

Paradoxical reaction to midazolam in children

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Midazolam is a short-acting benzodiazepine commonly used by anesthesiologists as a preoperative anti-anxiety medication or supplemental sedative in regional anesthesia and monitored anesthesia care. Moreover, a recent increase in the use of midazolam in children has been observed outside of operation rooms, such as mechanical ventilation in the intensive care unit, endoscopy, interventional angiography, and magnetic resonance imaging. The rapid onset, short duration, and anterograde amnesia are major reasons for midazolam to be considered a pre-procedural medication for children.

The administration routes for midazolam in children may vary, such as intravenous (IV), intramuscular, oral, and buccal; the most common method used by anesthesiologists is IV. The IV route in children is safe and effective for most cases, but sometimes unexpected reactions occur. These may include hallucination, disorientation, uncontrollable crying or verbalization, agitation, restlessness, involuntary movement, self-injury, and aggressive or violent behavior, which sometimes requires restraints. The generic term for such reactions is a paradoxical reaction (or a disinhibitory reaction). These paradoxical reactions may vary in different reports, but mostly manifest within 5 minutes of midazolam IV administration. Almost all of these reactions are preceded by a brief period of apparent, definite, and transient sedation, after which the child is suddenly aroused and cries in a state of intense agitation [1].

These paradoxical reactions have not gained attention among anesthesiologists, because they do not greatly affect the vital signs and are often not recalled due to the amnesia-producing properties of the drug itself. However, in cases of aggressive behavior, when the children do not recognize their parents, and

become uncontrollably agitated, the understanding of the causal factors and resolution is essential to reduce the effect of the shock on the children and even on the parents. Administration of additional midazolam, based on the judgment that its effect is insufficient, may be a major factor in worsening the situation.

Although the exact mechanism of such paradoxical reactions is unknown, several theories have been suggested. First, the inhibitory action of benzodiazepines may cause a loss of cortical restraint in some patients, leading to excitement [2]. This mechanism is similar to the effect of alcohol consumption in some subjects. Second, benzodiazepines have also been found to reduce serotonin neurotransmission [2]. A decrease in serotonin concentrations may precipitate aggressive behavior.

With regard to the risk factors for these reactions, dose of midazolam, younger age, gender, psychological background, alcohol abuse, and genetic background have been reported. Especially, genetic variability in the benzodiazepine receptors of GABA_A channels resulting from the multiple allelic forms may lead to abnormal pharmacodynamic responses in some [3]. In this issue of the Korean Journal of Anesthesiology, Shin et al. [4] report a study about paradoxical reactions to midazolam in preschool aged children. This study was performed by dividing the patients into four groups, based on age and midazolam dose (1–3 years, 0.05 mg/kg; 1–3 years, 0.10 mg/kg; 3–5 years, 0.05 mg/kg; and 3–5 years, 0.10 mg/kg). The incidence of paradoxical reactions was found to be related to younger age (odds ratio [OR] = 5.3) and higher dose of midazolam (OR = 3.0).

These reactions are not likely to resolve spontaneously over time and some sort of rapid tranquilization is necessary. As mentioned, administration of additional midazolam is

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not effective, but rather leads to delayed awakening. Low-dose ketamine (0.5 mg/kg), propofol, physostigmine, and haloperidol have been reported to be effective. Furthermore, recent reports have shown that flumazenil is effective for treatment of paradoxical reactions. Flumazenil is a competitive benzodiazepine antagonist with quick onset (1–2 min). Most paradoxical reactions in adults are treated successfully with 0.3–0.5 mg IV flumazenil, while retaining sedation and amnesia [5]. For pediatric patients, 0.01 mg/kg is usually effective [2]. However, it should be used cautiously if the patient has any history of cardiac arrhythmia or seizures controlled with

benzodiazepines [2].

Paradoxical reactions have a low prevalence and are not life threatening. However, considering that anesthesiologists' participation has been increasingly required for the pediatric sedation outside of operation rooms and that midazolam is the drug of choice, problems related to its use should be considered seriously. Early recognition and rapid pharmacological intervention are important to avoid aggravating the situation. In addition, thorough research on definite cause and ideal resolution is necessary in the future.

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