CASE REPORTS

Severe Withdrawal Syndrome Possibly Associated With Cessation of a Midazolam and Fentanyl Infusion

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A 40-month-old child was sedated with a fentanyl and midazolam infusion for 7 days. After the drugs were discontinued he became unresponsive and globally aphasic, and had marked thrombocytosis. He was hospitalized for 4 weeks, during which time his motor and cognitive status slowly improved, and had almost returned to baseline at time of discharge. Severe neurologic abnormalities have been reported with midazolam and fentanyl, administered separately or together, and seem to be a consequence of a withdrawal syndrome. Of interest, this patient had a reactive thrombocytosis at the time of onset of the withdrawal syndrome, and his decreased platelet count coincided with the return to normal cognitive and motor status. Based on this experience and other reports, we believe midazolam-fentanyl combination should be administered with caution.
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Midazolam and fentanyl are commonly given in combination for sedation to patients requiring surgery or intensive care. This combination is synergistic for analgesia and sedation associated with anesthesia.[1-5] It may have induced severe neurologic abnormalities in a young child.

Case Report

A 40-month-old, 15.4-kg boy was admitted to Children's Hospital of Michigan in January 1992 for an elective tracheolaryngoplasty. The child had normal mental development and no known drug allergy. His medical history included Pfeiffer syndrome with craniofacial stenosis, and recent tracheostomy. Tracheolaryngoplasty was

performed successfully on January 8, 1992, in what was considered an uneventful procedure. The patient was anesthetized during surgery with halothane. Other drugs given during surgery were gentamicin 40 mg in 500 ml normal saline for irrigation, 0.5% lidocaine with epinephrine 1:200,000, and cefazolin 300 mg intravenously 1 hour before the end of the procedure. The patient was paralyzed with pancuronium 1.5 mg intravenously every 10 minutes on the day of surgery; the next day this was replaced with vecuronium 1.5 mg every hour as needed for 6 days to allow for healing.

During this period, sedation and analgesia were provided with infusions of fentanyl 1 µg/kg/hour and midazolam 0.5 µg/kg/minute. The midazolam dosage was increased to 2 µg/kg/minute during the week due to the development of tolerance. Between January 10 and 15, the child experienced several episodes of hypotension that required dopamine and dobutamine infusions to maintain perfusion. The dosages were dopamine 7.5 µg/kg/minute between January 10 and 15, and dobutamine 5 µg/kg/minute from January 14 to 15. Four doses

of dexamethasone 5 mg intravenously were also ordered between January 15 and 16. During that time the midazolam and fentanyl infusion rates were decreased by 50%, and the child was observed closely for 14 hours. The infusion was discontinued early on January 17.

The child's recovery from sedation and analgesia was classified as uneventful. He awoke apparently normal, and could nod his head and answer questions. Although never documented by hospital personnel, on that day the boy apparently complained to his parents of temporary blindness. He was described as being agitated between January 16 and 18, and received secobarbital 50 mg once and chloral hydrate 225 mg twice for sedation. The child was seen to play with toys on the evening of January 17 and was discharged the next morning.

Once home, the family stated that the boy became unresponsive and lay in his bed in a fetal position, and was unable to recognize his parents. He was readmitted to the hospital the same day he was discharged.

On January 18 and 19 the patient was unresponsive, had nonpurposeful movements, and was globally aphasic. Computerized tomography of the head, electroencephalogram, and spinal tap were ordered to rule out a subdural hematoma or a cerebral ischemic event such as a stroke. The results were unremarkable. Laboratory values were normal with the exception of thrombocytosis peaking at 1,230,000/mm^3 on January 20, which coincided with his worse cognitive and motor status. The patient received aspirin 80 mg/day to prevent a possible thrombotic event while his platelet count was over 700,000/mm^3. The Division of Pharmacology was consulted after a review of the literature revealed published cases of neurologic abnormalities associated with midazolam and fentanyl infusions in children.[6]

After limited cognitive and motor improvement during the first week, the child was transferred to the rehabilitation unit for the next month. He was discharged on February 11. Four weeks after midazolam and fentanyl were discontinued, his motor and neurologic status were continuously improving and had returned to baseline except for speech that was still limited.

