ranges from $11 to $26. The AWP for a pre-filled etomidate syringe is approximately $30.[19]

Summary

Etomidate is a useful option for procedural sedation in children. It offers the advantages of a rapid onset and duration of action, as well as relatively few adverse effects. The potential for etomidate to block cortisol production appears to be its most significant drawback and limits its long-term use.

References

1. Zelicof-Paul A, Smith-Lockridge A, Schnadower D, et al. Controversies in rapid sequence intubation in children. Curr Opin Pediatr 2005;17:355-62.

2. Rothermel LK. Newer pharmacologic agents for procedural sedation of children in the emergency

department-etomidate and propofol. Curr Opin Pediatr 2003;15:200-3.
3. Sacchetti A, Stander E, Ferguson N, et al. Pediatric procedural sedation in the community emergency department: results from the ProSCED registry. Pediatr Emerg Care 2007;23:218-22.
4. Amidate® prescribing information. Hospira, Inc., May 2004. Available at www.drugs.com/pro/amidate.html (accessed 6/30/08).
5. Etomidate. *Drug Facts and Comparisons*. Efacts [online]. 2008. Available from Wolters Kluwer Health, Inc. (accessed 6/30/08).
6. Bramwell KJ, Haizlip J, Pribble C, et al. The effect of etomidate on intracranial pressure and systemic blood pressure in pediatric patients with severe traumatic brain injury. Pediatr Emerg Care 2006;22:90-3.
7. McDowall RH, Scher CS, Barst SM. Total intravenous anesthesia for children undergoing brief diagnostic or therapeutic procedures. J Clin Anesth 1995;7:273-80.
8. Dickinson R, Singer AJ, Carrion W. Etomidate for pediatric sedation prior to fracture reduction. Ann Emerg Med 2001;8:74-7.
9. Zuckerbraun NS, Pitetti RD, Herr SM, et al. Use of etomidate as an induction agent for rapid sequence intubation in a pediatric emergency department. Acad Emerg Med 2006;13:602-9.
10. Kienstra AJ, Ward MA, Sasan F, et al. Etomidate versus pentobarbital for sedation of children for head and neck CT imaging. Ped Emerg Care 2004;20:499-506.
11. Baxter AL, Mallory MD, Spandorfer PR, et al. Etomidate versus pentobarbital for computed tomography sedations: report from the Pediatric Sedation Research Consortium. Ped Emerg Care 2007;23:690-5.
12. Di Liddo L, D'Angelo A, Nguyen B, et al. Etomidate versus midazolam for procedural sedation in pediatric outpatients: a randomized controlled trial. Ann Emerg Med 2006;48:433-40.
13. Guldner G, Schultz J, Sexton P, et al. Etomidate for rapid-sequence intubation in young children: hemodynamic effects and adverse events. Acad Emerg Med 2003;10:134-9.
14. Sarkar M, Laussen PC, Zurakowski D, et al. Hemodynamic responses to etomidate on induction of anesthesia in pediatric patients. Anesth Analg 2005;101:645-50.
15. Ledingham IM, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. Lancet 1983;1(8336):1270.
16. Donmez A, Kaya H, Haberal A, et al. The effect of etomidate induction on plasma cortisol levels in children undergoing cardiac surgery. J Cardiothorac Vasc Anesth 1998;12:182-5.
17. den Brinker M, Hokken-Koelega AC, Hazelzet JA, et al. One single dose of etomidate negatively influences adrenocortical performance for at least 24h in children with meningococcal sepsis. Intensive Care Med 2008;34:163-8.
18. Sokolove PE, Price DD, Okada P. The safety of etomidate for emergency rapid sequence intubation of pediatric patients. Ped Emerg Care 2000;16:18-21.
19. 2007 Drug Topics Red Book. Montvale, NJ: Thompson Healthcare, 2007:228,415.

Pharmacology Literature Review

Inhaled tobramycin toxicity

The primary advantage of inhaled tobramycin for pulmonary infections is the ability to achieve adequate tissue concentrations with minimal systemic absorption. This case report describes increased serum tobramycin concentrations in an 80 day old infant (gestational age 32 weeks) who was treated with inhaled tobramycin, initially at a dose of 80 mg twice daily for 5 doses, which was increased to 300 mg once daily after no improvement. Two days after the high-dose regimen was started, a serum concentration of 10.6 mcg/mL was obtained and the drug was discontinued. Serum creatinine and urine output remained relatively unchanged. The authors recommend serum concentration monitoring and evaluation of renal function in all high-risk patients receiving inhaled tobramycin. This case also highlights the problems which may arise when treatment regimens developed in adults are extrapolated to infants. Abdulhamid I, Wise TL, Andrews S, et al. Elevated serum tobramycin concentrations after treatment with tobramycin inhalation in a preterm infant. **Pharmacotherapy 2008;28:939-44.**

Racial difference with ACE inhibitors

Several studies conducted in adults have suggested that angiotensin-converting enzyme (ACE) inhibitors are less effective in blacks than in whites. The authors of this paper conducted a meta-analysis of six trials conducted in children to determine if the same racial differences were present in younger patients. Stratification by race revealed that white children receiving high-dose therapy had significant reductions in both systolic and diastolic blood pressure from baseline ($p=0.003$ and $p<0.001$, respectively). In contrast, black children had no significant decline in either systolic or diastolic blood pressure. As in adults, black children may benefit from a different dosing strategy or alternative therapies to treat hypertension. Li JS, Baker-Smith CM, Smith PB, et al. Racial differences in blood pressure response to angiotensin-converting enzyme inhibitors in children: a meta-analysis. **Clin Pharmacol Ther 2008;84:315-9.**

Formulary Update

The Pharmacy and Therapeutics Committee did not meet during August. Their next meeting will be on 9/26/08.

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