Midazolam premedication delays recovery from propofol-induced sevoflurane anesthesia in children 1-3 yr

Hanna Viitanen MD,*
Päivi Annila MD PhD,†
Matti Viitanen MD,*
Arvi Yli-Hankala MD PhD,‡

Purpose: To study the effect of midazolam premedication on the recovery characteristics of sevoflurane anesthesia induced with propofol in pediatric outpatients.

Methods: Sixty children, one to three years, presenting for ambulatory adenoidectomy were randomly assigned in a double-blind fashion, to receive either 0.5 $mg \cdot kg^{-1}$ midazolam (Group M) or placebo (Group P) *po* 30 min before anesthesia. Anesthesia was induced with 10 $\mu g \cdot kg^{-1}$ atropine, 10 $\mu g \cdot kg^{-1}$ alfentanil, and 3-4 $mg \cdot kg^{-1}$ propofol *iv*. Tracheal intubation was facilitated with 0.2 $mg \cdot kg^{-1}$ mivacurium. Anesthesia was maintained with nitrous oxide/oxygen (FiO_2 0.3) and sevoflurane with controlled ventilation. Recovery characteristics were compared using the modified Aldrete scoring system, the Pain/Discomfort scale and measuring specific recovery end-points (emergence, full Aldrete score, discharge). A postoperative questionnaire was used to evaluate the children's well-being at home until 24 hr after discharge.

Results: Emergence from anesthesia (22 ± 9 *vs* 16 ± 6 min (mean ± SD), $P = 0.005$) and achieving full Aldrete scores (30 ± 11 *vs* 24 ± 16 min, $P = 0.006$) were delayed in patients receiving midazolam. Children in the placebo group were given postoperative analgesia sooner than those in the midazolam group (18 ± 11 *vs* 23 ± 8 min, $P = 0.009$). More children premedicated with midazolam suffered from arousal distress (20% *vs* 3%, $P = 0.04$) and scored higher on the Pain/Discomfort scale ($P = 0.004$) at 20 min after arrival in the recovery room. Discharge was not affected by premedication and well-being at home was similar in the groups.

Conclusions: Oral premedication with midazolam delays early recovery but not discharge after ambulatory sevoflurane anesthesia induced with propofol in children one to three years. Midazolam did not improve the quality of recovery.

Objectif : Étudier, chez des enfants, l'effet de la prémédication de midazolam sur la récupération de l'anesthésie ambulatoire au sévoflurane, induite au propofol.

Méthode : Soixante enfants, de 1-3 ans, admis pour une adénoïdectomie ambulatoire, ont participé à une étude randomisée à double insu et ont reçu soit 0,5 $mg \cdot kg^{-1}$ de midazolam (Groupe M), soit un placebo (Groupe P) *po* 30 min avant l'anesthésie. L'induction comprenait 10 $\mu g \cdot kg^{-1}$ d'atropine, 10 $\mu g \cdot kg^{-1}$ d'alfentanil, et 3-4 $mg \cdot kg^{-1}$de propofol *iv*. L'intubation endotrachéale a été facilitée par 0,2 $mg \cdot kg^{-1}$ de mivacurium et l'anesthésie maintenue sous ventilation contrôlée avec un mélange de protoxyde d'azote et d'oxygène (FiO_2 0,3) et du sévoflurane. On a comparé les caractéristiques de la récupération en utilisant le système de cotation modifié d'Aldrete, l'échelle douleur/inconfort et des mesures de seuils spécifiques de la récupération (réveil, cotation d'Aldrete complète, congé). Un questionnaire postopératoire a servi à évaluer l'état des enfants 24 h après le congé.

Résultats : Le réveil (22 ± 9 *vs* 16 ± 6 min (moyenne ± écart type), $P = 0,005$) et l'obtention de tous les scores d'Aldrete (30 ± 11 *vs* 24 ± 16 min, $P = 0,006$) ont été retardés chez les enfants du groupe midazolam. La demande d'analgésie postopératoire a été plus précoce chez les enfants du groupe placebo (18 ± 11 *vs* 23 ± 8 min, $P = 0,009$). Un plus grand nombre d'enfants du groupe midazolam a souffert d'anxiété du réveil 20 % *vs* 3 %, $P = 0,04$) et a présenté des scores plus élevés à l'échelle douleur/inconfort ($P = 0,004$), 20 min après l'arrivée en salle de réveil. La prémédication n'a pas influencé le moment du congé et le bien-être des enfants à la maison a été similaire dans les deux groupes.

