Case report: paradoxical midazolam reaction causing transient associative agnosia and expressive aphasia reversed by flumazenil in a pediatric patient

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Introduction

- Pediatric emergence delirium is a common and challenging problem for PACU staff.
- It is important to attempt to identify its etiology to tailor pharmacological treatment.
- While both emergence delirium and paradoxical reactions to midazolam have been well described, a link between these phenomena has not been extensively discussed.

Case Description

- Patient: 12-year-old female, 39 kg, ASA physical status I, no prior anesthetics
- Procedure: removal of nevus under general anesthesia, 13 min
- Anesthetic:
  - Premedication: midazolam 10 mg PO, 40 min prior to induction, calming effect
  - Induction: mask with 50% nitrous oxide and 5% sevoflurane
  - Maintenance: 2-4% sevoflurane
  - Airway: ventilation supported with mask as needed
- Fluids: Lactated Ringer’s 250 ml IV
- Medications: 1% lidocaine with epinephrine 3 ml mixed with 0.25% bupivacaine 3 ml, morphine 2 mg IV, ondansetron 4 mg IV
- Intraoperative course: vital signs stable, uneventful anesthetic
- Postoperative course:
  - Vital signs stable, uneventful PACU course.
  - Postoperative course: unable to speak and confusion about the situation
  - Patient had complete recall of postoperative events
  - Patient immediately felt calm, within minutes recognized her parents and PACU nurse administered flumazenil 0.2 mg IV
  - Patient transported to PACU peacefully sleeping, stable vitals
- Timeline:
  - 90 min post induction: patient became increasingly agitated
  - 120 min post induction: patient began crying and was anxious
  - 150 min post induction: patient was able to describe her perceptions and feelings.
  - 180 min post induction: patient was able to articulate children.

Potential Mechanisms

- Emergence delirium has been described in many ways, including nonpurposeful restlessness and agitation, thrashing, crying or moaning, disorientation, incoherence, and paranoid ideation.
- The child in our case report exhibited many of these symptoms, and due to the brevity of the procedure and limited exposure to other drugs, we decided to try flumazenil. This fully reversed her symptoms and lead us to attribute them to a paradoxical reaction to midazolam.
- Unlike many previous reports in the literature of paradoxical midazolam reactions, this patient had complete recall of the postoperative events and was able to describe her perceptions and feelings.
- Midazolam caused a transient associative agnosia and expressive aphasia.
- The inter-individual variability associated with this paradoxical reaction could have pharmacokinetic and/or pharmacodynamic components.
- Within the affected brain regions there could be different receptor densities, receptor subtype populations, or unusual genetic variants.
- Specifically, these symptoms could be mediated via GABA_A receptors in Broca’s area and along neural pathways in the occipitotemporal region.

Discussion

- We suggest that paradoxical reactions to midazolam represent a subset of emergence agitation, and that flumazenil should be used to treat these cases.
- Transient associative agnosia and expressive aphasia may, in fact, be a common problem with the offset of midazolam following anesthesia, but potentially obscured by the drug’s amnestic properties, and very difficult to detect in younger, less articulate children.
- It is important to diagnose and treat quickly to limit the amount of time the patient experiences this terrifying state.
- Further work is needed to determine which patients are predisposed to this phenomenon.

Conclusions

References

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