LORAZEPAM AS A PREMEDICATION

G. GALE AND S. GALLOON

THERE IS STILL NO CONSENSUS among anaesthetists about the primary function of drugs given as a premedication before anaesthesia and operation. Some believe that the main action is to increase patient comfort and alleviate anxiety while others hold that potentiation of weak anaesthetic agents and prevention of undesirable side-effects are more important. Morphine and its derivatives act in both areas and for this reason these and similar narcotics are the most frequently used premedications. However, this group of drugs does have side-effects and complications, and there will always be a search for a "better" premedication.

Lorazepam (7-chloro-5(0-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4 benzodiazepin-2-one) coded as Wy-4036, trade name Ativan, is one of the newer compounds in the benzodiazepine series, and has anti-anxiety and sedative actions with no effects on the cardiovascular or respiratory systems in clinical doses.[1,2] There have been two reports on its use as a hypnotic the night before operation[3,4] and three on its use as a premedicant. In these three premedication studies lorazepam was given by mouth and was compared with diazepam in two[5,6] and with mandrax in the third.[7]

METHOD

A double-blind random study of lorazepam as a premedication was designed, comparing its effects with pantopon, both injected intramuscularly. Healthy women admitted for uterine curettage (diagnostic or therapeutic) were selected for the study, and their informed consent was obtained the day before operation. At this time they were allocated a number on the random list. No medications were given the night before operation.

Approximately two and one-half hours before the operation was scheduled, a trained nurse visited the patient and assessed her state of sedation and arousability (on a scale of 1 = alert to 6 = fast asleep), and her anxiety (1 = no anxiety to 5 = very anxious). At this time the patient was also tested for anxiety by an adaptation of the Multiple Affect Adjective Check List (MAACL),[8] which is a self-rating scale performed purely by the patient. The scale is from 0 to 21, the higher numbers reflecting more anxiety. Two hours before the operation, the patient was given either lorazepam or pantopon intramuscularly in a weight-related dose; neither the patient, the nurse giving the injection, the trained nurse doing the tests or the anaesthetist, knew which drug had been injected. One and one-half hours after the injection the trained nurse visited the patient and repeated the observations and the self-rating anxiety scale (MAACL).

When the patient arrived in the operating-room suite, the anaesthetist assessed her sedation and anxiety, examined the injection site and asked about it, and

Department of Anaesthesia, University of Toronto and Toronto General Hospital, Toronto, Ontario.

measured pulse and blood pressure. He also showed the patient three cards, with one black and white object drawn on each, and asked her to identify the object. Anaesthesia was then induced with thiopentone sodium and maintained with nitrous oxide and oxygen and intermittent thiopentone. The nurses in the recovery room were asked to make certain observations, and on the morning following the operation the patient was again assessed by the trained nurse for anxiety and behaviour. The patient was also asked then if she remembered the picture cards; if she did not, she was shown one large sheet with all pictures and asked if she remembered any. She was also asked seven questions to test her recall of events from the time of premedication to induction of anaesthesia and a further two dealing with events after the operation.

Results

There were 33 patients in the lorazepam group and 35 in the pantopon group. Table I shows that the two drug groups are evenly matched in terms of age, weight and duration of operation.

The patient self-rating test of anxiety (Multiple Affect Adjective Check List, MAACL) showed a high index of anxiety just before the premedication (Figure 1). Sixty to ninety minutes after the injection, there was a significant reduction in the patients who had lorazepam and a smaller reduction, which was not significant, in the patients who had pantopon. Both groups showed a further highly significant reduction in the anxiety rating when tested again 24 hours after the operation.

The assessment of anxiety by the trained nurse showed a significant reduction of anxiety in both groups after the premedication and a further significant reduction 24 hours after the operation, correlating very well with the changes in the self-rating MAACL. The assessment of sedation and arousability by the nurse and the anaesthetist after the premedication showed no difference between pantopon and lorazepam; both groups showed a significant increase in sedation after the premedication.

The pulse, blood pressure and respiration were remarkably stable in all patients, with changes in mean pulse and blood pressure of less than 10 units.

