Benzodiazepines for Sedation in Infants and Children

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Abstract

Benzodiazepines are commonly used to provide sedation for infants and children undergoing intensive care or diagnostic and therapeutic procedures in a variety of clinical settings. This chapter focuses on Midazolam as representative of this class of drug. Midazolam provides sedation by altering the neuroinhibitory pathway mediated by gamma-aminobutyric acid. It is primarily metabolized by the hepatic cytochrome P450 enzyme subfamily and eliminated via the renal route. Plasma clearance of midazolam is affected by the degree of hepatic and renal immaturity in the newborn period. In addition, there is a large inter-individual variability in midazolam metabolism in neonates and children, leading to heterogeneity in drug handling.

Pediatric patients, especially neonates, are therefore susceptible to adverse effects associated with the use of midazolam. Transient neurologic, respiratory and cardiovascular reactions have been reported. Although most appeared to be transient, some studies suggest that neonates exposed to midazolam may have longer-term adverse neurodevelopmental effects. Furthermore, in review of literature to date, even though midazolam infusion is efficacious in sedating critically ill infants and children undergoing intensive care, the use of midazolam for procedural sedation in the pediatric population may be less efficacious than alternatives such as ketamine and may not be appropriate in all clinical circumstance. Therefore, until further research is done on the safety and efficacy of midazolam administration in infants and children, cautious use of this medication in this population is recommended.

Introduction

The provision of medical care for infants and children often requires diagnostic and therapeutic procedures, which are increasingly performed outside the operating room setting. These procedures are frequently associated with pain and stress. Stress is defined as "a physical, chemical, or emotional factor that causes bodily or mental tension and may be a factor in disease causation", and the response to stress can be directly related to the event causing stress, or can be non-specific. Despite the advances in pain assessment and management, the use of sedation to alleviate non-painful stress in infants and children continues to be relatively limited. This is partly due to the subjectivity of measuring stress, the relative inability of young children to verbalize stress, and the fear of untoward complications associated with sedative use.

However, the completion of most diagnostic and therapeutic procedures in infants and children often depends heavily on the success of sedation. In neonates undergoing intensive care, evidence also suggests that adequate sedation during invasive procedures such as mechanical ventilation may decrease stress and prevent complications such as pneumothoraces and intracranial hemorrhages. The goals of providing sedation to infants and children are to (a) minimize discomfort directly caused by the procedure; (b) decrease anxiety and negative psychological effects associated with the procedure, and (c) facilitate the performance of the procedure by controlling behavior. These goals must be achieved without compromising the safety of the patients during the procedure, and must return them to the state of health prior to the administration of sedation. The American Academy of Pediatrics has published guidelines for proper management and monitoring of children during sedation. These guidelines suggest the universal principles of pre-sedation medical evaluation with special attention to airway examination and preparation prior to the procedure, skilled personnel to administer appropriate drugs and monitoring during sedation, and observation post-sedation prior to discharge to ensure the safety and effectiveness of the sedation.

In older infants and children, a variety of pharmacologic agents have been used to provide sedation. These include benzodiazepines, barbiturates, chloral hydrate and phenothiazines. Of the benzodiazepines, midazolam and, to a lesser degree, lorazepam are most commonly used for sedation of pediatric patients. In this article, the pharmacological properties of benzodiazepines, and, more specifically, the developmental responses to benzodiazepines will be considered. The occurrence of various adverse effects associated with benzodiazepine use will also be discussed. Due to the vast amount of literature on the use of midazolam in infants and children, this chapter will consider the clinical applications of midazolam as representative of this class of drug in a variety of clinical settings, such as mechanical ventilation in intensive care units, preoperative sedation, sedation for ambulatory and emergency procedures, and treatment of opioid withdrawal.

Pharmacology of Benzodiazepines

The benzodiazepines modulate cerebral function in a dose-dependent fashion, producing varying degrees of neuronal inhibition ranging from anxiolysis, sedation, to anesthesia. This class of drug is also known for its effects of anterograde amnesia, muscle relaxation, and anti-convulsion; however, it does not provide analgesia. Considerable work has been done in order to understand the pharmacological properties and the mechanisms of cerebral effects of the benzodiazepines. Evidence suggests that benzodiazepines act on specific receptors and alter the pathway...
mediated by gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system (CNS). Once activated, the benzodiazepine receptors enhance the effectiveness of GABA-ergic neurotransmission by facilitating ion movement across the subsynaptic chloride channels, leading to a dampening of neuronal excitation. The central benzodiazepine receptors are high affinity binding sites, which are associated with GABA receptors in the neuronal membranes. The areas of the CNS with the highest density of benzodiazepine receptors include the cerebral cortex, the cerebellum, the limbic system, and the basal ganglia. The functionality of each receptor relies on the presence of three classes of subunits: alpha, beta, and gamma. Variants exist within each class of subunit, leading to a certain degree of heterogeneity of benzodiazepine receptors within the CNS. This may partly explain the differences in clinical effects of the various benzodiazepines.

