A DOUBLE-BLIND STUDY OF DIAZEPAM, DROPERIDOL, AND MEPERIDINE AS PREMEDICATION IN CHILDREN

PATRICK M. F. MCGARRY, M.B., F.F.A.R.C.S.I.*

ONE OF THE PRINCIPAL CONCERNS of the anaesthesiologist is the preoperative psychic sedation of the patient. The narcotic drugs have been the time-honoured medications used to attain this, but in recent years more attention has been focussed on the tranquillizing drugs. Psychic sedation is even more desirable in children.¹ Few anaesthetists relish dealing with a crying and apprehensive child. Even fewer are capable of allaying their fears. It was felt that the anxiolytic properties of diazepam and droperidol might overcome the emotional difficulties of children in the preoperative phase and possibly decrease the need for post-operative sedatives and analgesics in the recovery room. A double-blind study was set up to evaluate these drugs and compare them to a placebo. However, when case no. 30 was reached in the series, it was decided that for comparison purposes a standard premedicant, meperidine, should be included. Another randomized test was therefore compiled to include a meperidine group. This will account for the unequal numbers in the different groups. Regarding these differences in population among the four groups, particularly the meperidine group which had ten fewer, it is of course statistically preferable to have equal numbers among groups. However, it was considered justifiable to proceed with the numbers given, as they are sufficiently large. In the various analyses presented, mean responses for a given parameter were used so that a population of 40 should give nearly as great a randomization of response as one of 50.

METHOD AND MATERIALS

One hundred and ninety children between the ages of 2 years and 8 years who were to undergo adenotonsillectomy were chosen, and only those who were graded physical status 1 were included. An information sheet was given to each parent explaining the objects of the study, and stating that investigative drugs were to be used. They were requested to inform the ward staff if they objected to their child being included in the study. Only two parents did so. A registered nurse was engaged to supervise the project, i.e. to administer the drugs, complete the initial documentation, take the children to the operating room, and when possible to assist in their recovery from anaesthesia. One child was omitted from the series because he inadvertently received double the dose of droperidol; 189 children were therefore left in the project.

The mean age and weight of the children are shown in Table I. They were divided into four groups on a randomized basis:

*Assistant Professor, Faculty of Anaesthesia, University of Manitoba; Department of Anaesthesia, Grace General Hospital, Winnipeg.

- Group 1 – diazepam 0.4 mg/kg + atropine 0.2–0.4 mg
 Group 2 – droperidol 0.05 mg/kg + atropine 0.2–0.4 mg
 Group 3 – meperidine 1.1 mg/kg + atropine 0.2–0.4 mg
 Group 4 – placebo + atropine 0.2–0.4 mg

TABLE I

Drug	Number of patients	Mean age (years)	Mean weight (lbs.)
Diazepam and atropine	48	5.3	43.7
Droperidol and atropine	50	5.2	45.0
Meperidine and atropine	40	5.5	47.4
Placebo and atropine	51	5.0	44.3
Total	189	5.3	45.1

On the night prior to operation the premedication in each group was ordered for each child. The nurse in charge of the project chose the correct one in the morning according to the randomized list of which she had the only copy. The parameters which were analysed are shown in Table II.

All the subjective parameters were graded 0 to 4. Acceptance of the mask was graded 0 to 3. All patients were induced with nitrous oxide plus oxygen 4/4 plus halothane. Succinylcholine approximately 1.1 mg/kg was given for intubation. Anaesthesia was maintained with N₂O plus O₂ plus halothane, using a non-rebreathing technique.

RESULTS

Before premedication

Statistical analysis of the three parameters (co-operation, apprehension, and restlessness) demonstrated, as expected, no significant difference between the three groups.

Prior to induction

Statistical analysis (analysis of variance) of the seven parameters which were individually analysed demonstrated that there was a significant difference between the four groups ($F = 3.22, p = 0.05$).