Conclusion : La prémédication orale de midazolam a retardé la récupération, mais non pas le congé à la suite de l'anesthésie ambulatoire au sévoflurane, induite avec du propofol chez des enfants de un à trois ans. Le midazolam n'a pas amélioré la qualité de la récupération.

From the Department of Surgery and Anaesthesia, Central Hospital of Seinäjoki,* 60220 Seinäjoki, Finland, University of Tampere, Medical School,† Tampere, Finland, Anaesthesia Research Group, Department of Obstetrics and Gynaecology, Helsinki University Central Hospital,‡ Helsinki, Finland.

Address correspondence to: Dr. H. Viitanen, Department of Surgery and Anaesthesia, Central Hospital of Seinäjoki, 60220 Seinäjoki, Finland; Fax: 358-6-4154091; E-mail: msv@sci.fi.

Supported by a grant from the Medical Research Fund of Tampere University Hospital.

Accepted for publication May 2, 1999

MIDAZOLAM is a safe and effective premedicant in children.[1,2] Its elimination half-life (1.2 hr)[3] makes it especially suitable for short-lasting procedures. However, the role of premedication in ambulatory anesthesia is still controversial mainly because of concern over delayed recovery. Midazolam does not appear to delay recovery after halothane anesthesia.[1,2] However, when midazolam premedication and intravenous (*iv*) anesthetic induction is followed by inhalational anesthesia[4,5] or propofol maintenance,[6] prolonged sedation or delayed recovery have ensued. Synergistic hypnotic interaction reported between midazolam and propofol[7,8] or thiopental[9] could, in part, explain the delay in recovery in studies where these agents have been used.

Propofol is a short-acting *iv* anesthetic often used in the ambulatory setting because of its favourable recovery characteristics. In Finland, propofol was licensed for use in children < three years in 1998. It prolongs early recovery after sevoflurane anesthesia in children aged one to three years.[10] Premedication with midazolam may increase postoperative sedation and delay recovery further. On the other hand, postoperative sedation could improve the quality of recovery by decreasing the incidence of agitation and delirium described upon awakening from sevoflurane anesthesia.[11,12]

This double-blind, placebo-controlled study was designed to test the hypothesis that midazolam premedication delays recovery but lessens adverse postoperative behaviour after short ambulatory sevoflurane anesthesia induced with propofol in children aged one to three years.

Methods

After obtaining approval from the institutional Ethics Committee and written informed parental consent, we studied 60 children (ASA I - II), aged one to three years, presenting for ambulatory adenoidectomy. According to a computer-generated random numbers listing, each child was randomly assigned, in a double-blind fashion, to receive 0.5 $mg \cdot kg^{-1}$ midazolam (Group M) or placebo (Group P) *po* approximately 30 min before induction of anesthesia. All observers, as well as the children and their parents, were unaware of the contents of the oral premedicant. Children were excluded if they had known allergy to the drugs being used, or recent or chronic medication that could interact with midazolam.

