Title: Postoperative Paradoxical Reaction to Midazolam Treated with Intranasal Flumazenil

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Introduction: Although uncommon, midazolam-induced agitation, confusion, crying, and combative behavior occurs in 1 – 2% after premedication[1-3]. Postoperative agitation, however, is much less often associated with midazolam. We describe a child who developed both preoperative and postoperative agitation and where nasal administration of flumazenil, 4 hours after the midazolam preoperative dose, resulted in quick resolution of symptoms.

Case Report: A 2 year old, 12.3 kg, previously healthy boy, scheduled for circumcision, became severely agitated 45 minutes after being given oral midazolam, 0.5 mg/kg. He started screaming, writhing, and became quite aggressive. Anesthesia was induced with sevoflurane via mask, a peripheral i.v. and an LMA were placed, and sevoflurane was switched to isoflurane (1.5% on end-tidal monitoring) in air/oxygen (FIO2 = 0.4). For analgesia, the patient received a penile block with 0.25% bupivacaine, 1.5 mL, acetaminophen, 600 mg rectally, and two doses of fentanyl, 10 mcg i.v. The intraoperative course was uneventful. The LMA was removed under deep anesthesia, the patient was given propofol, 10 mg i.v. and then taken to the recovery room. He awoke 45 minutes later both calm and cooperative. Vital signs were stable and showing no signs of pain or discomfort, he received no other medications. Sixty minutes after surgery he was given a popsicle and taken to his parents. Shortly thereafter, over 3 hours after receiving midazolam, he again became severely agitated and progressively worsened over the next 10-15 minutes. Attempts to comfort him, including food, drink, and parental soothing, were unsuccessful. After 20 minutes, the patient was given propofol, 20 mg, and went to sleep in his mother's arms. The intravenous catheter was removed while he slept in the hope that this would decrease his agitation. He awoke a few minutes later and over the next 5 minutes returned to his previous agitated state. After another 20 minutes, flumazenil, 12 mcg/kg, was given nasally. Within 15 minutes the patient stopped thrashing and screaming then smiled and wanted a popsicle. He left the hospital 1 hour later. A follow up call approximately 7 hours after discharge revealed the patient had continued to do well, was pain-free, and had been acting like his normal self, playing with his brother around the house.

Discussion: Although our patient's behavior was similar to what can be seen during sevoflurane awakening there were some important differences: there was a long interval between awakening and the onset of agitation; there was no change after a "propofol nap;" and the symptoms presented 90 minutes after discontinuing the anesthetic. Also, this patient had an identical reaction preoperatively after midazolam premedication. Although the rapid improvement after flumazenil administration does not conclusively demonstrate that the agitation was caused by midazolam, it appears highly likely. Midazolam should be considered a possible cause of post-operative agitation even several hours after its administration.

References

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