Double-Blind Comparative Trial of Parenteral Lorazepam and Papaveretum in Premedication

A. J. COLEMAN, L. T. BEES

SUMMARY

Lorazepam, a new sedative drug of the benzodiazepine group, was compared in a double-blind study with a papaveretum/hyoscine mixture in a series of 50 patients awaiting surgery.

No difference between the drugs in terms of sedation or side-effects was detected.

S. Afr. Med. J., **48**, 862 (1974).

Lorazepam is a new 1 - 4 benzodiazepine with potent sedative, hypnotic, tranquillising and muscle-relaxant propertes.[1-3] The chemistry,[4] pharmacology,[5] toxicology[6] and biotransformation[7] of lorazepam have been described and there have been favourable reports of its use as an oral premedication in surgery.[8-10]

We compared the premedicant properties of parenteral lorazepam with those of a papaveretum/hyoscine mixture (Omnopon and scopolamine).

METHODS

Fifty patients scheduled for elective surgery and clinically free of neurological or cardiopulmonary disease were investigated on a double-blind basis. Twenty-five patients received lorazepam, and 25 a mixture of papaveretum and hyoscine. Lorazepam 5 mg, or 20 mg papaveretum and 0,4 mg hyoscine were given, except to 2 patients in each group. These individuals weighed less than 55 kg and doses given were therefore halved.

The method of study was similar to that described by Nisbet and Norris,[11,12] Norris and Wallace[13] and Norris and Baird.[14] Patients were first seen in hospital on the day before operation. Considerable attention was paid to the patients' comfort and attempts were made to put them at ease by explanation and reassurance. At the end of the interview each patient was classified as being either unconcerned, moderately apprehensive or extremely apprehensive about the impending surgery. Heart rate was measured using a SAN-E1-2D16 pulse meter and a finger photo-cell. Blood pressure was measured by the standard auditory method using a sphygmomanometer arm cuff with attached mercury manometer. The lowest steady heart rate and blood pressure were noted and served as ward control measurements.

Department of Anaesthetics, University of Natal, Durban
A. J. COLEMAN, M.B. B.S., F.F.A., *Professor and Head*
L. T. BEES, S.R.N., *Technician*

Date received: 23 October 1973.

On the following day the premedicant drugs were given by deep injection into the triceps muscle. The patients were reassessed one hour later in the quiet environment of an anaesthetic room. Three sets of measurements were made on each patient, which allowed comparison of findings after premedication with those in the ward, thus enabling a scoring system to be evolved. Points for 'anxiety rating' were awarded thus:

Subjective state in the anaesthetic room

Apprehensive	0
Fully awake	1
Drowsy	2

Subjective change in state from ward to anaesthetic room

Apparent improvement, change in state 1 - 2, or 2 - 3	2
No change	1
Apparent deterioration, change in state 2 - 1	0

Objective change from ward to anaesthetic room

Fall in blood pressure >10 mmHg	2
No change	1
Rise in blood pressure >10 mmHg	0
Fall in heart rate >10 beats/min	2
No change	1
Rise in heart rate >10 beats/min	0

Objective change after stimulation (the patient was told that he was going to be given oxygen to breathe; thereupon anaesthetic breathing apparatus was gently placed over the mouth and nose)

Rise in blood pressure >10 mmHg	0
No change	1
Rise in heart rate >10 beats/min	0
No change	1

This gives the maximum possible score of 10, only 4 points of which are dependent on subjective observations. Patients scoring 0 - 4 were considered poorly sedated, those scoring 5 and 6 moderately well sedated, those scoring 7 - 10 well sedated.

Measurement of Forearm Blood Flow

In 10 patients (5 from each group) forearm blood flow was measured using a mercury-in-Silastic strain-gauge plethysmograph. The gauge was energised by a model 270 plethysmograph (Parks Electronic). Recordings were made on a 5″ potentiometric recorder (Esterline Angus). The technique of venous occlusion plethysmography involves the intermittent compression of a cuff placed on the upper arm which is rapidly inflated from a reservoir

to a pressure less than diastolic pressure. This results in swelling or increase in volume of the limb distal to the cuff. The assumption is made that the swelling is entirely due to blood inflow and that the rate of swelling equals the rate of blood flow. In the present study no arterial occlusion cuff was placed round the wrist. Flow measured therefore represents both forearm and hand components.