After arrival in the operating room, routine monitoring was applied and pre-induction heart rate, blood pressure (Cardiocap™, Datex; Finland) and oxygen saturation (Capnomac Ultima™, Datex, Finland) were recorded. Atropine, 10 $\mu g \cdot kg^{-1}$, *iv* was administered immediately after venous cannulation (facilitated by EMLA® cream, Astra, Sweden) and 10 $\mu g \cdot kg^{-1}$ alfentanil 60 sec before induction of anesthesia. Lidocaine, 10 mg, *iv* was used to minimize pain on injection with propofol. Anesthesia was induced with 3 $mg \cdot kg^{-1}$ propofol with increments of 0.5 $mg \cdot kg^{-1}$ to achieve acceptance of the face mask and gentle manual ventilation. Tracheal intubation was facilitated with 0.2 $mg \cdot kg^{-1}$ mivacurium. Anesthesia was maintained with sevoflurane in nitrous oxide 70% in oxygen. The inspired sevoflurane concentration was adjusted to maintain blood pressure within ± 20% of initial readings. After intubation a suppository of 20 $mg \cdot kg^{-1}$ acetaminophen[13] was given for postoperative analgesia. Oxygen saturation and end-tidal carbon dioxide values were monitored continuously (Capnomac Ultima™, Datex, Finland). Ventilation was controlled to maintain $P_{ET}CO_2$ between 33-42 mmHg. Heart rate and blood pressure were recorded before intubation, after intubation and every five minutes during surgery. At the end of surgery, sevoflurane and nitrous oxide were discontinued and oxygen 100% delivered. The oropharynx was suctioned and the trachea extubated, while the child was still asleep, as soon as spontaneous breathing was adequate.

In the recovery room, vital signs (heart rate, blood pressure, oxygen saturation) were monitored until the child was fully awake. Parents were allowed to enter the recovery room once the child had woken up. Recovery and behaviour of the children was assessed by a specially trained nurse, who was blinded to the premedication protocol. The following recovery times (from discontinuation of sevoflurane and nitrous oxide) were recorded: (1) time to making sounds; (2) time to opening eyes spontaneously (= emergence); (3) time to scoring full points on the modified Aldrete score[14–16] (Table I); (4) time to interacting with the nurse or parent (= interaction); (5) time to spontaneous drinking; (6) time to ambulating according to age; and (7) time to achieving discharge criteria. The discharge criteria included being fully awake, stable vital signs for at least 30 min, no bleeding, no signs of pain or vomiting and ambulating according to age.

Any adverse events (vomiting, airway difficulty) were recorded. Oxycodone, 0.05 $mg \cdot kg^{-1}$ *iv* (Oxanest®, Leiras, Finland), was given for postoperative pain relief at the discretion of the recovery nurse. An assessment of Pain/Discomfort was made using the scoring system based on Hannallah *et al.*[17] (Table I). Scores were recorded every 10 min after arrival in the recovery room for the first 30 min, then every 15 min until discharge. For statistical purposes, if the

TABLE I The modified Aldrete score[14–16] and the Pain/Discomfort scale.[17]

Modified Aldrete Score		*Pain/Discomfort Scale*	
	Score		*Score*
Activity		**Crying**	
Not moving	0	Not crying	0
Non-purposeful movement	1	Responding to comforting	1
Moving limbs purposefully	2	Not responding to comforting	2
Respiration		**Moving**	
Apneic/needs maintenance	0	None	0
Shallow or limited	1	Restless	1
Deep breathing or coughing	2	Thrashing	2
Consciousness		**Agitation**	
Unresponsive	0	Asleep or calm	0
Responding to stimuli	1	Mild	1
Fully awake	2	Hysterical	2
O_2 saturation			
< 90%	0		
90-94%	1		
≥ 95%	2		

TABLE II Demographic data.

	Midazolam	*Placebo*
n	30	30
Age (mo)	28 ± 11	26 ± 11
Weight (kg)	14 ± 2	14 ± 2
Duration of surgery (min)	13 ± 4	13 ± 6
Duration of anesthesia (min)	21 ± 5	22 ± 7
Premedication to end of surgery (min)	57 ± 13	51 ± 15

Mean ± SD

total score on the Pain/Discomfort scale at any evaluation point exceeded three (the child was crying inconsolably, thrashing or hysterical), the child was regarded as suffering from arousal distress.

A postoperative questionnaire was given to the parents who were asked to record the well-being (pain, vomiting, tiredness, sleep) of the child until 24 hr after discharge.

