Tips For Tots

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Premedication, Preoperative Preparation, and Parents

Midazolam

- Midazolam is currently the most popular premedication used in children in the preoperative period. Several recent studies have focused attention on its pH and composition when administered in the oral form.
- The commercial preparation of midazolam was studied in a multi-center study by Coté et al, and found to be effective in doses as low as 0.25 mg/kg. This is in contrast to several earlier studies that found lower doses to be inconsistent in their sedative effects[1,2,3]. The study also found that the bioavailability of the agent was 36% higher than anticipated. Onset time was 10-20 minutes in the majority of patients and the majority of patients found the taste acceptable. The authors postulate that the reason for the efficacy of the lower dose is differences in pH and possibly the composition of syrup in which the medication is mixed.
- Since then there have been 2 studies claiming that midazolam mixed with Syrpalta syrup has a faster onset time than the commercially available product and a greater absorption [4,5]. Another study found that the addition of bicitra to the mixture speeds the onset time[6] (but oh what a taste-yuck)
  - Brosius and Bannister measured sedation scores (Observers Assessment of Alertness/Sedation-OAA/S) as well plasma levels of midazolam in 50 healthy children 2-10 years old undergoing minor surgery. The children received either commercially available midazolam syrup or IV midazolam mixed in Syrpalta syrup. The pH of the commercially available preparation was lower (2.5-3.6) versus the Syrpalta preparation (4.5-5). They found both lower sedation scores and higher plasma levels in the patients who received the Syrpalta preparation. They postulate that the higher pH may increase oral mucosal absorption, thus decreasing first pass metabolism.
  - Midazolam exists as equilibrium between water soluble and lipophilic form. The proportion of each is pH dependant. At a pH < than 2.5 the water soluble form predominates, at a pH > 4.5 the molecule exists almost entirely in the lipophilic form.
- There are some disadvantages to the use of large doses of oral midazolam. Viitanen et.al and Valley et.al et.al demonstrated that recovery after sevoflurane or desflurane anesthesia was prolonged (although others have not found any differences) in recovery times)[7]. Pundit investigated the use of oral transmucosal midazolam at a lower dose [8]. They mixed 0.2mg/kg of IV midazolam with a thick strawberry syrup, and administered it by placing small aliquots on the patients' tongue. They studied 44 children and found that 95% found the taste of the medication acceptable and 95%

successfully separated from their parents. They didn't specifically look at recovery, so it is unclear whether the lower dose would speed recovery.

- On the other end of the spectrum, Shimonaka and colleagues found that they did not achieve adequate sedation with 0.5 or 1.0 mg/kg doses of oral midazolam in infants and children undergoing cardiovascular surgery. Their patients required 1.5mg/kg of oral midazolam to achieve adequate sedation for anesthetic induction. There were no complications or change in vital signs.
- There are also several studies examining long-term effects of midazolam. Kain et al had a lower incidence of negative post operative behaviors in children who had received a midazolam premed for about a week after surgery [19.20]. Other Drugs

Clonidine

- Fazi et.al compared clonidine 4ug/kg and midazolam 0.5mg/kg for pre-anesthetic sedation in healthy children undergoing tonsillectomy +/- adenoidectomy [9]. Under the conditions of the study clonidine provided no advantages to midazolam and was associated with a higher incidence of postoperative pain and excitement.
- Other studies that show premedication with oral clonidine 4ug/kg to be comparable to diazepam 0.2mg/kg, and superior to placebo. It may also decrease PONV in strabismus patients, after propofol anesthesia [10,11,12].

