Oral midazolam in paediatric premedication

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Summary

In a premedication study involving 135 children, aged 1 - 10 years, four regimens were investigated: (*i*) no premedication; (*ii*) oral trimeprazine tartrate 2 mg/kg, methadone 0,1 mg/kg, droperidol 0,15 mg/kg (TMD); (*iii*) intramuscular midazolam (Dormicum; Roche) 0,15 mg/kg; and (*iv*) oral midazolam 0,45 mg/kg. All premedications were given 60 minutes before a standard halothane anaesthetic. No impairment of cardiovascular stability occurred but after premedication the mean oxygen saturation decreased by 1,6% and 1,1%, respectively, in the intramuscular midazolam and TMD groups. Overall, children under 5 years of age behaved less satisfactorily in the holding room and at induction, than those over 5 years ($P < 0,01$). Midazolam, intramuscularly and orally, produced more satisfactory behaviour than the other two regimens ($P < 0,05$) and, combined with a 70% more rapid recovery than the TMD regimen ($P < 0,05$), suggests that oral midazolam is a more effective paediatric premedication agent than placebo or TMD.

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Paediatric premedication should alleviate anxiety,[1,2] thereby providing less sympathetic system stimulation.[3] It also provides the pharmacological foundation upon which the anaesthetic is based,[1,4] and as such should result in minimal disturbance to the body's physiological stability.[5] Intramuscular midazolam 0,1 - 0,2 mg/kg has been shown to be a good paediatric premedicant.[2,6,7] Unfortunately, injections are one of the major fears of the hospitalised child[8,9] and oral premedication is preferred. Although a paediatric oral midazolam formulation is not available, we have demonstrated reliable absorption following oral administration of the injectable form.[10] In children under 10 years of age, oral midazolam (Dormicum; Roche) 0,45 mg/kg and intramuscular midazolam 0,15 mg/kg, both gave mean serum midazolam levels of close to 60 ng/ml at 60 minutes.[10]

This suggests that oral midazolam 0,45 mg/kg would be suitable for paediatric premedication. This hypothesis was investigated by comparing midazolam with a documented effective oral premedication[11,12] of trimeprazine tartrate 2 mg/kg, methadone 0,1 mg/kg and droperidol 0,15 mg/kg, which is widely used in South Africa.[2,13]

Patients and methods

The Ethical Committee of Tygerberg Hospital gave permission for the study, the Medicines Control Council gave permission to use midazolam via an unregistered route in children, and the parents signed consent forms explaining the procedure.

The subjects were children aged 1 - 10 years, American Society of Anesthesiologists grades I and II, scheduled for inguinal area surgery on a morning list. There were to be 30 children per group, allocation being by random card draw.

All the children had oral 5% dextrose water 4 hours before anaesthesia. Induction of anaesthesia was with halothane in a 50% nitrous oxide:oxygen mixture via an Ayres T-piece with a 1-litre Jackson-Rees bag and a Rendell-Baker mask of appropriate size, at a fresh gas flow of 3 times the calculated minute volume. Maintenance of anaesthesia was with halothane 1,5% using the same gas mixture and flow rates. An intravenous infusion of normal saline 3 ml/kg/h was used intra-operatively and continued until the child took oral fluids postoperatively. A caudal block was inserted using our standard technique, bupivacaine 0,25% 0,7 ml/kg.[14] The duration of the anaesthetic and the surgery was noted. Pethidine 1 mg/kg by intramuscular injection 4-hourly as needed was available to all children postoperatively. Premedication was given 1 hour before anaesthesia according to one of four regimens: (*i*) a control group with no premedication; (*ii*) an oral premedication composed of trimeprazine tartrate 2 mg/kg, methadone 0,1 mg/kg, droperidol 0,15 mg/kg (TMD);[2,11-13] (*iii*) intramuscular midazolam 0,15 mg/kg;[2,6,7] and (*iv*) oral midazolam 0,45 mg/kg — this was prepared to a strength of 3 mg/ml using raspberry syrup, as previously described.[10]

All the assessments were done by a nursing sister trained in research techniques. She was unaware which group the patients belonged to. Three aspects were investigated:

1. Behaviour stability before anaesthesia: (*i*) holding room assessment using a 4-point subjective scale:[2,15] A = calm and co-operative, B = drowsy but rousable, C = crying or struggling, D = asleep, not easily rousable; A and B were satisfactory, while C and D were unsatisfactory; and (*ii*) induction behaviour assessment using a 4-point subjective scale:[2] A = no crying, B = less than 5 cries, C = more than 5 cries, D = active crying or fighting; A and B were satisfactory, while C and D were unsatisfactory.