Further analysis of the overall combined scores (Fig. 1) showed that there was no significant difference between the droperidol and placebo groups; however, the diazepam group and the meperidine group were significantly better

TABLE II

Before premedication	Prior to induction	In recovery room
Blood pressure	Co-operation	Blood pressure
Pulse	Relaxation	Pulse
Respiratory rate	Apprehension	Respiratory rate
Co-operation	Restlessness	Recovery time
Apprehension	Confusion	Nausea and vomiting
Restlessness	Slurred speech	Narcotic requirement
	Level of consciousness	
	Acceptance of mask

FIGURE 1. Overall combined scores of subjective symptomatology.

than the placebo and droperidol groups. There was no difference between diazepam and meperidine.

Level of consciousness. Analysis of variance demonstrated that there was a significant difference between the four groups ($F = 3.23$, $p = 0.05$). Patients in the droperidol and diazepam groups were better sedated than those in the other two groups (Table III).

Anaesthetists' and surgeons' opinion of sedation. The overall evaluation demonstrated that the patients in the diazepam group were judged to be better sedated than those in the other groups. When the surgeons' opinion was analysed the results were even more conclusive in favour of the diazepam group ($p = 0.01$). The meperidine and droperidol groups were judged to be better sedated than the placebo patients ($p = 0.05$).

Acceptance of mask. Patients in the diazepam group accepted the mask better than patients in any of the other three (Table IV). However, there was a significant difference ($p = 0.05$) only between diazepam and droperidol.

TABLE III
LEVEL OF CONSCIOUSNESS

Drug	Number of patients	Awake, alert	Awake, drowsy	Easily aroused	Difficult to arouse	Cannot arouse	Mean score
Diazepam and atropine	45	32	10	3	—	—	0.36
Droperidol and atropine	50	32	9	8	1	—	0.56
Meperidine and atropine	40	32	7	1	—	—	0.23
Placebo and atropine	51	41	9	1	—	—	0.22

TABLE IV
ACCEPTANCE OF MASK

Drug	Yes	No	Total number of patients
Diazepam and atropine	37	11	48
Droperidol and atropine	27	22	49
Meperidine and atropine	27	13	40
Placebo and atropine	34	17	51

TABLE V

Drug	Total operating time (min)		Recovery time (min)	
	range	mean	range	mean
Diazepam and atropine	12-46	25.6	1-14	6.9
Droperidol and atropine	10-50	24.2	1-15	7.6
Meperidine and atropine	11-50	25.5	1-21	7.0
Placebo and atropine	15-63	26.5	1-13	5.6*

* $p = 0.05$.

After induction

There was no difference between any of the groups for total operating time (Table V).

From the analysis of variance ($F = 2.78$) of recovery time it can be concluded that the three active drugs produced a significantly longer recovery period than the placebo group (Table V).

Postoperative narcotic requirement. The incidence of narcotic requirement was high in all four groups (Table VI). In all, 75 per cent of the patients required a narcotic in recovery room, which was disappointing. Statistical analysis did not demonstrate any significant difference between the four groups.

Adverse effects

Nausea. Analysis showed that there was no significant difference between the four groups, but there was a strong trend in favour of the droperidol group. This was further confirmed when applied to the incidence of vomiting, as can be seen in Table VII. Droperidol has strong antiemetic properties. It appears that there is no statistical difference between the diazepam and placebo groups. In other words, diazepam appears to have no antiemetic properties. Furthermore, the incidence of vomiting in the meperidine group is more than twice that of

TABLE VI
POSTOPERATIVE NARCOTIC REQUIREMENT

Drug	Mean dosage of narcotic required (mg)	Percentage requiring narcotic	Actual number of patients
Diazepam and atropine	22	87.5	42
Droperidol and atropine	21	72.0	36
Meperidine and atropine	22	75.0	30
Placebo and atropine	21	84.0	43

the placebo group. It can be concluded that meperidine appears to have significant emetic properties.

Incidence of nightmare and enuresis postoperatively. The parents and/or guardians were all contacted within seven to ten days postoperatively, and information elicited with regard to the child's behaviour after leaving hospital. Attention was focussed on disturbed sleep and incidence of enuresis. The latter occurrence did not appear to be a reliable indicator, as we discovered that quite a number of the children had this complaint preoperatively. Nightmares, however, were a comparatively frequent occurrence. Table VIII shows that the diazepam group had a significantly smaller incidence of nightmares than any of the other three groups. When a correlation was made between acceptance of the mask and incidence of nightmares, it appears that with the exception of the placebo group there was no correlation. In the placebo group, however, there was a strong correlation ($p = 0.01$), as shown in Table IX.