Ketamine

- Ketamine in doses of 3-6mg/kg po is an effective sedative and anxiolytic in pre-operative pediatric patients. There was one study, however that found the side effects of oral ketamine to be unacceptable. These included increased sedation, dysphoria and hallucinations [13].
- More recent studies have renewed interest in the drug, particularly when used in combination with midazolam.
  - Trabold et al found that adding 1.8mg/kg or 3mg/kg of ketamine to 0.5 mg/kg oral midazolam improved sedation at induction and did not prolong emergence or discharge from the PACU [14]
  - Funk et.al compared ketamine 3mg/kg added to oral midazolam (0.5mg/kg) to ketamine (6mg/kg) or midazolam (0.5mg/kg) alone. They found separation and anxiolysis to be better with the combination of ketamine and midazlom, than with either drug alone. They surveyed parents 1 and 7 days later and found a higher incidence of emesis or vertigo in the patients who had received only ketamine. There were no differences in negative behaviors in any of the groups [13]

Oral Transmucosal Fentanyl

- All studies have shown that the taste and form of OTFC is more acceptable to children, the anxiolysis and side effects are similar to midazolam

What about Parental Presence at Induction of Anesthesia (PPIA)?

- The clinical evidence really supports the use of premedication for anxiolysis *vs.* PPIA, however parents want to be with their kids [15-18]
- The majority of studies show that parents are more satisfied and report feeling less anxious if they are allowed to accompany their children to the OR
- The same studies also show that premedication is more effective than PPIA in reducing the child's anxiety and that the combination of PPIA and midazolam has no additional benefits
- The majority of parents of healthy children undergoing a subsequent surgery, chose PPIA regardless of what the previous intervention had been (PPIA, midazolam, midazolam + PPIA, or no intervention)
- Kain and his group recently measured the physiologic effects on the parents of having them accompany their children to the OR and found that PPIA is associated with ↑HR and skin conductance level, although none of the parents in the study developed any electrocardiogram abnormalities [17].
- There are 2 studies (both by Kain et.al) that show anxious children have a higher incidence of negative postoperative behaviors for up to 1 week after the surgery. Premedicating children with midazolam helped to decrease this [19.20].

Bottom line: whatever works best in your institution or practice to help reduce children's anxiety is worthwhile. Midazolam may be effective in smaller doses, but particular attention needs to be paid to the formulation being used. Consider adding oral ketamine to midazolam in a very anxious child, or a child who has previously failed midazolam sedation. PPIA is mostly for the benefit of the parents

Tips for Maintenance and Extubation

- What agent should I use for my LMA or in a patient I want to do a deep extubation on?
  - Awake LMA removal during isoflurane anesthesia may result in increased adverse airway events. 13% of patients in one study developed significant laryngospasm with oxygen desaturation, when isoflurane was used for awake LMA removal. Patients who had received sevoflurane did well whether the LMA was removed deep or awake.
  - Deep extubation is still very popular among many anesthesia care providers. Valley et.al has investigated the difference in emergence times and characteristics between desflurane and sevoflurane. There was a higher incidence of airway complications in the desflurane group, although none were serious. Valley et.al also looked at isoflurane compared tosevoflurane in a previous study and found that the incidence of minor airway complications were the same. In both studies the use of opioids was avoided until after arousal; and midazolam use was discouraged.
  - The incidence of airway complications with the use of isoflurane and halothane appear to be the same with deep extubation. However, in patients extubated awake the incidence of coughing and airway obstruction was higher with isoflurane compared to halothane.
  - In all the above mentioned reports, the discharge times were similar

Tip: Avoid desflurane for deep extubation and avoid isoflurane for awake LMA removal

Emergence Agitation (EA)