2. Physiological stability. This was measured in the supine position at the premedication ward round, on arrival in the holding room and under stable anaesthesia before surgery. All of the apparatus underwent standard testing procedures before each list.

(a) *Respiration*. Oxygen saturation was measured with an ear probe connected to an Ohmeda Biox Model 3700 oximeter. End-expired carbon dioxide levels were measured with a Normocap CD-102 Datex capnograph connected to a Rendell-Baker mask on an Ayres T-piece. Time was spent in alleviating fear and measurements were then averaged over the first three breaths. End-expired carbon dioxide levels tended to increase from five breaths. The respiratory rate was visually counted.

(b) *Cardiovascular system*. Pulse and systolic blood pressure readings were taken with a Critikon Dinamap model 1846SX. Cuff sizes were chosen to cover two-thirds of the arm.

3. Recovery behaviour: (*i*) the recovery times[2] of airway reflexes were taken from when 100% oxygen was administered until the Guedel airway was spontaneously expelled; the time to taking the first oral fluids was also recorded, the fluid being offered routinely by the nursing staff when the children were awake; and (*ii*) vomiting in the first 24 hours after anaesthesia was recorded.

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Statistical analysis

The Kruskal-Wallis test was used on the data for ages, weights and recovery times. Physiological parameters were compared using side-by-side boxplots[16] to assess intergroup comparisons of means and standard deviations. To take into account the correlation between successive measurements on the same patient, a repeated-measures analysis of variance was used.[17] The mean profiles of the groups were tested for parallelism. If parallelism was rejected, the groups were compared at each time point separately by Tukey's Student's range test.[18] If interaction was present, each group was analysed individually for a significant time effect by a repeated-measures analysis of variance.

Behaviour parameters were compared by χ^2 analysis, with multiple comparisons for proportions.[16] In all the statistical analysis, a P-value of $< 0,05$ was taken as significant.

Results

There were 135 children entered into the trial. The four groups were comparable for age, numbers of patients above and below 5 years and weight (Table I).

Table II shows the pre-anaesthetic behaviour patterns. Unsatisfactory behaviour in the holding room was: controls, all 10 in unsatisfactory group crying; TMD group, 5 crying and 8 asleep; intramuscular midazolam group, all 3 crying; the oral midazolam group, 4 crying and 1 30-month old child asleep. The midazolam groups were both more satisfactory than the other two groups ($P < 0,05$). Age proved to be important for holding-room behaviour. Across all four test groups, 6 out of 58 children > 5 years exhibited unsatisfactory behaviour compared with 25 out of 77 < 5 years ($P < 0,01$). Behaviour at induction was also worse in children < 5 years, 35 out of 77, compared with those > 5 years, 8 out of 58 ($P < 0,01$).

There was a strong correlation between unsatisfactory holding-room behaviour and an unsatisfactory induction; 19 out of 31 children with unsatisfactory holding-room behaviour experienced an unsatisfactory induction, compared with 25 out of 104 with satisfactory holding-room behaviour ($P < 0,01$). Of the 8 TMD group children asleep in the holding room, 4 awoke with a startled irritable reaction at induction.

Table III gives the physiological parameters. The intramuscular midazolam group had a 36% increase in the respiratory rate at the holding-room measurement, significantly more than the control or TMD groups ($P < 0,05$). No other inter-group respiratory rate differences were seen. All of the groups averaged a rate of 31-34/min in the recovery room. The holding-room oxygen saturation decreased by 1,1% and 1,6%, respectively, for the TMD and intramuscular midazolam groups. This was significant, compared with the control group ($P < 0,05$). End-expired carbon dioxide levels were not affected by any of the three premedication regimens, all four groups having similar values at all measurement times. A significant increase in systolic blood pressure, 11%, was seen in the control group in the holding room ($P < 0,05$). None of the other groups had this increase. All four groups decreased their systolic blood pressure significantly under anaesthesia ($P < 0,05$) but no inter-group differences were seen. Pulse rates were unchanged by premedication or anaesthesia. All surgery was completed in 15 minutes and no anaesthetic lasted longer than 30 minutes.