TABLE VII
ADVERSE EFFECTS (VOMITING)

Drug	Percentage vomiting	Actual number of patients
Diazepam and atropine	20.8	10
Droperidol and atropine	4.0	2
Meperidine and atropine	45.0	18
Placebo and atropine	17.6	9

TABLE VIII

Drug	Percentage having nightmares	Actual number of patients
Diazepam and atropine	12.5	6
Droperidol and atropine	23.0	12
Meperidine and atropine	30.0	12
Placebo and atropine	26.5	13

TABLE IX
CORRELATION BETWEEN ACCEPTANCE OF MASK AND INCIDENCE OF NIGHTMARES IN THE POSTOPERATIVE PHASE

Acceptance of mask	Percentage of patients having nightmares			
	diazepam and atropine	droperidol and atropine	meperidine and atropine	placebo and atropine
Good	10.5 (4)*	29.0 (7)	38.0 (10)	18.0 (6)
Poor	18.0 (2)	23.0 (5)	31.0 (3)	54.0 (9)

*Brackets indicate actual number of patients.

DISCUSSION

The pharmacological effects of diazepam have been well documented. It has been found to produce a calm, relaxed state,² particularly in patients with cardiovascular disease. Anticonvulsant and muscle relaxing properties³ with little or

no depression of respiration or circulation,⁴ plus absence of extrapyramidal⁶ and autonomic⁷ side effects, have also been described. In children, particularly in the 4-to-8-year age group, the experience with oral diazepam has been satisfactory.⁸ Bush,⁹ however, found it unsatisfactory in children, and considers meperidine and atropine to be superior.

Droperidol belongs to a group of psycho-active drugs called the butyrophenones. They produce inhibition of psychomotor activity.¹⁰ Droperidol has been used as a premedicant in paediatric anaesthesia in a dose of 0.2 mg/kg, and has been found to have significantly more sedative action than morphine.¹⁰ However, doubt was cast on its adequacy in arousing situations such as induction of anaesthesia.

In this study the overall results showed that none of the three active drugs adversely affected the cardiorespiratory parameters measured, and no complications were recorded. However, irrespective of the drug used, the pulse rate was high on arrival in the recovery room (range 134–143). The level of consciousness just prior to the induction of anaesthesia (Table III) demonstrated that diazepam and droperidol were better sedatives than meperidine or the placebo. Despite this, the droperidol group did not accept the mask too well. This appeared to be related to the startle reaction with this drug which has been commented on by others.^{10,11} It is interesting to note that the placebo group had a better acceptance of the mask overall than either the meperidine or the droperidol group. This placebo effect is well known.¹²

Amnesic properties have been ascribed to diazepam.¹³ An attempt was made at gauging this by interviewing the children on the first postoperative morning. It was impossible in most instances to get a valid response without resorting to leading questions.

The high incidence of children requiring analgesics in the recovery phase was unexpected except in the placebo group. This is contrary to other experiences when diazepam was used for induction of anaesthesia.¹⁴ As can be seen in Table VI, there is a trend in favour of meperidine, but this was outweighed by the high incidence of vomiting. Other authors have had similar experiences.^{15,16} Droperidol appears to have strong antiemetic properties, whereas diazepam has not. Used orally, diazepam has been credited with antiemetic effects,^{8,9,14,17} but the present study does not support this finding.