Statistical analysis

Analyses were performed with a Statistical Package for Social Sciences (SPSS; Chicago, IL, USA) version 6.1 for Windows. Results are presented as mean ± SD, 95% confidence intervals (CI) or number (%). Demographic data were analyzed with Student's t test. Differences in premedication, recovery times and the Pain/Discomfort scores were assessed using the Mann-Whitney *U* test. The incidences of children with postoperative sequelae were compared with the Chi-square test or Fisher's Exact test, where appropriate. A *P* value < 0.05 was considered significant. It was predicted that in order to detect a 25% difference in discharge times, with a mean value of 80 min and a SD of 20 min, a minimum of 28 patients would be required in each group. This gave the study a power of 80% at $\alpha = 0.05$.

Results

The two groups were comparable in age, weight, duration of surgery and anesthesia and premedication time to end of anesthesia (Table II). The mean dose of propofol required for induction of anesthesia was lower in group M (3.1 ± 0.1 $mg \cdot kg^{-1}$) than in group P (3.2 ± 0.3 $mg \cdot kg^{-1}$) ($P = 0.007$).

Early recovery (emergence, full Aldrete scores) was delayed with midazolam but discharge was not affected by premedication (Table III). Adverse events in the recovery room were few and did not differ between groups (Table IV). The Pain/Discomfort scores were higher at 20 min after arrival in the recovery room in group M compared with group P ($P = 0.004$) (Figure 1). Also, more children premedicated with midazolam suffered from arousal distress at 20 min in the recovery room (6 (20%) *vs* 1 (3%) ($P = 0.04$) (Figure 2) but the total number of children with arousal distress did not differ between groups (9 (30%) *vs* 5 (17%) in

TABLE III Recovery times in the two study groups.

Recovery variable (min)	*Midazolam*	*Placebo*	*P* ‡
Making sounds	19 ± 7	15 ± 7	0.008
CI	17 - 22	12 - 17	
Emergence	22 ± 9	16 ± 6	0.005
CI	19 - 26	14 - 19	
Full Aldrete score	30 ± 11	24 ± 16	0.006
CI	26 - 34	18 - 30	
Interaction	37 ± 19	25 ± 12	0.004
CI	29 - 45	19 - 30	
Spontaneous drinking	56 ± 15*	62 ± 28†	0.7
CI	47 - 65	47 - 77	
Walking	65 ± 22	61 ± 30	0.4
CI	55 - 73	49 - 73	
Discharge	83 ± 23	78 ± 29	0.1
CI	75 - 92	67 - 88	

Mean ± SD and 95% confidence intervals (CI).
* $n = 15$; † $n = 13$. ‡ Mann-Whitney U test.

TABLE IV Adverse events and need for additional pain relief after anesthesia in the recovery room and at home during the first 24 hr after discharge.

	Midazolam	*Placebo*
Recovery room	$n = 30$	$n = 30$
Vomiting	1 (3)	2 (7)
Laryngospasm	2 (7)	3 (10)
Oxycodone required	30 (100)	27 (90)
Arousal distress	9 (30)	5 (17)
Home	$n = 29$	$n = 28$
Vomiting	3 (10)	1 (4)
Pain	14 (48)	16 (57)
Analgesic treatment	13 (45)	18 (64)
Bad tempered	6 (21)	6 (21)
Drinking less	6 (21)	4 (14)
Tiredness*	14 (48)	7 (25)
Disturbed sleep†	4 (14)	7 (25)

Number (%). No differences between groups.
* Playing less than normal or lying down. † Waking up often or nightmares.

group M and P, respectively) ($P = 0.2$) (Table IV). Five (17%) children in group M compared with one (3%) child in group P had arousal distress lasting over 10 min ($P = 0.08$).

Oxycodone was given for postoperative pain relief to all except three children in group P (Table IV). The first dose of oxycodone was given earlier to children in group P (18 ± 11 min) than in group M (23 ± 8 min) ($P = 0.009$). Fifteen (50%) children in group M received oxycodone twice compared with nine (30%) in group P ($P = 0.08$). The mean dose of oxycodone did not differ between groups (0.07 ± 0.2 $mg \cdot kg^{-1}$ *vs* 0.06 ± 0.02 $mg \cdot kg^{-1}$ in group M and P, respectively) ($P = 0.2$).

All the questionnaires except for one from the midazolam group and two from the placebo group were returned. The well-being of children at home was similar in both groups (Table IV).