Blood flow was measured every 20 seconds in the anaesthetic room preceding the 'standard stimulus' and every 10 seconds thereafter. During the prestimulus control period, flow measurements were continued until a 'steady state' appeared to exist. The mean of the last 5 readings were taken as the prestimulus forearm blood flow. After stimulation, measurements were made every 20 seconds for a period of 1½ minutes. The peak value was taken as post-stimulus blood flow. It was assumed that the forearm blood flow would be increased by fear and anxiety, and that a well-sedated patient would show minimal changes after stimulation.

RESULTS

The capacities of the drugs to allay anxiety are illustrated in Tables I and II. Sedation scores 0 - 4 are considered as 'poor', 5 - 6 'fair', and 7 - 10 'good'. The mean score for lorazepam (7,72 ±1,86) was slightly less than that for papaveretum (8,00 ±1,89), but in the numbers tested the difference is not statistically significant. Similarly, when the drugs are compared with respect to the number of patients with 'good', 'fair', or 'poor' sedation, there was no significant difference.

TABLE I. SEDATION SCORES

Drug	Mean (SD)	Good (7 - 10)	Fair (5 - 6)	Poor (0 - 4)
Lorazepam	**7,72 (1,86)**	**19**	**3**	**1**
Papaveretum and hyoscine	**8,00 (1,89)**	**20**	**5**	**2**

TABLE II. APPREHENSION

	Lorazepam		Papaveretum and hyoscine	
	Ward control	1 hour after drug	Ward control	1 hour after drug
Absent	**0**	**11**	**0**	**14**
Slight	**10**	**7**	**8**	**5**
Moderate	**14**	**4**	**15**	**4**
Marked	**1**	**3**	**2**	**2**

Blood Pressure and Heart Rate (Tables III and IV)

Lorazepam: The mean heart rate in the ward prior to administration of lorazepam was 72,9 beats/min. One hour after lorazepam there was a drop in heart rate to 67,0 beats/min ($P<0,025$). After challenge there was a significant increase in heart rate to 72,9 beats/min ($P<0,001$). Systolic arterial blood pressure fell significantly, from a mean value of 125 mmHg to 117,4 mmHg ($P<0,025$). After stimulation it increased significantly, to 121,2 mmHg ($P<0,001$). Forearm blood flow was significantly increased after challenge in this group—by about 3 ml/100 ml.

TABLE III. LORAZEPAM

Observation	Ward control	Theatre control	After challenge
Heart rate (beats/min)	**72,9**	**67,0***	**72,9¶**
SD	**10,16**	**11,99**	**14,46**
% change		**−8%**	**+9%**
Systolic blood pressure (mmHg)	**125,0**	**117,4‡**	**121,2†**
SD	**13,92**	**14,01**	**16,53**
% change		**−6%**	**+3%**
Diastolic blood pressure (mmHg)	**79,3**	**78,3**	**80,6**
SD	**13,67**	**9,16**	**11,43**
% change		**−1%**	**+3%**
Forearm flow (ml/100 ml)		**4,58**	**7,81**
SD		**2,74**	**7,71**
% change			**+71%**

Level of significance: * $P<0,025$; † $P<0,010$; ‡ $P<0,005$; ¶ $P<0,001$.

Papaveretum and hyoscine: There were significant decreases in both heart rate ($P<0,005$) and systolic blood pressure ($P<0,001$) one hour after administration of papaveretum and hyoscine. After challenge, heart rate ($P<0,001$), systolic blood pressure ($P<0,010$) and forearm blood flow ($P<0,010$) were increased.