Discussion

Fentanyl and midazolam are frequently administered in combination. Their popularity for induction of anesthesia is based at least in part on literature reports of synergism.[2, 7] Three groups of 60 women had induction of anesthesia with fentanyl, midazolam, or a combination of the two. The group receiving combination therapy required 75% less fentanyl and 77% less midazolam than the other two groups.[2] Similar results were obtained with a combination of alfentanil plus midazolam; when given together, the doses could be decreased by 78% and 68%, respectively.[7]

Unfortunately, not only desirable effects are enhanced when these drugs are administered together. Moderate to severe decreases in blood pressure, cardiac index, and stroke index occurred in patients receiving the combination for coronary artery bypass graft, in contrast to a control group receiving only high-dose fentanyl.[4] Decreases in heart rate and blood pressure were also reported when fentanyl was combined with diazepam for anesthesia induction in a study of 72 patients.[8] The frequency of apnea and hypoxemia was also increased when midazolam and fentanyl were combined, compared with each drug alone.[9]

Known side effects of midazolam and fentanyl include respiratory depression, hallucinations, and impaired memory.[10] Of importance to this case are a number of reports describing unexpected events associated with the agents. Tolerance, for example, was reported by several investigators.[11-14] This phenomenon led to increased dosages of the drugs, dependence on mechanical ventilation, and neurologic side effects. Tolerance with drug accumulation was also reported with fentanyl,[15] midazolam,[16, 17] midazolam and morphine,[18] and midazolam and fentanyl.[6] These reports described possible withdrawal syndromes consisting of neurologic abnormalities precipitated by abrupt cessation of the drugs.

The withdrawal syndromes were treated in some cases by restarting and slowly tapering the offending agents. For example, after a 7-day course of midazolam and morphine, the syndrome was controlled by giving and tapering diazepam over 7 days.[18] One group tapered diazepam over 3 weeks after 6 days of midazolam infusion.[16] Others, however, did not taper the dosages of midazolam and fentanyl, and fentanyl alone,[6, 15] and the withdrawal syndrome lasted from 1–6 weeks in the four patients they reported. This length of time compares well with that in our patient, which was at least 4 weeks.

In addition to neurologic side effects, our

patient experienced a hypotensive episode necessitating a dopamine drip during the midazolam-fentanyl infusions, with a marked elevation of his platelet count after discontinuation of these two drugs. Although hypotension was reported during midazolam infusion in six babies age 12–36 hours,[19] we are unaware of any report of thrombocytosis associated with either agent, and the relationship in our patient is unclear. On the other hand, reactive thrombocytosis was reported after acute withdrawal from alcohol[20] and myelosuppressive drugs,[21] and was observed in patients with chronic or acute inflammatory disorders.[22]

The thrombocytosis in this child could well have been a reactive manifestation of a possible fentanyl and midazolam withdrawal syndrome. Furthermore, a relationship between the deterioration in motor and cognitive status and this reactive thrombocytosis was seen when comparing indexes of cognitive and motor status observed daily by his mother with the patient's platelet count. Cognitive status was defined as poor (unable to talk), vocalize without meaning, limited vocalization, or normal (based on mother's assessment). Motor status was defined as poor (move without purpose), limited (move with purpose but not normal), or normal (based on mother's assessment). Of interest, available data suggest that the return to a normal platelet count coincided with a return to normal motor and cognitive status. These observations are in agreement with a possible reactive thrombocytosis induced by a withdrawal syndrome.

Midazolam, because of its relatively short half-life of 1–4 hours,[10] is a widely used benzodiazepine for induction of anesthesia. However, with respect to tolerance and development of a withdrawal syndrome, several studies and expert commentaries suggest that the shorter a benzodiazepine's half-life, the greater the possibility of these untoward reactions when the drug is discontinued rapidly.[23–25] One suggested method for treating benzodiazepine-induced withdrawal syndrome is to coadminister a longer-acting opiate and benzodiazepine, such as morphine and diazepam, during the early phase and slowly taper the dosage.[16, 18]

Our patient may have benefited from such an approach. A return to a normal cognitive and motor status would have confirmed our suspicion of a withdrawal syndrome. Unfortunately, it was not possible for us to readminister these drugs, as the family was extremely sensitive to any pharmacologic treatment.

Neither the intensive care unit (ICU) syndrome nor a steroid psychosis could explain this patient's disorder. The ICU syndrome consists of psychologic reactions ranging from fear to delirium, usually appears during the ICU stay, and disappears within 48 hours after discharge from the unit.[26] Our patient's clinical picture, very much consistent with a stroke, could never really substantiate a steroid psychosis, which is also usually related to dosage.[27] Prolonged neuromuscular blockade has been reported after vecuronium administration.[28–30] In these patients, however, neuromuscular function continued to be suppressed for days after the drug was discontinued. In contrast, our patient's neuromuscular function returned to normal for 24 hours before worsening.

This case report suggests that a midazolam-fentanyl combination may not have been appropriate for long-term analgesia and sedation in this child. The abrupt discontinuation of the drugs was possibly associated with a severe withdrawal syndrome. A reactive thrombocytosis paralleled the severity of the decline in motor and cognitive status. Based on our experience and other published case reports, this drug combination should be given with extreme caution. When it is to be administered for a long period of time, substituting the either drug for longer-acting agents (e.g., diazepam, morphine) may be necessary. The dosage can then be tapered slowly over 1[18] to 3 weeks[16] to avoid a withdrawal syndrome.

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