Discussion

Our hypothesis was partly confirmed. Oral premedication with midazolam delayed early recovery from sevoflurane anesthesia induced with propofol, though discharge time was not prolonged. However, midazolam premedication did not improve the quality of recovery from anesthesia.

The delay in early recovery may be a result of residual sedation from midazolam after brief anesthesia. The maximal sedative effect of oral midazolam occurs at 30 min after ingestion[2] but serum concentration peaks at 50- 60 min,[3] which coincided with the end of anesthesia in our study. Interaction between midazolam and propofol could also have contributed to the delay in recovery. Propofol has been shown to prolong emergence after sevoflurane anesthesia of short duration (< 30 min).[10] In addition, midazolam has been reported to enhance the hypnotic effect of propofol[7,8] in humans. This synergistic effect has been suggested to derive from $GABA_A$ receptor interactions in the central nervous system[8] and has been confirmed experimentally.[18] In the present study, the use of alfentanil preoperatively may have further contributed to the delay in emergence in the group receiving midazolam as a similar synergistic hypnotic interaction has been reported between midazolam, propofol and alfentanil.[7]

In earlier studies, midazolam was found not to delay recovery after halothane anesthesia,[1,2] while a delay in both recovery and discharge was seen when propofol or thiopental were used for induction of halothane or isoflurane anesthesia.[4,19] These controversial findings may be due to differences in the premedication dose and anesthetic times but interaction between the premedicant and *iv* anesthetics could possibly also account for the differing results. Indeed, Morley-Forster and colleagues found that midazolam prolonged sedation after halothane anesthesia induced with thiopental, when compared with an inhalational induction with halothane.[5]

Adverse events were few in both groups and no serious complications occurred. The incidence of vomiting was low and is in accordance with previous studies with sevoflurane anesthesia for adenoidectomy.[10,20] However, our hypothesis that midazolam premedication might provide more calm awakening from anesthesia was not confirmed. Children receiving midazolam were more in distress at 20 min after arrival in the recovery room and continued to be so during the whole recovery period.

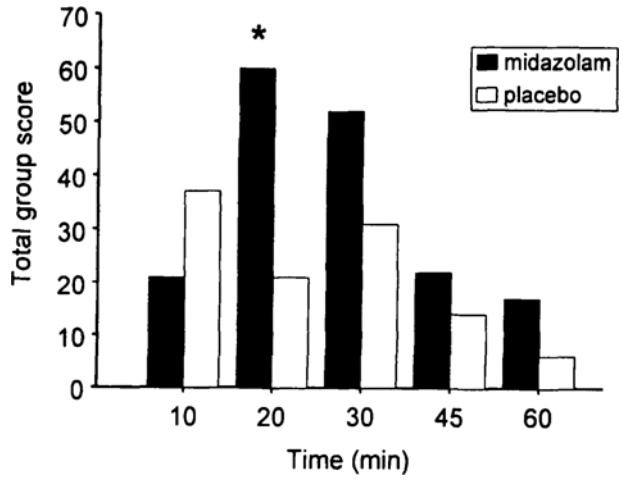

FIGURE 1 Total group score for Pain/Discomfort in the two study groups at different time points (min) in the recovery room. * $P = 0.004$ (Mann-Whitney U test).

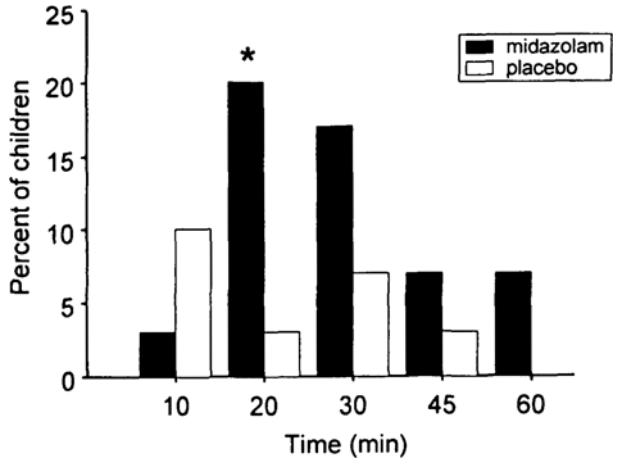

FIGURE 2 Percent of children with arousal distress in the two study groups at different time points (min) in the recovery room. * $P = 0.04$ (Fisher's Exact test).