- The hottest topic in pediatric anesthesia right now, probably because of the increased popularity of the short acting volatile agents [25-40].
- Several articles highlighted the problem in the late "90s. Wells and Rasch reported 4 cases of fear, agitation and paranoia that occurred after sevoflurane anesthesia, 3 were in children one was in an adult. All the patients on subsequent questioning denied the presence of pain, but did report extreme fear [25].
- Welborn et.al found a 55% incidence of EA in children in patients receiving desflurane for adenoidectomy +T&T, compared to a 10-20% incidence in children who received either sevoflurane and/or halothane. Interestingly none of the patients received opioids until after the surgery.
- Cravero et.al did an elegant study examining the incidence of EA in healthy children undergoing MRI with either Sevoflurane or halothane. Since these procedures have no pain associated with them, the issue of adequate analgesia was eliminated as a variable. The incidence of moderate to severe EA in the Sevoflurane group was 80% and 12% in the halothane group. This incidence was reduced in a follow up study to12% by the administration of 1ug/kg of IV fentanyl 10 minutes prior to the end of surgery.
- Likewise several other investigators have found the administration of small doses of fentanyl (1-2ug/kg) can significantly reduce the incidence of EA in patients administered a sevoflurane anesthetic.
- Cohen et.al found that it required on average 2.5ug/kg of IV fentanyl to decrease the incidence of EA in patients undergoing adenoidectomy with desflurane anesthesia. He also investigated the effects of midazolam and propofol (given at the start of the procedure) in helping to reduce to the incidence of EA in patients undergoing adeno-tonsillectomy with desflurane and found no effect from either medication.
- In a similar study he and his colleagues investigated the effects of fentanyl 2.5ug/kg IV on patients undergoing adenoidectomy with either sevoflurane or desflurane. The incidence of EA was similar in both groups, but that the time to emergence and extubation was significantly shorter in the Desflurane group. None of the patients in any of his studies had received premedication.
- Galinkin et.al used intranasal fentanyl (2ug/kg), in patients having myringotomy and tube placements, with either halothane or sevoflurane anesthesia. They reported a decreased incidence of EA (2%) with both the fentanyl groups vs. the placebo groups. As part of the study they confirmed that administering 2ug/kg fentanyl intranasally achieved adequate analgesic levels. All patients in the study also received 0.5mg/kg

midazolam combined with 10mg/kg acetaminophen pre-operatively. Discharge times were not prolonged and the incidence of side effects was not increased.

- Cole and his colleagues found that the incidence of EA was highest on arrival to the PACU, however some children who arrived asleep, developed EA later during their recovery
- Interestingly 2 studies have found that the use of isoflurane has a higher incidence of EA than sevoflurane does. (Hmmmmmmmmmmmmmmm)
- There are a multitude of investigations trying to better delineate the cause of EA and the effects of various interventions on the incidence of EA. Auno et.al and Voepel-Lewis et.al have shown that age is a factor in the incidence of EA. Preschoolers, male gender, pre-operative anxiety and difficult inductions have all been associated with an increased incidence of EA. Midazolam premedication, adequate analgesia, clonidine(2ug/kg), dexmedetomidine (0.3ug/kg) and halothane have been found in many studies to help.
- Gas, schmass I'll just useTIVA. There is a lower incidence of EA (9-44% depending on the study). One study found emergence times for propofol/remifentanil was longer than for desflurane, 2 others found that emergence times for sevoflurane and propofol alone were similar.

Tip: To decrease or prevent EA make sure the patient receives adequate analgesia, additional fentanyl or consider using halothane (if it's still even available) or TIVA. Midazolam premedication in anxious patients may help

A few last thoughts

- Dolastron may be cheaper and seems to be as effective as ondansetron for preventing PONV
- The combination of dexamethasone and ondansetron has been shown to be the most effective currently available therapy to prevent PONV.
- Intranasal fentanyl (2ug/kg) seems to help both treat pain post myringotomy and improve the quality of emergence.
- Ketorolac, both IM and IV seem to provide superior analgesia to acetaminophen or acetaminophen + codeine (administered pre-op) and have a very low incidence of side effects