Observations in the recovery room showed that the pantopon patients woke up much more quickly than the lorazepam patients (Table II). Because there was a significant difference in the thiopentone dosage (0.45 mg/kg/min. in the lorazepam group but only 0.36 mg/kg/min. in the pantopon group), the effect of this larger dose on the recovery times was assessed. Table III shows that when 500 mg or less of thiopentone was given, the pantopon group stayed in the recovery room 75 minutes and the lorazepam group 96 minutes. When 525 mg or more of thiopentone

TABLE I

	Total	Mean age	S.D.	Weight (kg)	S.D.	Anaes. time	S.D.
Lorazepam	33	26.8	8.4	56.1	8.9	20.7	9.0
Pantopon	33	29.3	10.6	58.2	9.6	21.18	9.8

Age, weight and duration of anaesthesia in the two drug groups. (There were actually 35 patients in the pantopon group, but there were no records of age and weight in two of these.)

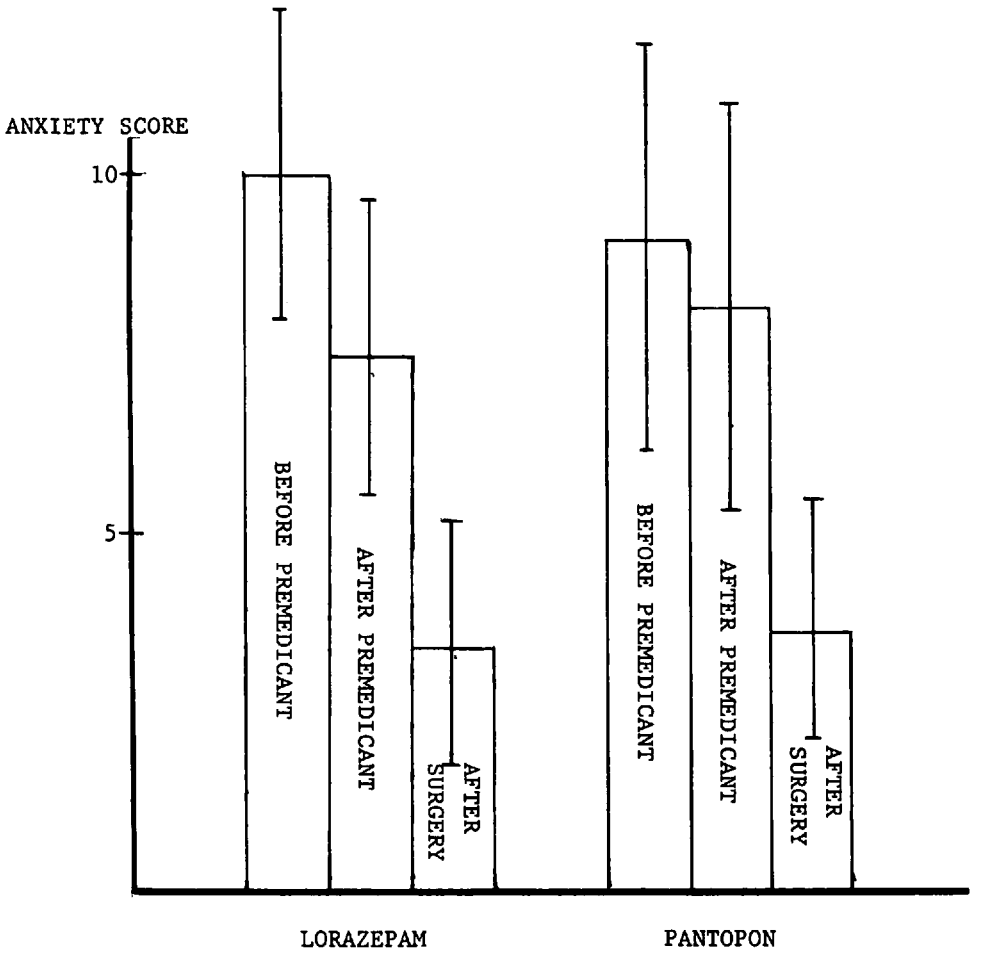

FIGURE 1. Mean score and standard deviation of the patient self-rating test (MAACL) before and after the premedication and after the surgery, with lorazepam and pantopon.