We used a modified Pain/Discomfort scale based on the Objective Pain Scale (OPS) created by Hannallah *et al.* for children.[17] This scale has been used in several studies to guide analgesic treatment[21] or to assess postoperative behaviour.[15,20] A limitation of this scale is that it does not discriminate between pain and agitation due to other causes. Therefore, we did not use it as a guide for analgesic treatment but rather as a descriptive evaluation of the behaviour of the child. In the present study, the same nurse evaluated each child and administered the rescue analgesic postoperatively. Therefore, we believe that the evaluation of the Pain/Discomfort scores and decision to give the child oxycodone was not confounded by variation in observation.

The peak Pain/Discomfort scores coincided fairly well with the time to emergence in both groups (16 *vs* 22 min after end of anesthesia in group P and M, respectively). Pain may have been an important contributing factor for increased distress upon awakening in both groups as it is now a currently held opinion that traditional rectal doses of acetaminophen (10-20 $mg \cdot kg^{-1}$) are too low to provide adequate postoperative pain control in the immediate recovery period.[22] Children in the placebo group were given oxycodone earlier (18 *vs* 23 min) and this may be one reason for the subsequent significant difference in the Pain/Discomfort scores at the 20-min time point in the recovery room. Children in group P may have been oriented and analgesed at this time while the premedicated children were in early emergence accounting for the higher distress scores.

However, it is recognized that other factors, apart from pain, may contribute to agitation and excitement upon awakening in children, e.g. psychological immaturity,[11] young age,[12] temperament and use of analgesics.[23] Also, considerable postoperative confusion[4] and agitation[5] have been described after premedication with midazolam. Furthermore, while it is recognized that premedication reduces the incidence of preoperative anxiety and distress on induction of anesthesia,[1,2] the effect of premedication on immediate[23–25] or long-term[26,27] postoperative behavioural patterns is controversial. In our study, although the higher Pain/Discomfort scores and incidence of arousal distress after 20 min in the recovery room may only reflect different stages of emergence in the study groups, our findings show that the premedicated children remained more in distress during the whole recovery period onwards. On the basis of these findings we postulate that midazolam does not improve the well-being of the child at the time of emergence and may even have a negative effect on the early recovery period in some children.

In conclusion, premedication with oral midazolam delayed early recovery without affecting discharge time after sevoflurane anesthesia induced with propofol in children one to three years. Midazolam did not improve the quality of immediate recovery in this patient group.

Acknowledgments

We wish to thank Riitta Kataja-Rahko RN, Aila Autio RN, and the personnel of the ENT surgical unit of the Central Hospital of Seinäjoki for their help and cooperation during this study.

References

1 *McMillan CO, Spahr-Schopfer IA, Sikich N, Hartley E, Lerman J.* Premedication of children with oral midazolam. Can J Anaesth 1992; 39: 545–50.

2 *Weldon BC, Watcha MF, White PF.* Oral midazolam in children: effect of time and adjunctive therapy. Anesth Analg 1992; 75: 51–5.

3 *Payne K, Mattheyse FJ, Liebenberg D, Dawes T.* The pharmacokinetics of midazolam in paediatric patients. Eur J Clin Pharmacol 1989; 37: 267–72.

4 *Cray SH, Dixon JL, Heard CMB, Selsby DS.* Oral midazolam premedication for paediatric day case patients. Paediatr Anaesth 1996; 6: 265–70.

5 *Morley-Forster P, McAllister JD, Vandenberghe H, et al.* Does thiopentone delay recovery in children premedicated with midazolam? Paediatr Anaesth 1997; 7: 279–85.

6 *Bevan JC, Veall GRO, Macnab JA, Ries CR, Marsland C.* Midazolam premedication delays recovery after propofol without modifying involuntary movements. Anesth Analg 1997; 85: 50–4.