Selected References

1. Feld LH, Negus JB, White PF. Oral Midazolam Preanesthetic Medication in Pediatric Outpatients. Anesth 73: 831-4,1990
2. Parnis SJ, Foate JA, van der Walt JH. Oral Midazolam is an Effective Premedication for Children Having Day-Stay Anaesthesia. Anaesth Intensive Care 20:9-14,1992.
3. Coté CJ, Cohen IT, Suresh S. A Comparison of Three Doses of a Commercially Prepared Oral Midazolam Syrup in Childre. Anesth Analg 94: 37-43, 2002
4. Khalil SN, Vije HN, Kee SS. A Paediatric Trial Comparing Midazolam/Syrpalta Mixture With Premixed Midazolam Syrup(Roche) Paed Anaesth 13:205-209, 2003.
5. Brosius KK, Bannister CF. Midazolam Premedciation in Children: A Comparison of Two Oral Dosage Formulations on Sedation Score and Plasma Midazolam Levels. Anesth Analg 96: 392-5, 2003
6. Lammers CR, Rosner JL, Crockett DE. Oral Midazolam with an Antacid May Increase the Speed of Onset of Sedation in Children Prior to General Anaesthesia. Paed Anaesth 12: 26-8, 2002
7. Brosius KK, Bannister CF. Effect of Oral Midazolam Premedication on the Awakening Concentration of Sevoflurane, Recovery Times and Bispectral Index in Children. Paedi Anaesth 11:585-90, 2001.
8. Pandit UA, Collier PJ, Malviya S. Oral Transmucosal Midazolam Premedication for Preschool Children. Can J Anaesth 48: 191-95,2001
9. Fazi L, Jantzen EC, Rose JB. A Comparison of Oral Clonidine and Oral Midazolam as Preanesthetic Medications in thePediatric Tonsillectomy Patient. Anesth Anal 92: 56-61,2001
10. Mikawa K, Nishina K, Maekawa N, Obara H. Oral clonidine premedication reduces postoperative pain in children. Anesth Analg. 1996 Feb; 82(2): 225-30
11. Mikawa K, Maekawa N, Nishina K, Takao Y, Yaku H, Obara H. Efficacy of oral clonidine premedication in children. Anesthesiology. 1993 Nov; 79(5): 926-31.
12. Ramesh VJ, Bhardwaj N, Batra YK. Comparative study of oral clonidine and diazepam as premedicants in children. Int J Clin Pharmacol Ther. 1997 May; 35(5): 218-21.
13. Funk W, Jakob W, Riedl T, Taeger K. Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone.Br J Anaesth. 2000 Mar; 84(3): 335-40
14. Trabold B, Rzepecki A, Sauer K, Hobbhahn A comparison of two different doses of ketamine with midazolam and midazolam alone as oral preanaesthetic medication on recovery after sevoflurane anaesthesia in children.Paediatr Anaesth. 2002 Oct; 12(8): 690-3
15. Kain ZN, Mayes LC, Wang SM, Caramico LA, Hofstadter MB Parental presence during induction of anesthesia versus sedative premedication: which intervention is more effective? Anesthesiology. 1998 Nov; 89(5): 1147-56; discussion 9A-10A.
16. Kain ZN, Mayes LC, Wang SM, Caramico LA, Krivutza DM, Hofstadter MB. Parental presence and a sedative premedicant for children undergoing surgery: a hierarchical study. Anesthesiology. 2000 Apr; 92(4): 939-46

