



## Clinical Communications: Pediatrics



### SUCCESSFUL FLUMAZENIL REVERSAL OF PARADOXICAL REACTION TO MIDAZOLAM IN A CHILD

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□ **Abstract—Background:** Greater attention to and management of anxiety and pain in pediatric patients signifies a healthy evolution in the care of children in emergency departments (EDs). Interventions to address such distress may involve unanticipated adverse effects. Midazolam, a benzodiazepine commonly administered to children for anxiolysis, may precipitate paradoxical agitation and delirium, a rare but alarming effect that warrants prompt identification and treatment. **Case Report:** The case presented is that of a 4-year-old girl who received oral midazolam and developed a paradoxical reaction, which was reversed successfully with flumazenil. This is the first such case report in an ED involving a child. **Why Should an Emergency Physician Be Aware of This?:** Emergency physicians must stay abreast of the adverse and unintended effects of the treatments provided. The literature on benzodiazepine-induced paradoxical reactions is reviewed, and flumazenil as well as other treatment options and anxiolytic alternatives are presented. © 2015 Elsevier Inc.

□ **Keywords—**paradoxical reaction; midazolam; flumazenil; anxiolysis

#### INTRODUCTION

The care of pediatric patients in emergency department (ED) settings has evolved, with greater attentiveness to the anxiety engendered in children that such care often comprises. Forceful physical restraint termed “brutacaine”

has been used throughout the history of acute pediatric care, but more humane and sensitive approaches are needed (1,2). Behavioral strategies and distraction techniques employed by health care providers and, when available, Certified Child Life Specialists, may aid in the accomplishment of minor procedures, but certain scenarios are not amenable to nonpharmacologic methods.

Procedural sedation and analgesia (PSA) is a key component of ED pediatric care, commonly provided for complex laceration repair, abscess incision and drainage, burn debridement, and fracture reduction. Pharmacologic anxiolysis is typically sufficient for less painful and complex procedures. The American Society of Anesthesiologists defines minimal sedation or anxiolysis as “a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and physical coordination may be impaired, airway reflexes and ventilatory and cardiovascular functions are unaffected” (3). Numerous agents have been administered through various routes to achieve this state, but midazolam is commonly given.

Any PSA agent has the potential to result in oversedation or other untoward effect. The following case is the first report known to present the successful flumazenil reversal of a paradoxical reaction (PR) induced by oral midazolam in a child in an ED setting and reviews treatment options for pharmacologic anxiolysis gone awry.

## CASE REPORT

A 4-year-old girl presented to the ED with a laceration to the inner aspect of her upper lip on the left, resulting from a fall. The patient had been accidentally pushed by a playmate, causing her to fall and strike her upper lip on the metal step of a ladder. There was no loss of consciousness or vomiting. After a brief period of crying, the patient's baseline personality and behavior returned to normal. The injury occurred 2 h prior to presentation; the patient's last oral intake was 3 h prior to arrival.

Immunizations were complete for age. Past medical history was positive for asthma, eczema, and obesity. Medications included inhaled albuterol as needed for wheezing. Surgical history was positive for adenotonsillectomy at age 4 years for obstructive sleep apnea. There were no adverse reactions to general anesthesia. Her development was normal, with no behavioral or psychiatric disorders.

On physical examination, the patient was an alert, cooperative, obese female. Glasgow Coma Scale score was 15. Vital signs were: heart rate 86 beats/min, respiratory rate 16 breaths/min, blood pressure 135/71 mm Hg sitting, oral temperature 36.6°C, room air oxygen saturation 99%, and weight 41.8 kg. The patient had a normal external cranial examination and a normal neurologic examination without any evidence of intracranial injury. Cervical spine was nontender with full range of motion. Oropharyngeal examination proved a challenge, as the child grew tearful and uncooperative with intraoral inspection. There was a 1½–2-cm jagged laceration to the mucosa of the inside of the left upper lip, which did not cross the vermilion border but was gaping. The laceration did not extend into submucosal tissue. The teeth, gums, and remainder of the oral mucosa were normal. There was no residual tonsillar tissue, but the child's tongue was large and her neck short. The remainder of the examination was normal.

Considering the length and gaping quality of the laceration, sutured repair vs. observation options were reviewed with the parents. Parents elected sutured repair. Oral midazolam and local anesthesia with injectable lidocaine were decided for pain management. Midazolam 10 mg (0.24 mg/kg) was administered orally. Fifteen minutes after midazolam and prior to preparatory activities for lidocaine injection or laceration repair, the patient began to flail, kick, scream, and writhe. Her heart rate increased to 164 beats/min and respiratory rate increased to 34 breaths/min. Blood pressure measurement attempts were unsuccessful, but room air oxygen saturation remained 100%. Efforts to calm the patient through verbal reassurance by parents, nurses, and physicians were unsuccessful. The patient was assessed as having a PR to

midazolam. Vascular access was established 8 min after PR onset and flumazenil 0.2 mg (~0.005 mg/kg) was rapidly administered intravenously in the next minute. The patient immediately began to calm, and over the next 15 min had completely returned to baseline behavior and personality. Heart rate decreased to 105 beats/min and respiratory rate decreased to 20 breaths/min. After 1 h, the patient was active, oriented, and playful.

The risks of PSA with ketamine were decided to outweigh the advantages when accounting for the patient's obesity, unfavorable oropharyngeal anatomy, short neck, and the oral location of the laceration. After another hour of further observation, the patient was discharged with instructions to make an appointment with her primary care physician in 2 days for recheck, and to return to the ED sooner if there were acute behavior changes or signs of infection or bleeding. The parents were advised to notify future physicians caring for their daughter that midazolam had resulted in PR and should be avoided. The patient did not return to the ED for any complication. At her follow-up appointment with her primary care physician, the laceration was noted to be healing well.

## DISCUSSION

The potential for such adverse effects as that described above cannot be overstated. In the ED in which the above case occurred, midazolam is administered orally for the purpose of anxiolysis on a daily basis. Furthermore, midazolam and other benzodiazepines (BZDs) are prescribed in pediatrics for a number of other indications: acute anticonvulsant therapy in the seizing patient, chemical restraint in the agitated psychiatric patient, procedural as well as postintubation sedation, and occasionally for muscle relaxation as well. As such, the emergency physician should be facile with the pharmacology and clinical actions of this class of drugs.

Chemically, BZDs are highly lipophilic, with variably rapid access across the blood–brain barrier (4,5). BZDs are specifically active on inhibitory neurotransmitter gamma-aminobutyric acid (GABA) type A chloride receptors, enhancing GABA activity and promoting neuronal depression through reduced cerebral metabolism and cerebral blood flow (5,6). Clinical BZD effects are observed in dose- and concentration-dependent relationship: anxiolysis and anticonvulsant activity is accomplished at lower doses, with sedation, amnesia, and hypnosis becoming apparent as dose and concentration are pushed higher. Anxiolytic BZD dosing has little clinically significant effect on cardiorespiratory function, but higher parenteral dosing results in decrease in upper airway muscle tone, depressed ventilatory

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