7 *Short TG, Plummer JL, Chui PT.* Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil. Br J Anaesth 1992; 69: 162–7.

8 *McClune S, McKay AC, Wright PMC,Patterson CC, Clarke RSJ.* Synergistic interaction between midazolam and propofol. Br J Anaesth 1992; 69: 240–5.

9 *Short TG, Galletly DC, Plummer JL.* Hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. Br J Anaesth 1991; 66: 13–9.

10 *Viitanen H, Tarkkila P, Mennander S, Viitanen M, Annila P.* Sevoflurane-maintained anesthesia induced with propofol or sevoflurane in small children: induction and recovery characteristics. Can J Anesth 1999; 46: 21–8.

11 *Aono J, Ueda W, Mamiya K,Takimoto E, Manabe M.* Greater incidence of delirium during recovery from sevoflurane anesthesia in preschool boys. Anesthesiology 1997; 87: 1298–300.

12 *Westrin P, Beskow A.* Sevoflurane causes more postoperative agitation in children than does halothane. Anesthesiology 1997; 87: A1061.

13 *Houck CS, Berde CB, Anand KJS.* Pediatric pain management. *In*: Gregory GA (Ed.). Pediatric Anesthesia, 3rd ed. New York: Churchill Livingstone Inc., 1994: 743–71.

14 *Aldrete JA, Kroulik D.* A postanesthetic recovery score. Anesth Analg 1970; 49: 924–34.

15 *Sury MRJ, Black A, Hemington L, Howard R, Hatch DJ, Mackersie A.* A comparison of the recovery characteristics of sevoflurane and halothane in children. Anaesthesia 1996; 51: 543–6.

16 *Carpenter RD, Sikich N, Levine M, Lerman J.* Anaesthesia for insertion of ear tubes in children: comparison of propofol, thiopentone and halothane. Paediatr Anaesth 1997; 7: 25–31.

17 *Hannallah RS, Broadman LM, Belman AB, Abramowitz MD, Epstein BS.* Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for control of post-orchiopexy pain in pediatric ambulatory surgery. Anesthesiology 1987; 66: 832–4.

18 *McAdam LC, MacDonald JF, Orser BA.* Isobolographic analysis of the interactions between midazolam and propofol at $GABA_A$ receptors in embryonic mouse neurons. Anesthesiology 1998; 89: 1444–54.

19 *McCluskey A, Meakin GH.* Oral administration of midazolam as a premedicant for paediatric day-case anaesthesia. Anaesthesia 1994; 49: 782–5.

20 *Rieger A, Schröter G, Philippi W, Hass I, Eyrich K.* A comparison of sevoflurane with halothane in outpatient adenotomy in children with mild upper respiratory tract infections. J Clin Anesth 1996; 8: 188–93.

21 *Welborn LG, Hannallah RS, Norden JM, Ruttiman UE, Callan CM.* Comparison of emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric ambulatory patients. Anesth Analg 1996; 83: 917-20.

22 *Birmingham PK, Tobin MJ, Henthorn TK, et al.* Twenty-four-hour pharmacokinetics of rectal acetaminophen in children. An old drug with new recommendations. Anesthesiology 1997; 87: 244–52.

23 *O'Kelly SW, Voepel-Lewis T, Tait AR.* Postoperative behaviour and emergence delirium in pediatric patients: a prospective study. Anesthesiology 1997; 87: A1060.

24 *Cole JW, Murray DJ, Hirshberg GE, Pence HC, McAllister J.* Emergence delirium in children: a common postoperative problem. Anesth Analg 1997; 84: S422.

25 *Holm-Knudsen RJ, Carlin JB, McKenzie IM.* Distress at induction of anaesthesia in children. A survey of incidence, associated factors and recovery characteristics. Paediatr Anaesth 1998; 8: 383–92.

26 *McGraw T, Kendrick A.* Oral midazolam premedication and postoperative behaviour in children. Paediatr Anaesth 1998; 8: 117–21.

27 *Kain ZN, Mayes L, Wang SM, Hofstadter MB, Bagnall A.* Effect of premedication on postoperative behavioral outcomes in children. Anesthesiology 1997; 87: A1032.