The recovery phase parameters are given in Table IV. An overall emesis incidence of 14% occurred, with no inter-group differences. All of the vomiting was mild. The mean recovery time assessed by expelling the airway was significantly prolonged in the TMD group compared with all three of the other groups ($P < 0,05$). The same applied to taking the first oral fluids ($P < 0,001$).

Discussion

The modern use of regional techniques[19,20] or rapidly acting intravenous opiates[21,22] makes routine analgesic premedication unnecessary. Anxiolysis, rather than analgesia or sedation, is the aim of modern premedication[1,4,13] with the goal of obtaining calm and co-operative behaviour in patients. Intramuscular midazolam provides this in children awaiting anaesthesia,[2,6,7]

TABLE I. NO. OF CHILDREN IN EACH GROUP, AGES AND WEIGHTS (MEAN ± SD)

	Control group	TMD	Intramuscular midazolam	Oral midazolam
Total No.	**33**	**35**	**33**	**34**
No. < 5 yrs	**19**	**21**	**16**	**21**
Mean age (yrs)	**5,7 ± 3,7**	**5,5 ± 3,5**	**6,4 ± 3,8**	**5,5 ± 3,6**
Mean weight (kg)	**15,8 ± 6,5**	**16,2 ± 7,2**	**16,7 ± 6,1**	**16,1 ± 7,0**

No differences were shown.

TABLE II. BEHAVIOUR IN THE PRE-ANAESTHETIC PHASE

	Control group		TMD		Intramuscular midazolam		Oral midazolam	
	< 5 yrs	> 5 yrs	< 5 yrs	> 5 yrs	< 5 yrs	> 5 yrs	< 5 yrs	> 5 yrs
Holding room								
Satisfactory	**10**	**13**	**12**	**10**	**14**	**16**	**16**	**13**
Unsatisfactory	**9**	**1**	**9**	**4**	**2***	**1**	**5***	**0**
Induction								
Satisfactory	**6**	**12**	**13**	**10**	**11**	**16**	**12**	**12**
Unsatisfactory	**13**	**2**	**8**	**4**	**5***	**1**	**9**	**1**

Differences (*) were shown in children under five years of age ($P < 0,05$).

TABLE III. PHYSIOLOGICAL PARAMETERS (MEAN ± SD)

	Control group			TMD			Intramuscular midazolam			Oral midazolam		
	A	B	C	A	B	C	A	B	C	A	B	C
Respiratory rate/min	23 ± 3	25 ± 6	47 ± 12	22 ± 3	24 ± 5	42 ± 12	22 ± 3	30* ± 6	43 ± 10	23 ± 3	26 ± 4	45 ± 8
Oxygen saturation (%)	96,3 ± 1,6	96,7 ± 1,7	98,3 ± 1,5	96,8 ± 1,2	95,7* ± 2,0	97,5 ± 1,9	96,3 ± 1,4	94,7* ± 2,3	97,7 ± 1,7	96,3 ± 1,5	95,9 ± 2,3	98,1 ± 1,7
End-expired CO_2 (%)	4,1 ± 0,39	4,1 ± 0,49	4,9 ± 0,73	4,0 ± 0,31	4,2 ± 0,47	5,2 ± 0,95	4,1 ± 0,32	4,3 ± 0,52	5,4 ± 0,82	4,1 ± 0,34	4,2 ± 0,56	5,0 ± 0,78
Pulse/min	100 ± 16	99 ± 17	98 ± 22	101 ± 14	99 ± 20	105 ± 22	101 ± 17	98 ± 17	101 ± 24	101 ± 15	100 ± 17	100 ± 20
Systolic blood pressure (mmHg)	96 ± 10	107* ± 11	89 ± 14	95 ± 8	97 ± 12	80 ± 14	101 ± 10	105 ± 11	88 ± 14	100 ± 7	101 ± 9	86 ± 14