TABLE II

	Lorazepam		Pantopon	
	Mean	S.D.	Mean	S.D.
Time from finish of operation to patients opening their eyes	29.4	23.4	7.4	8.9
Time from finish of operation to the response to command	31.9	23	9.8	11.0
Total time in recovery room	103.7	42.1	75.9	24.4

Recovery times (mean and standard deviation, in minutes) after anaesthesia with lorazepam or pantopon as a premedication.

was given the pantopon group stayed in the recovery room 98 minutes and the lorazepam group 135 minutes. Thus it appears that there are two factors which prolong recovery time; one is the larger thiopentone dose, the second is an effect attributable to lorazepam.

TABLE III

Dose of thiopentone	Both groups		Lorazepam		Pantopon	
	500 mg or less	525 mg or more	500 mg or less	525 mg or more	500 mg or less	525 mg or more
Recovery times to opening eyes	16	40	26	42	7	20
Recovery times to response to command	18	44	28	46	9	35
Total recovery room time	87	126	96	135	75	98

Mean recovery times (in minutes) after anaesthesia with lorazepam or pantopon as a premedication, broken down into low and high doses.

TABLE IV

	After premedication (Patient recall)		In recovery room (Nurses' observation)		After surgery (Patient recall)	
	Nausea	Vomiting	Nausea	Vomiting	Nausea	Vomiting
Lorazepam	4	2	3	2	11	13
Pantopon	11	7	13	12	20	22

The incidence of nausea and vomiting after lorazepam and pantopon. The difference between the two groups (both with nausea and with vomiting) is significant ($p < 0.01$).

Twenty-four hours post-operatively each patient was asked if she recalled seeing any picture cards before the operation. Thirty-four out of thirty-five pantopon patients recalled seeing three picture cards but only 18 out of 33 lorazepam patients had such recall. Another lorazepam patient recalled one card. This difference between the recall of the pantopon group and the lorazepam group was highly significant ($p < 0.001$). The patient was then asked "What was on the cards?" Here again the lorazepam group had a low recall score compared to the pantopon group, with a highly significant difference between the groups ($p < 0.001$).

Where memory for the cards was incomplete or inaccurate, a composite picture was presented to the patient, and she was asked if she recognized any of it. The result of these questions indicated that many patients in the lorazepam group were able to recognize pictures in the composite that they had been unable to recall, but even with this aid to memory there was still a highly significant difference between the two groups ($p < 0.001$). Five of the seven questions about events from the time of premedication to induction demonstrated significantly less recall after lorazepam than after pantopon. The two questions dealing with post-operative events demonstrated less recall in the lorazepam group than the pantopon group with one question, the other showed no difference.

Twenty-five per cent of the pantopon patients and 51.5 per cent of lorazepam patients subsequently rated the injection as uncomfortable. The incidence of nausea and vomiting was greater in the pantopon group than in the lorazepam group in all periods looked at (Table IV). The difference was statistically highly significant. In the pantopon group, 12 patients had headaches, three after premedication, eight immediately post-operatively and one the day after operation. In the lorazepam group headache occurred in only one patient after premedication and in two patients the day after operation.

Discussion

The Multiple Affect Adjective Check List (MAACL), as adapted by Wassenaar and Lancee,[8] is a practical and sensitive assessment of anxiety, the patient herself rating how she feels in her mind, regardless of how she shows outwardly to an observer. The MAACL score in fact correlated significantly with the trained nurse's anxiety assessment, and both tests indicate that lorazepam allays anxiety as well as, if not better than, pantopon. The reduction of anxiety must surely be one of the main aims of the premedication. It was interesting, too, that when the patients were asked the day after the operation to grade their pre-operative anxiety, there was little recall for the anxiety that was shown to be present by the MAACL and the nurse's rating. This can only mean that a retrospective questionnaire, as used by Feldman,[9] is less accurate than these assessments, because of drug-induced amnesia and because anxiety is diminished when viewed with hindsight.

The degree of sedation assessed by the nurse correlated very well with the assessment by the anaesthetist, and both showed no difference between lorazepam and pantopon. Nisbet and Norris[10] suggested the use of a scoring system to assess sedation and anxiety. This combination is not satisfactory because sedation can be assessed by observation of the patient, but anxiety is a state of mind, physical signs of which may not always be evident. Therefore a test like the MAACL which shows the patient's inner feelings is likely to be more sensitive.