Probably the most interesting aspect of this study was the incidence of emotional disturbances after the children returned home. The most frequent symptoms of postoperative emotional upset have been described as enuresis, aggressive behaviour, and night terrors.¹⁸ The latter was the one most frequently reported by the parents during this trial. This aspect of anaesthesia and surgery is all too often overlooked, although the psychiatric literature is replete with references to it.^{19–24} Evidence is readily available showing lifelong disturbances and emotional maldevelopment after adenotonsillectomy. Distrust of doctors, hospitals, anaesthesia, and surgery; anxiety, phobias, and unfavourable personality changes have all been reported after operative procedures in general and adenotonsillectomy in particular. There is no doubt that the operation is one of great psychological significance in childhood,²⁵ and one which demands greater

attention than is generally paid it. Prophylactic measures recommended include careful preparation, avoidance of separation anxiety, and finding the opportune time for operation. The value of the preoperative visit is continuously stressed, as is the proper handling of the child by all medical and nursing personnel. The value of good premedicant drugs has received scant attention from the psychiatrists. This study demonstrated that the incidence of postoperative emotional disturbances could be significantly reduced with the use of diazepam.

Many of the parents contacted were extremely worried by their child's behaviour on returning home from hospital. In some instances the child had been continuously disturbed for up to one week, screaming and crying at night. In other instances children refused to sleep in their own beds and insisted on sleeping with the parents. The family stress was considerable.

The children in this series had the benefit of a nurse assigned to the project, who devoted much time to allaying fears, answering questions, and explaining the procedure, so that they arrived in the operating room in optimal mental condition. Despite this the incidence of nightmares ranged from 12.5 to 30 per cent. This leaves room for intensive investigation in the use of drugs for preoperative medication in children, in an effort to obviate distressing and harmful psychological sequelae.

SUMMARY

A double-blind study is described, using diazepam, droperidol, and meperidine for premedication in children. The evaluation indicated that diazepam was the better drug.

Even though droperidol appears to be a very strong sedative, the children in this group were not as well prepared for surgery. However, since droperidol appears to have strong antiemetic properties, it can be concluded that it also can be useful as premedication to anaesthesia in children.

Although most children in the meperidine group appeared to be well prepared for surgery, with little or no sedation, we would consider this drug a poor premedication because of a high incidence of postoperative vomiting.

Diazepam had the added advantage in that postoperative emotional disturbances were less frequent than with meperidine. None of the active drugs used decreased the incidence of postoperative analgesic requirement.

RÉSUMÉ

On a fait une étude à double inconnu, en se servant du diazépam, du dropéridol et de la mépéridine en prémédication chez les enfants. On a estimé que le diazépam était le meilleur produit.

Même si le dropéridol semble être un très puissant sédatif, les enfants de ce groupe n'étaient pas aussi bien préparés pour la chirurgie; cependant, comme le dropéridol semble avoir de puissantes propriétés anti émétiques, on peut conclure que le dropéridol peut aussi être utile comme agent de prémédication à l'anesthésie chez les enfants.

Bien que la plupart des enfants du groupe prémédiqué à la mépéridine ont

semblé bien préparés pour la chirurgie, sans sédation ou presque, nous sommes enclins à considérer ce produit peu désirable en prémédication à cause de la fréquence consécutive de vomissements postopératoires.

Le diazépam avait aussi cet avantage que les troubles émotionnels postopératoires ont été moins fréquents que lors des prémédications à la mépéridine.

Aucun des produits utilisés n'a diminué le besoin d'analgésiques postopératoires.

ACKNOWLEDGMENTS

This study was supported by a grant from Hoffman-La Roche Laboratories. Grateful acknowledgment is made for the help given by the members of the Department of Anaesthesia, Grace General Hospital, Winnipeg, and to Mrs. D. Sandstrom, R.N., who applied herself so diligently to the project.