A = premedication ward round; B = pre-anaesthetic in holding room; C = during stable anaesthesia before surgery.
* $P < 0,05$.

as does nasal administration,[23] while the rectal route gives variable results.[24,25]

The present clinical results confirm the efficacy of oral midazolam, as suggested from pharmacokinetic data.[10] Holding-room behaviour was peaceful in the oral and intramuscular midazolam groups. Nursing management was easy and all were awake, except 1 2½-year-old child in the oral midazolam group. In contrast, the unpremedicated group required considerably more nursing staff attention, especially for those < 5 years of age, where half were crying. In the TMD group the number of children crying was similar to that in the midazolam groups. However, one-quarter were deeply asleep, which would have contributed to the prolonged recovery time in that group.

The marked influence of age < 5 years on the behaviour of children awaiting anaesthesia or undergoing induction,[9,26] was well demonstrated. This may indicate a greater degree of anxiety in the younger child[27] or a better ability to deal with the anxiety in school-age children.[26]

Premedication had less of an effect on behaviour at induction than in the holding room, indicating the need for a sympathetic approach at this stage. Disturbed holding-room behaviour was a useful indicator of potential problems at induction, since 61% of the children with agitated holding-room behaviour experienced unsatisfactory inductions. Only 24% of those with satisfactory holding-room behaviour developed poor induction behaviour. Heavy premedication to the extent of unrousability to gentle shaking is not a sure protection against irritability and crying at induction,[2,28] as was demonstrated in the TMD group.

While premedication is primarily aimed at psychological aspects, physiological homeostasis must be maintained perioperatively.[5,15,28] Respiratory function was stable in all groups. There was no evidence of decreased alveolar ventilation as the end-expired carbon dioxide level did not alter between the ward and the holding room. Thus the small decrease in the holding room oxygen saturation seen in the TMD and intramuscular midazolam groups raises the possibility that the deterioration in the ventilation-perfusion ratio that occurs under anaesthesia in the supine position[29] may start under the influence of premedication agents. Further studies may clarify this.

Stable cardiovascular parameters were a feature of all four regimens. The significant 11% systolic blood pressure rise in the unpremedicated group while awaiting anaesthesia probably indicated anxiety.[3]

During the early recovery phase a child is at risk of respiratory obstruction,[30] vomiting[31] with aspiration, and hypoxia.[32] Hence, the shorter this time the better. Both midazolam regimens had as rapid an early recovery as the unpremedicated group, but the TMD premedication prolonged this phase by 72%. This is explained by the short elimination half-life of midazolam in children, 1,2 ± 0,34 hours,[10] compared with the long elimination half-lives of the agents in the TMD group, of 6 - 25 hours.[33,34] In addition to the immediate advantages of a rapid recovery, the ability to take oral fluids safely is important.[35,36] The unpremedicated group and both midazolam groups took oral fluids 3 - 4 hours earlier than the TMD group. This would be particularly beneficial in outpatient anaesthesia.

The incidence of emesis — 14% — was unaffected by the type of premedication, and there was no correlation with patients who received postoperative pethidine. These findings support Smith and Manford's[37] assumption that vomiting in children after minor procedures is mainly due to gastric irritation from swallowed anaesthetic gases.

We conclude from the improved pre-anaesthetic behaviour, and the lack of increased systolic blood pressure at that time, that intramuscular and oral midazolam provided an anxiolytic action in the young child. Oral midazolam 0,45 mg/kg was a

TABLE IV. RECOVERY PHASE

Parameter	Control group	TMD	Intramuscular midazolam	Oral midazolam
Vomiting (No.)	**5**	**5**	**4**	**5**
Airway out (min)	**10,8 ± 7,0**	**17,8 ± 12,0***	**11,3 ± 6,3**	**12,3 ± 5,9**
Fluid taken (min)	**277 ± 119**	**488 ± 176****	**305 ± 125**	**247 ± 100**

* $P < 0,05$.
** $P < 0,001$.

worthwhile premedication for children aged 1 - 10 years, when the time of anaesthesia was reliable and postoperative analgesia was provided by regional block.

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