Case report of prolonged emergence after the use of ketamine as premedication and potential explanation

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Introduction: Premedication before induction of anesthesia is used in the pediatric population to facilitate separation fears or facilitate anesthetic induction. There are several medications and routes that have been used as the sole agent or in combination with others. The ideal premedication is readily accepted by patients, has instantaneous onset of action, brief duration of action, and no cardiovascular or respiratory depression. Since no such drug exists, we individualize a premedication regimen when needed. At times we encounter uncooperative adult patients requiring the need for premedication. We will present one adult patient managed at Boston Children’s Hospital with cerebral palsy who required ketamine premedication for facilitation of anesthetic induction and had an extremely prolonged emergence.

Case: A 26 year old male with a history of cerebral palsy, developmental delay, and poor communication presented for dental rehabilitation. He was 170cm tall, and weighed 60kg. His past medical history was significant for multiple lower extremity orthopedic procedures. He had no allergies and took no medications. His parents reported prior difficult anesthetic inductions due to un-cooperation. He had femoral osteotomies 2 years ago at a different hospital and received ketamine 500mg (8mg/kg) orally and midazolam 20mg mixed with apple juice prior to anesthesia. According to his parents, he had a hard time drinking the premedication, so we decided to premedicate with ketamine intramuscularly. He received ketamine 240mg (4mg/kg) intramuscularly. Within 5 minutes he was deeply sedated. An IV was placed and midazolam 2mg with glycopyrrolate 0.2mg was given. Induction proceeded with propofol 300mg and vecuronium 6mg and was followed by nasal intubation. The anesthesia was maintained with 30% oxygen, 70% N2O, and 0.4% end tidal isoflurane. Blood loss was minimal.

Results: The patient was breathing spontaneously and extubated at the end of the two hour procedure. He was transferred to recovery and awakened four hours later. Premedication with ketamine prolonged his recovery and ultimately his discharge from the hospital. Previously when premedicated with ketamine, his recovery was not prolonged.

Discussion: There are several possibilities to explain the extremely prolonged emergence from anesthesia. One is residual anesthetics other than ketamine, like isoflurane. Messieha et. al. concluded that BIS monitors reduced time to discharge in children requiring intramuscular sedation and general anesthesia for outpatient dental rehabilitation. The reliability of BIS monitors with ketamine is another issue, but inhalational anesthetic overdose will certainly delay wake up. In this case, the end-tidal isoflurane level was less than 0.1% after the procedure. The susceptibility of patients with cerebral palsy to inhalational agents may be different from that of normal patients, but his end tidal isoflurane concentration was much less than MAC awake. Also, midazolam was given with ketamine. Ketamine has psychomimetic effects such as hallucinations and is used with midazolam frequently. There is data that suggests the combination of ketamine and midazolam for premedication will delay recovery and discharge when given orally. In this case, midazolam was given intravenously, and its half life will be prolonged. Another explanation is that inhalational anesthetic agents may decrease the metabolism of ketamine. Ketamine metabolism depends on hepatic blood flow and medications that decrease hepatic blood flow may diminish ketamine clearance and increase ketamine plasma concentration. Isoflurane preserves hepatic blood flow more so than other inhalational anesthetics, but this explanation is lower on the list of possibilities. The third possibility is that in this case a relatively large dose of ketamine was used. Ketamine levels and norketamine levels may have been high enough to decrease this patient’s level of consciousness. Unfortunately there is no available data to prove this. Ebert et al showed that S-norketamine has clinically significant affinity to the NMDA
receptor.\textsuperscript{4} It would be interesting to see the plasma level of ketamine or norketamine after a large dose.

This patient was premedicated with oral ketamine in his past operation. There is a report that the combination of ketamine and midazolam is a good choice for premedication. Funk et al compared oral midazolam 0.5mg/kg, ketamine 6mg/kg, and midazolam 0.5mg/kg+ ketamine 3mg/kg. They showed that the success rate of achieving anxiolysis with combination therapy was 90\%, compared with 70\% with midazolam alone, or 51\% with ketamine alone.\textsuperscript{5} Although Verghese et. al. showed that ketamine and midazolam can delay recovery and discharge,\textsuperscript{6} uncooperative patients will need some premedication. In those cases, ketamine may be a good alternative.

Although this is an adult patient, this case is relevant to pediatric anesthesia because many pediatric patients require premedication prior to induction of anesthesia. This case presents the "unpredictable" nature of ketamine with larger doses, and it may be wise to limit its dose to its low range. Also if the pharmacokinetics of ketamine and the effect of norketamine are further investigated, we will have more control and understanding with the usage of this medication. Finally, as this case demonstrates, when anesthetizing uncooperative patients, you might expect a long recovery from premedication.

\textsuperscript{1} Messieha et. al. Bispectral Index System monitoring reduces time to discharge in children requiring intramuscular sedation and general anesthesia for outpatient dental rehabilitation. Pediatr Dent 26:256, 2004
\textsuperscript{2} Verghese et. al. Ketamine and midazolam is an appropriate premedication combination in uncooperative children undergoing brief ambulatory procedures. Pediatric Anaesth 13:228, 2003
\textsuperscript{3} Reilly et. al. The effect of halothane on drug metabolizing capacity and hepatic blood flow. Anesthesiology 63: 70, 1985
\textsuperscript{4} Ebert et. al. Norketamine, the main metabolite of ketamine is a non-competitive NMDA receptor agonist in the rat cortex and spinal cord. Eur J Pharmacol 333(1): 99, 1997
\textsuperscript{5} Funk et. al. Oral preanaesthetic medication for children: double- blind randomized study of a combination of midazolam and ketamine vs. midazolam or ketamine alone. Br J Anaesth 84: 33, 2000
\textsuperscript{6} Verghese et. al. Ketamine and midazolam is an inappropriate premedication combination in uncooperative children undergoing brief ambulatory procedures. Pediatric Anaesth 13:228, 2003