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Midazolam: Use in the Pediatric Intensive Care Population

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Sedation is an integral component of patient care in the Pediatric Intensive Care Unit (PICU). There are numerous factors that contribute to anxiety and distress in critically ill children including separation from parents, unfamiliar faces, and invasive procedures. Patients can often be more effectively managed through sedation, resulting in improved patient outcomes. Benzodiazepines are commonly used for sedation in the PICU with midazolam typically being the agent of choice. This brief review will focus on midazolam and its use in the pediatric population.

Mechanism of Action

Midazolam is an imidazolebenzodiazepine that has central nervous system (CNS) depressant effects at all levels of the CNS including the limbic and reticular formation. It acts on the receptor complex of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter. Binding to this receptor complex facilitates the opening of chloride channels so that chloride can enter the cell and hyperpolarization can occur. This makes it difficult for excitatory neurotransmitters to depolarize the cell resulting in clinical effects like CNS depression and amnesia.[1]

Indications

Midazolam is currently indicated for sedation, anxiolysis, and amnesia preoperatively or during procedures, for induction of general anesthesia before other anesthetics are administered, for sedation of intubated and mechanically ventilated patients, and as a supplement to nitrous oxide and oxygen. Unlabeled uses include treatment of epileptic seizures and as an alternate for termination of refractory seizures.[2]

Use in Children

Midazolam has been administered by multiple routes in the pediatric population but is most commonly administered by continuous intravenous (IV) infusion in the intensive care setting. Rosen et al. performed a retrospective study to evaluate midazolam sedation in 55 PICU patients. Most of the patients were admitted with respiratory insufficiency. Sedation was initiated with a bolus of 250 mcg/kg over 3 to 5 minutes followed by a continuous infusion of 0.4-2 mcg/kg/min. The range could be increased to 4 mcg/kg/min after 48 hours if necessary. The mean infusion rate was 0.92 ± 0.54 mcg/kg/min. The median duration of sedation was 74 hours. Inadequate sedation occurred during less than 10% of the total infusion time. No adverse respiratory events were observed with the use of midazolam in this study. Older children reported amnesia for the duration of the midazolam infusion.[3]

Another study involving the pediatric intensive care population was performed by Booker et al. who evaluated the use of midazolam in 50 pediatric patients, age 6 months to 9 years, following open-heart surgery. Patients received a 200 mcg/kg bolus of midazolam prior to surgery after which an infusion was started at a rate of 2 mcg/kg/min and continued for the duration of the procedure. Upon returning to the PICU, patients were evaluated for recovery and then restarted on the midazolam infusion at an initial rate of 2 mcg/kg/min after a bolus of 200

mcg/kg. The patients were also begun on a morphine drip at that time. The midazolam infusion rate ranged from 1.6 to 9.4 mcg/kg/min. The mean duration of infusion after returning to the intensive care unit was 46.7 hours and the mean time to recovery was 102 minutes. Recovery time did not correlate with age or weight. Overall, 49 (98%) of the patients were ready for removal of the tracheal tube within 4 hours of stopping the infusion. Only one patient demonstrated irritation at the site of infusion. The authors concluded that a midazolam infusion, in conjunction with morphine, provided effective sedation. This continuous infusion regimen also proved to be more effective than intermittently administered sedative regimens.[4]

Pharmacokinetics/Pharmacodynamics

Midazolam is a water soluble agent that becomes lipid soluble at physiologic pH, allowing it to cross the blood brain barrier.[1] The mean absolute bioavailability of midazolam following IM administration is >90%. Oral midazolam undergoes significant intestinal absorption and first pass metabolism resulting in a bioavailability of ~36% in pediatric patients. The volume of distribution (V_d) of midazolam in pediatric patients, age 6 months to 16 years, receiving 0.15 mg/kg IV is 1.24 to 2.02 L/kg. Congestive heart failure, chronic renal failure, hepatic impairment, obesity, and advanced age all increase V_d. In addition, midazolam is 97% plasma protein bound, primarily to albumin.[5]