Two methods were used to study memory, recall and recognition. The practical significance of recall is considerable. The patient may not recall going down the corridors to the operating room and seeing the operating table or the ventilator. However, if she were to go through another operation the next day she might recognize the corridor, table or ventilator. If she does not repeat the procedure, memory connections become weaker with time and intervening events, so that even recognition becomes less probable. Thus, the meaningful measure of loss of memories regarding surgical events is the loss of recall and not loss of recognition, providing amnesia for events associated with the pain and discomfort of the operation. The lorazepam group of patients experienced a dramatic and convincing failure to recall not only the picture cards but also events that they experienced on their way to the operation. However, when the lorazepam patients were presented with the composite pictures, they were able to improve their memory score. This recognition score was still significantly lower than the score obtained by the pantopon group.

The amount of thiopentone sodium used for the operation was significantly greater in the lorazepam group than the pantopon. This is not unexpected because pantopon is analgesic and lorazepam is not, but it did complicate the analysis of recovery times. All the time-intervals recorded (for example, response to commands) were longer for lorazepam than for pantopon, but only part of this difference was due to the higher doses of thiopentone. When the times were related to doses of thiopentone less than and more than 500 mg (Table III) it became evident that part of the longer recovery was due to higher doses of thiopentone, but that lorazepam did in fact also contribute to the longer recovery.

Looking at the side-effects of premedicants, the pantopon patients had consider-

ably more headaches than the lorazepam patients. Nausea or vomiting occurred in 60 per cent of patients in the pantopon group but in only 42 per cent of the lorazepam group. Vomiting also seemed to be more severe in the pantopon group because an antiemetic, dimenhydrinate (Gravol), had to be given intra-muscularly in this group to five patients in the recovery room and to 13 patients on the ward, but to only one patient in the recovery room and three patients on the ward in the lorazepam group. The incidence after the pantopon compares loosely to a report by Dundee *et al.*,[11] who used the technique of thiopentone with nitrous oxide and oxygen to examine emesis in patients having a dilatation and curettage. He found an incidence of nausea and vomiting in the first six hours post-operatively of 53.8 per cent after premedication with meperidine (Pethidine) 100 mg with atropine; this is only slightly less than the incidence of nausea and vomiting in the pantopon group in the present study, but is higher than that found in the lorazepam group. Dundee also found that longer anaesthesia times were associated with more nausea and vomiting, but we did not specifically look at this factor, other than the fact that the mean duration of anaesthesia was comparable in the two groups (Table I).

More patients complained that the injection was painful after lorazepam than after pantopon, but 2 hours and 24 hours later there was no difference between the two drugs. The pain associated with lorazepam is almost certainly due to the propylene glycol in the solution, and is well known to occur with all drugs in the benzodiazepine family.

Summary

A double-blind random study compared the effects of lorazepam and pantopon as intra-muscular premedication in healthy women for uterine curettage (D & C). Anxiety, as assessed by a self-rating test by the patient and by a trained observer, showed a significant reduction at one and one-half hours after lorazepam and a smaller reduction after pantopon, which was not significant. Sedation was satisfactory with no significant difference between the two drugs in the change before and after the premedication. Lorazepam showed much more amnesia than pantopon ($p < 0.001$). The patients who had lorazepam required higher doses of thiopentone for the operation, and this, in part, led to longer intervals in recovery times after lorazepam. However, it is suggested that lorazepam itself was partly responsible for the longer recovery. Pantopon was followed by more nausea, vomiting and headaches, than lorazepam. The intra-muscular injection of lorazepam hurt more patients than did pantopon, but other local complications were negligible and comparable in both groups. The results of this study show that lorazepam produces better reduction of anxiety and much more amnesia than pantopon, with comparable sedation and much less nausea and vomiting. The only disadvantage of lorazepam is the lack of analgesia and, therefore, the need for more anaesthesia during the operation. The conclusion is that lorazepam is a very satisfactory premedication and warrants more use as such.