The Effect of Age

As with many other classes of drugs, the pharmacodynamic and pharmacokinetic properties of benzodiazepines vary with age. Studies comparing the responses to midazolam between elderly and younger adult patients showed that, even though there is no significant age-related difference in pharmacokinetic properties, the more pronounced clinical effects of midazolam in elderly patients could be explained by differences in pharmacodynamic response. Similarly, in clinical studies, it has been shown that neonates, particularly those born preterm, also have a higher neurologic sensitivity toward the benzodiazepines compared with older infants and children. However, from limited data, it has been shown that such difference in response to benzodiazepines may be related to the developmental ontogeny of benzodiazepine metabolism, leading to observed variations in pharmacokinetic parameters.

Benzodiazepine Pharmacokinetics in Infants and Children

In neonates and children, particularly those receiving intensive care, midazolam, amongst all benzodiazepines, has been most often prescribed and studied. Midazolam has long been considered the ideal sedative for neonates and children, particularly those receiving intensive care. Its water solubility presents a unique advantage over other benzodiazepines in this population for its fast onset and short duration of action, and rapid rate of receptor association-dissociation and elimination. The dosage of benzodiazepines administered to neonates and children should be calculated based on milligram per kilogram of body weight.

Pharmacokinetics

After administration, midazolam is extensively metabolized through hepatic microsomal oxidation and glucuronidation; its major active metabolite, 1-hydroxymidazolam, is then eliminated via the renal route. In the liver, midazolam is biotransformed by the cytoschrome P450 3A (CYP 3A) enzyme subfamily. In adults, it has been shown that plasma clearance of midazolam correlates with level of CYP 3A 4 and CYP 3A 5 activities. Within the first two weeks of birth, as a result of the ontogeny of the hepatic CYP 3A 4 and 5 activity, a considerable reduction in plasma clearance of midazolam, in the order of 1.5 to 5 times, has been demonstrated. In addition, a significant heterogeneity within individual neonates in the maturational rate of CYP 3A activity exists. Coinciding with a reduced hepatic metabolism is the variability in renal maturation, which also shows inter-individual variations, and could potentially lead to a decrease in renal elimination of the active metabolite of midazolam.

Together, these two age-dependent factors contribute significantly to the delay in plasma clearance of midazolam in this population compared with older infants, children, and adults. These findings were confirmed by population pharmacokinetic studies of midazolam in the neonates.

Furthermore, inter-individual variability in midazolam metabolism has been demonstrated. The heterogeneity in illness severity, and the multiple comorbid conditions, such as sepsis and hypotension, may have partly contributed to such variability. As midazolam clearance is dependent on adequate perfusion of the major organs, changes in hemodynamic status, as seen in conditions such as sepsis or patent ductus arteriosus, and the correction of these conditions, may significantly affect the clearance of midazolam. The prenatal exposure of betamethasone, which may induce activity of the CYP 3A enzymes, may influence the clearance of midazolam as well.

In children, there also appeared to be a large inter-individual variability in midazolam pharmacokinetic parameters. Furthermore, the uncertain contribution of the active metabolite, and the nature of the critical illnesses may also contribute to the heterogeneity in drug handling in the population studied. Contrary to neonates, however, studies have consistently shown that the plasma clearance of midazolam and lorazepam in children is higher than that in adults, which was thought to be related to a higher metabolic turnover and/or a smaller volume of distribution in the former age group.

Routes of Administration

Midazolam is currently available in intravenous (IV) and intramuscular (IM) forms, and oral syrup has recently become available for use in ambulatory settings. In addition, there have been reports of the IV preparation being administered through other transmucosal routes, such as rectal (PR), sublingual (SL) and intranasal (IN) routes in children.

The IM route of midazolam administration is quite comparable to the IV administration, owing to the over 90% bioavailability of midazolam by this route. Whereas lorazepam has similar characteristics, other more lipophilic benzodiazepines such as diazepam are much more variable in systemic absorption after IM injections compared to midazolam.

In a dose-finding study, the dose of oral midazolam required for sedation was at least three times the usual intramuscular dose of 0.15 mg/kg. Overall, the time to reach peak midazolam serum concentration is significantly longer after an oral dose, compared with that given by IM or rectal routes. However, serum concentration stayed at above the therapeutic level for up to 2 hours with the oral dose of 0.45 mg/kg. In addition, adolescents, similar to young adults, were found to have a much slower absorption rate compared with young children. Because of first pass effect, the bioavailability of oral midazolam is considerably lower than that of IM midazolam, although results from studies were highly variable. The clearance rate and elimination half-life in children seemed to be shorter than that of adults, although these disposition characteristics were also found to be highly variable and not necessarily related to age or dose of midazolam administered.

Despite the effects of first pass metabolism and the variability of rectal pH affecting absorption of midazolam in children, PR administration of midazolam has been shown to have a relatively fast onset of action. At a dose of 0.35 mg/kg, plasma concentration reaches an adult sedative level within minutes, and the