Midazolam is a short-acting benzodiazepine with onset of sedation typically occurring within 3 to 5 minutes after IV injection. Anesthesia induction occurs in 1.5 to 2.5 minutes when the drug is administered IV.[2] The duration of action is 2 to 6 hours with recovery of sedation usually beginning within 5 to 30 minutes.[1] Midazolam undergoes hepatic metabolism through the cytochrome P450 system to form multiple metabolites. The primary metabolite of midazolam, 1-α-hydroxymidazolam, is at least as potent as midazolam with a 20% affinity for the benzodiazepine receptor. It has a half-life of approximately 1 hour.[2,5] Midazolam metabolites are conjugated and eliminated renally. Incomplete development of hepatic and renal function in neonates leads to slower metabolism and prolonged elimination.[6,7] Pediatric patients have demonstrated similar or higher clearance rates (0.19 to 0.8 L/hr/kg) and similar or shorter terminal half-lives (0.78 to 3.3 hours) when compared to adults. Prolonged infusion may lead to metabolite accumulation.[5] Maintaining the lowest effective infusion rate will minimize accumulation.

Drug Interactions

Synergy occurs when midazolam is used in combination with anesthetics and other CNS depressants. An increased sedative effect may also be noted when midazolam is administered concomitantly with medications that inhibit CYP3A4 such as erythromycin, azole antifungals (e.g. itraconazole, fluconazole), diltiazem, verapamil, and cimetidine. Conversely, theophylline may decrease the sedative effect of midazolam.[2,5,9]

Flumazenil is a benzodiazepine antagonist that can be used to rapidly reverse the sedative and CNS effects of midazolam. It competitively inhibits midazolam activity at the recognition site on the GABA receptor complex.[5,8,9]

Adverse Effects

Intravenous midazolam has been associated with respiratory depression and respiratory arrest in both adult and pediatric patients. Continuous monitoring of respiratory and cardiac function should be performed during midazolam infusions and resuscitative equipment should be readily available. Midazolam should not be administered by rapid injection in the neonatal population due to reports of severe hypotension and seizures.[2,5]

Other adverse events commonly reported in the pediatric population include desaturation, apnea, hypotension, paradoxical reactions, hiccups, seizure-like activity, and nystagmus. The possibility of withdrawal exists in patients receiving midazolam, particularly over an extended period of time. Symptoms of withdrawal can include anxiety, tremor, restlessness, insomnia, confusion, and seizures. Midazolam should be gradually tapered to prevent the occurrence of withdrawal symptoms.[10,11]

Midazolam contains 1% benzyl alcohol as a preservative. Benzyl alcohol toxicity has been associated with gasping baby syndrome in premature infants. This was described in patients who received $\geq$ 98 mg/kg/day of benzyl alcohol in IV fluids, which is 20 to 50 times the maximum safe dose. However, the concentration of benzyl alcohol in midazolam is not sufficient to cause toxicity.[12]

Dosing Recommendations

Midazolam HCl for injection is available as 1 mg/ml and 5 mg/ml concentrations in multiple vial sizes. Midazolam HCl syrup is available in 118 ml vials that contain 2 mg of midazolam per ml. In the pediatric intensive care setting, the IV route is most often utilized. To induce sedation in neonates, continuous infusion at 0.5 mcg/kg/min is recommended for patients <32 weeks gestational age, and 1 mcg/kg/min for those patients ≥32 weeks gestational age. Neonatal patients should not receive a loading dose.

To induce sedation, anxiolysis, and amnesia in the pediatric population, IV, IM, and oral routes can be utilized. IM administration is usually effective at 0.1 to 0.15 mg/kg, up to 0.5 mg/kg. Intravenous continuous infusion should be preceded by a loading dose of 0.05 to 0.2 mg/kg over 2 to 3 minutes. Continuous infusion should be initiated at a rate of 0.06 to 0.12 mg/kg/h (1 to 2 mcg/kg/min). Rate can be adjusted and supplemental doses may be necessary to achieve the desired clinical effect. Oral midazolam syrup is indicated as a single dose of 0.25 to 1 mg/kg with a maximum dose of 20 mg.[2,5]

Summary

Midazolam is a short acting benzodiazepine that can provide safe and effective sedation in the pediatric intensive care setting. Its pharmacological properties contribute to effective individual management and improved patient outcomes compared to other agents within this therapeutic class. While midazolam is more expensive than other benzodiazepines, its shorter elimination half-life and water solubility are significant benefits in pediatric patients.