REFERENCES

1. ECKENHOFF, J. E. Preanaesthetic Sedation of Children. *A.M.A. Arch. Otolaryngol.* 51: 441 (1953).
2. TOURNETTA, F. J. Diazepam as Preanaesthetic Medication. *Anaesth. & Analg.* 44: 449 (1965).
3. RANDALL, L. O.; HEISE, G. A.; SCHALLEK, W.; BAGDON, R. E.; BANZIGER, R.; BORIS, A.; MOE, R. A.; & ABRAMS, W. B. Pharmacological and Clinical Studies on Valium, a New Psychotherapeutic Agent of the Benzodiazepine Class. *Curr. Ther. Res.* 3: 405 (1961).
4. TICKTIN, H. E. & TRUJILLO, N. P. Evaluation of Diazepam for Pre-endoscopy Medication. *Am. J. Digest. Dis.* 10: 979 (1965).
5. MASPOLI, M. Le Valium®: Son Action sur la respiration. *Schweiz. Med. Wchnschr.* 97: 320 (1967).
6. MCCLISH, ANDRÉ. Diazepam as an Intravenous Induction Agent for General Anaesthesia. *Canad. Anaesth. Soc. J.* 13: 562 (1966).
7. BOZZA MARRUBINI, M. & TRETOLA, L. Diazepam as a Preoperative Tranquillizer in Neuro-anesthesia: A Preliminary Note. *Brit. J. Anaesth.* 37: 934 (1965).
8. DOWELL, T. Diazepam Premedication in Paediatric Patients. *Diazepam in Anaesthesia*. Bristol: John Wright & Sons (1968).
9. BUSH, G. H. Diazepam as a Premedication in Children. *Diazepam in Anaesthesia*. Bristol: John Wright & Sons (1968).
10. WERRY, J. S. & DAVENPORT, H. T. The Psychological Effects of Pre-Medication for Paediatric Anaesthesia: A Pilot Study. *N.Z. Med. J.* 64: 641 (1965).
11. CLARK, M. M. Droperidol in Pre-operative Anxiety. *Anaesthesia*. 24: 36 (1969).
12. DOBKIN, A. B.; MALIK, K.; & ISRAEL, J. S. Double-blind Study of Hydroxine, Promethazine, Secobarbital, and a Placebo for Preanaesthetic Medication. *Canad. Anaesth. Soc. J.* 12: 499 (1965).
13. BRANDT, A. L. & OAKES, F. D. Preanaesthesia Medication. *Anaesth. & Analg.* 44: 125 (1965).
14. KYLES, J. R. Observations on the Use of Diazepam in Anaesthesia. *Diazepam in Anaesthesia*. Bristol: John Wright & Sons (1968).
15. CORMIER, A.; GOYETTE, M.; KEÉRI-SZÁNTÓ, M.; & BHEAULT, J. A Comparison of the Action of Meperidine and Diazepam in Anaesthetic Premedication. *Canad. Anaesth. Soc. J.* 13: 368 (1966).
16. HASLETT, W. H. K. A Controlled Study of Diazepam and Chlordiazepoxide as Premedication for a Standard Operation. *Diazepam in Anaesthesia*. Bristol: John Wright & Sons (1968).
17. ROLLASON, W. N. Diazepam as an Intravenous Induction Agent for General Anaesthesia. *Diazepam in Anaesthesia*. Bristol: John Wright & Sons (1968).
18. BOLANDE, R. P. Ritualistic Surgery: Circumcision and Tonsillectomy. *New England J. Med.* 280: 591 (1969).
19. FRIES, M. The Child's Ego Development and the Training of Adults in His Environment. *Psychoanalyt. Stud. Child.* 2:85 (1966).
20. JESSNER, L.; BLOM, G. E.; & WALDFOGEL, S. Emotional Implications of Tonsillectomy and Adenoidectomy in Children. *Psychoanalyt. Stud. Child.* 7: 126 (1952).

21. COLEMAN, L. L. Psychosomatic Aspects of Diseases of the Eye, Ear, Nose, and Throat. *Laryngoscope*. 59: 709 (1949).
22. COLEMAN, L. L. The Psychologic Implications of Tonsillectomy. *New York State J. Med.* 50: 1225 (1950).
23. FREUD, A. The Role of Bodily Illness in the Mental Life of Children. *Psychoanalyt. Stud. Child*. 7: 69 (1952).
24. ROSEN, M. & BRUETON, M. Emotional Disturbances in Children Having Tonsillectomy and Adenoidectomy. *Excerpta Medica: Fourth World Congress of Anaesthetologists*, 168: 47 (1968).
25. LIPTON, SAMUEL D. On the Psychology of Childhood Tonsillectomy. *Psychoanalyt. Stud. Child*. 17: 363 (1962).