TABLE IV. PAPAVERETUM AND HYOSCINE

Observation	Ward control	Theatre control	After challenge
Heart rate (beats/min)	**72,0**	**64,2‡**	**72,2¶**
SD	**11,37**	**13,24**	**16,65**
% change		**−11%**	**+4%**
Systolic blood pressure (mmHg)	**130,2**	**117,2¶**	**121,8†**
SD	**15,06**	**16,39**	**20,03**
% change		**−10%**	**+4%**
Diastolic blood pressure (mmHg)	**80,2**	**75,3**	**76,7**
SD	**10,75**	**9,89**	**11,55**
% change		**− 6%**	**+2%**
Forearm flow (ml/100 ml)		**5,78**	**8,23***
SD		**2,49**	**1,62**
% change			**+42%**

Level of significance: * $P<0,025$; † $P<0,010$; ‡ $P<0,005$; ¶ $P<0,001$.

Side-Effects

There were no complaints of local reactions, nausea or vomiting after administration of lorazepam or papaveretum and hyoscine. No nausea or vomiting were reported in the one hour following surgery in this series.

All patients received a 'sleep dose' of thiopentone for induction of anaesthesia, and were maintained thereafter on N_2O and O_2 (70% and 30%) and 1 - 2% halothane. Three patients in each group received intubating doses of a non-depolarising muscle relaxant, pancuronium. No untoward reactions were noted.

DISCUSSION

Methods of assessing the sedative effects of drugs are open to criticism. There is much to commend subjective assessment by the patient, but this method may be invalidated by influence of the observer, by amnesia, or by other factors. This has resulted in the frequent use of scoring systems which make use of both subjective and objective responses relating to sedation. The results obtained in this study suggest that pre-operative sedation by either lorazepam or papaveretum was satisfactory. There was no difference in the cardiovascular effects of the two drugs, and no untoward reaction in relation to induction of anaesthesia, in subsequent maintenance in the operating theatre, or in postoperative course, was detected.

In conclusion, it would appear that the quality of sedation and the side-effects following lorazepam were similar to those of papaveretum and hyoscine. There have been no reports of habituation or addiction associated with lorazepam; the drug is therefore not subject to the habit-forming drug restrictions. Lorazepam appears to be an acceptable alternative premedication to the papaveretum mixture and merits more extensive clinical trials.

We should like to thank Dr G. A. Ball of Wyeth Laboratories (Pty) Ltd, and Mrs V. G. Norton.

This study was supported in part by the South African Medical Research Council.

REFERENCES

1. Norton, M. L. (1969): Paper presented at the 14th Annual Scientific Session of the Michigan Society of Anesthesiology, Detroit, Michigan, May 1969.
2. Krakowski, A. J. (1965): Psychosomatics, **6**, 26.
3. Janecek, J., Vestre, N. D., Schiele, B. C. and Zimmermann, R. J. (1966): J. Psychiat. Res., **4**, 199.
4. Bell, S. C., McCaully, R. J., Gochman, C., Childers, S. J. and Gluckman, M. I. (1968): J. Med. Chem., **11**, 457.
5. De Silva, J. A. F. and Kaplan, J. J. (1966): J. Pharm. Sci., **55**, 1278.
6. De Silva, J. A. F., Schwartz, M. A., Stefanovic, V., Kaplan, J. and D'Asconte, L. (1964): Analyt. Chem., **36**, 2099.
7. De Silva, J. A. F., Koechlin, B. A. and Bader, G. (1966): J. Pharm. Sci., **55**, 692.
8. Reyes Retona, H. (1972): Mex. J. Anest., **21**, 67.
9. Turner, D. J. (1973): Current Medical Research and Opinion, **1**, 302.
10. Wilson, J. (1973): *Ibid*, **1**, 308.
11. Nisbet, H. I. A. and Norris, W. (1963): Brit. J. Anaesth., **35**, 618.
12. Norris, W. and Nisbet, H. I. A. (1963): *Ibid.*, **35**, 473.
13. Norris, W. and Wallace, P. G. M. (1971): *Ibid.*, **43**, 785.
14. Norris, W. and Baird, W. L. M. (1967): *Ibid.*, **39**, 503.