17. Kain ZN, Caldwell-Andrews AA, Mayes LC, Wang SM, Krivutza DM, LoDolce ME Parental presence during induction of anesthesia: physiological effects on parents. Anesthesiology. 2003 Jan; 98(1): 58-64.
18. Kain ZN, Caldwell-Andrews AA, Wang SM, Krivutza DM, Weinberg ME, Mayes LC. Parental intervention choices for children undergoing repeated surgeries. Anesth Analg. 2003 Apr; 96(4): 970-5
19. Kain ZN, Wang SM, Mayes LC, Caramico LA, Hofstadter MB. Distress during the induction of anesthesia and postoperative behavioral outcomes. Anesth Analg. 1999 May; 88(5): 1042-7
20. Kain ZN, Mayes LC, Wang SM, Hofstadter MB. Postoperative behavioral outcomes in children: effects of sedative premedication. Anesthesiology. 1999 Mar; 90(3): 758-65.
21. Pappas AL, Sukhani R, Lurie J, Pawlowski J, Sawicki K, Corsino A. Severity of airway hyperreactivity associated with laryngeal mask airway removal: correlation with volatile anesthetic choice and depth of anesthesia. J Clin Anesth. 2001 Nov;13(7):498-503.
22. Valley RD, Ramza JT, Calhoun P, Freid EB, Bailey AG, Kopp VJ, Georges LS. Tracheal extubation of deeply anesthetized pediatric patients: a comparison of isoflurane and sevoflurane. Anesth Analg. 1999 Apr; 88(4): 742-5.
23. Valley RD, Freid EB, Bailey AG, Kopp VJ, Georges LS, Fletcher J, Keifer A .Tracheal extubation of deeply anesthetized pediatric patients: a comparison of desflurane and sevoflurane.Anesth Analg. 2003 May; 96(5): 1320-4
24. Pounder DR, Blackstock D, Steward DJ. Tracheal extubation in children: halothane versus isoflurane, anesthetized versus awake. Anesthesiology. 1991 Apr;74(4):653-5.
25. Wells LT, Rasch DK. Emergence "delirium" after sevoflurane anesthesia: a paranoid delusion? Anesth Analg. 1999 Jun; 88(6): 1308-10
26. Welborn LG, Hannallah RS, Norden JM, Ruttimann UE, Callan CM. Comparison of emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric ambulatory patients. Anesth Analg. 1996 Nov; 83(5): 917-20.
27. Cravero J, Surgenor S, Whalen K. Emergence agitation in paediatric patients after sevoflurane anaesthesia and no surgery: a comparison with halothane. Paediatr Anaesth. 2000; 10(4): 419-24.
28. Cravero JP, Beach M, Thyr B, Whalen K. The effect of small dose fentanyl on the emergence characteristics of pediatric patients after sevoflurane anesthesia without surgery. Anesth Analg. 2003 Aug; 97(2): 364-7
29. Cravero JP, Beach M, Dodge CP, Whalen K. Emergence characteristics of sevoflurane compared to halothane in pediatric patients undergoing bilateral pressure equalization tube insertion.J Clin Anesth. 2000 Aug; 12(5): 397-401
30. Cohen IT, Hannallah RS, Hummer KA The incidence of emergence agitation associated with desflurane anesthesia in children is reduced by fentanyl.Anesth Analg. 2001 Jul; 93(1): 88-91.
31. Cohen IT, Finkel JC, Hannallah RS, Hummer KA, Patel KM The effect of fentanyl on the emergence characteristics after desflurane or sevoflurane anesthesia in children. Anesth Analg. 2002 May; 94(5): 1178-81

32. Cohen IT, Drewsen S, Hannallah RS. Propofol or midazolam do not reduce the incidence of emergence agitation associated with desflurane anaesthesia in children undergoing adenotonsillectomy. Paediatr Anaesth. 2002 Sep; 12(7): 604-9
33. Galinkin JL, Fazi LM, Cuy RM, Chiavacci RM, Kurth CD, Shah UK, Jacobs IN, Watcha MF.Use of intranasal fentanyl in children undergoing myringotomy and tube placement during halothane and sevoflurane anesthesia. Anesthesiology. 2000 Dec; 93 (6): 1378-83
34. Cole JW, Murray DJ, McAllister JD, Hirshberg GE. Emergence behaviour in children: defining the incidence of excitement and agitation following anaesthesia. Paediatr Anaesth. 2002 Jun; 12(5): 442-7.
35. Aono J, Ueda W, Mamiya K, Takimoto E, Manabe M. Greater incidence of delirium during recovery from sevoflurane anesthesia in preschool boys. Anesthesiology. 1997 Dec; 87(6): 1298-300
36. Voepel-Lewis T, Malviya S, Tait AR. A prospective cohort study of emergence agitation in the pediatric postanesthesia care unit. Anesth Analg. 2003 Jun; 96(6): 1625-30
37. Kulka PJ, Bressem M, Tryba M. Clonidine prevents sevoflurane-induced agitation in children. Anesth Analg. 2001 Aug; 93(2): 335-8,
38. Ibacache ME, Munoz HR, Brandes V, Morales AL. Single-dose dexmedetomidine reduces agitation after sevoflurane anesthesia in children. Anesth Analg. 2004 Jan; 98(1): 60-3
39. Cohen IT, Finkel JC, Hannallah RS, Hummer KA, Patel KM. Rapid emergence does not explain agitation following sevoflurane anaesthesia in infants and children: a comparison with propofol. Paediatr Anaesth. 2003 Jan; 13(1): 63-7.
40. Uezono S, Goto T, Terui K, Ichinose F, Ishguro Y, Nakata Y, Morita S. Emergence agitation after sevoflurane versus propofol in pediatric patients. Anesth Analg. 2000 Sep; 91(3): 563-6.