References

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Literature Review

Clarithromycin pharmacokinetics

The pharmacokinetic profile of clarithromycin, a macrolide antibiotic, is featured in this review. The author discuses differences between children and adults, as well as the pharmacokinetics of clarithromycin in patients with hepatic or renal disease. Special consideration is given to the impact of clarithromycin drug interactions involving cytochrome P450 3A enzymes. The article also includes an extensive bibliography, with over 100 references cited. Rodvold KA. Clinical pharmacokinetics of clarithromycin. **Clin Pharmacokinet 1999;37:385-98.**

Hydroxyurea during pregnancy

Hydroxyurea is increasingly being used in the management of patients with sickle cell disease. It is currently classified as a pregnancy category D drug by the Food and Drug Administration, meaning that evidence of fetal risk exists. Despite this warning, there have been several reports of women who have become pregnant while taking hydroxyurea. The authors present two cases of women who were exposed to hydroxyurea during the first trimester. In both cases, the drug was discontinued as soon as the pregnancy was diagnosed, at approximately 4 and 5 weeks gestation. Both patients delivered healthy infants. Additional case reports are reviewed, that together with the two cases presented, suggest that hydroxyurea may not be as teratogenic as previously thought. The authors suggest that further research and follow-up of exposed children are necessary before making any further claims of safety, but these cases are welcome news for practitioners discussing this issue with pregnant patients. Byrd DC, Pitts SR, Alexander CK. Hydroxyurea in two pregnant women with sickle cell anemia. **Pharmacotherapy 1999;19:1459-62.**

Methylphenidate tolerance

This series of trials was designed to evaluate different methods of dosing methylphenidate and to identify tolerance in test subjects. Three methods of dosing were tested: twice daily using regular release methylphenidate, a bolus dose followed by a maintenance dose, and an ascending regimen with the higher dose at the end of the day. Thirty-eight children (ages 7 to 12 years) with attention deficit hyperactivity disorder were enrolled in this four-period, double-blind, randomized crossover study. The testing involved a classroom simulation from 7 AM to 6 PM on 4 consecutive Saturdays. Scores from standardized tests revealed that the twice daily method provided the best response. The authors concluded that bolus dosing early in the day was unnecessary and that close spacing of doses led to the development of drug tolerance and declining test scores. Swanson J, Gupta S, Guinta D, et al. Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. **Clin Pharmacol Ther 1999;66:295-305.**

Single isomer drugs for asthma

With the recent release of levalbuterol, there has been considerable interest in the role of single isomer drugs in the management of asthma. Racemic albuterol, a mixture of the two stereoisomers, has been used successfully in the treatment of children with asthma for many years. While racemic albuterol has many benefits, it has been associated with a significant number of adverse effects, including central nervous system stimulation, hypertension, and hypokalemia. Levalbuterol, the active single isomeric form of albuterol, appears to provide a more potent bronchodilator effect with fewer toxicities. The author of this review provides a brief background on the treatment of asthma and the use of racemic albuterol. He then focuses the remainder of the article on beta agonists and the potential benefits of levalbuterol. This review will be useful to those who are unfamiliar with this new drug entity. The only failing of the review is a lack of cost-benefit analysis. Blanchard NR. The role of single isomer drugs in the treatment of childhood asthma. **J Pediatr Pharm Pract 1999;4:258-63.**

Second Edition of PMET Now Available

A second edition of The Pediatric Medication Education Text (PMET) has recently been published by two members of the *Pediatric Pharmacotherapy* staff, in conjunction with the American College of Clinical Pharmacy. This resource is targeted at health care providers who counsel the parents of young children on medications. The second edition of the book features instructions for administering 230 commonly prescribed medications.

The single page instructions are meant to be photocopied and given to parents by physicians, nurses, or pharmacists. The text is written at approximately the 6th grade reading level and uses a standard question and answer format. Both English and Spanish versions are provided for each drug. PMET meets all current Food and Drug Administration regulations for written medication information. A searchable CD-ROM version is under development.

PMET is available for $40. For more information or to place an order, contact the American College of Clinical Pharmacy by phone at (816) 531-2177, by fax at (816) 531-4990, by mail to ACCP, 3101 Broadway, Suite 380, Kansas City, MO 64111, or through their website at http://www.accp.com.

Formulary Update

The actions of the Pharmacy and Therapeutics Committee during their December meeting were presented in the previous issue. The next meeting of the P&T Committee will be 1/28/00.

If you have any comments or suggestions for future issues, please contact us at Box 274-11, UVA Medical Center, Charlottesville, VA 22908 or by phone (804) 982-0921, fax (804) 982-1682, or e-mail to mlb3u@virginia.edu.