Résumé

Une étude à double insu, comparant le Lorazepam et le Pantopon comme agents de prémédication par voie IM a été effectuée chez des jeunes femmes en bonne santé, devant subir un curetage.

L'anxiété évaluée par la patiente elle-même ainsi que par un observateur entraîné était diminuée 1 h. et 1:30 h. après l'administration du Lorazepam; un effet légèrement inférieur était noté après le Pantopon (différence non significative). L'action sédative était satisfaisante et comparable avec les deux agents.

L'amnésie produite par le Lorazepam a été plus marquée qu'avec le Pantopon (p 0.001).

Les patientes prémédiquées au Lorazepam ont nécessitié des doses plus fortes de Thiopentone, ce qui allongea la période de recouvrance. Cependant, le Lorazepam semble également contribuer à un éveil plus long.

L'administration de Pantopon a donné lieu à plus de nausées, de vomissements et de céphalées comparativement au Lorazepam. Mais ce dernier a provoqué une douleur plus intense au site d'injection.

Les autres complications locales étaient négligeables dans les deux groupes d'étude.

Les résultats de cette étude, montrent que le Lorazepam est meilleur anxiolytique et occasionne moins de nausées et de vomissements, avec une sédation comparable au Pantopon. Son seul désavantage est qu'il a un faible effet analgésique et nécessite plus d'agents anesthésiques pendant l'intervention.

On peut conclure d'après cette étude que le Lorazepam est un bon agent de prémédication.

ACKNOWLEDGMENTS

We would like to thank Dr. R.A. Gordon, Chairman of the Department of Anaesthesia, University of Toronto, for his constant support and help throughout the study. Our thanks to S. Symington, R.N., for her competent command of the various tests on the patients, to the Pharmacy Department of the Toronto General Hospital for preparing the double-blind syringes, and to the nurses on the Gynaecological Wards for their co-operation. We are most grateful to Dr. W. Wassanaar, Associate Medical Director, of Wyeth Ltd., for his constant support and help from the beginning of the study, and to Wyeth Ltd., for supplying the lorazepam and pantopon and for their financial support. Finally, our thanks are due to Mr. W.J. Lancee, Head of Biomathematics, Department of Psychiatry, Research Division, Toronto General Hospital, for the magnificent computer runs and statistical analysis.

REFERENCES

1. COMER, W.H., ELLIOTT, H.W., NOMOF, N., *et al.* Pharmacology of parenterally administered lorazepam in man. J. Int. Med. Res. *1*: 216 (1973).
2 ELLIOTT, H.W., NOMOF, N., NAVARRO, G., *et al.* Central nervous system and cardiovascular effects of lorazepam in man. J. Clin. Pharmacol. & Therap. *12*: 468 (1971).
3. POWELL, W.F. & COMER, W.H. Controlled comparison of lorazepam and pentobarbital as hypnotics for presurgical patients. Anesth. & Analg. *52*: 267 (1973).
4. POWELL, W.F. & COMER, W.H. Double-blind controlled comparison of lorazepam and glutethimide as night-before-operation hypnotics. Anesth. & Analg. *52*: 313 (1973).
5. PAYMASTER, N.J. Lorazepam (Wy 4036) as a pre-operative medication Anaesthesia *28*: 521 (1973).
6. MAGBAGBEOLA, J.A.O. A comparison of lorazepam and diazepam as oral premedication for surgery under regional anaesthesia. Brit. J. Anaes. *46*: 449 (1974).

7. NORRIS, W. & WALLACE, P.G.M. Wy 4036 (Lorazepam) a study of its use in premedication. Brit. J. Anaes. *43*: 785 (1971).
8. WASSENAAR, W., & LANCEE, W.J. The measurement of anxiety in patients going to surgery. In Press (1975).
9. FELDMAN, S.A. A comparative study of four premedications. Anaesthesia *18*: 169 (1963).
10. NISBET, H.I. & NORRIS, W. Objective measurement of sedation. II. A simple scoring system. Brit. J. Anaes. *35*: 618 (1963).
11. DUNDEE, J.W., NICHOLL, R.M., & MOORE, J. Studies of drugs given before anaesthesia. III. A method for the studying of their effects on postoperative vomiting and nausea. Brit. J. Anaes. *34*: 527 (1962).