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Parenteral premedication with Lorazepam — a dose/response study

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Summary

The dose/response characteristics of lorazepam when administered parenterally as a premedicant drug were studied. The parameters studied included its' sedative and amnesic effects as well as effects on the cardiovascular and respiratory systems. Intramuscular and intravenous routes using doses 2 mg, 3 mg and 4 mg were compared. The findings suggest that lorazepam's sedative and amnesic effects were more pronounced with the intravenous route, and that in both routes the incidence and degree of sedation and of amnesia were dose dependant. There were minimal changes in arterial blood pressure, pulse rate or quality of respiration. We recommend that due to local logistic factors, the intravenous route might be more suitable, affording a more rapid onset of sedation before induction of anaesthesia, provided that close nursing observation is available. Furthermore, lorazepam 2 mg intravenously is just as effective as the larger doses with less incidence of nausea and vomiting associated with the larger doses.

Résumé

Nous avons étudié les doses/réponses caractéristiques du lorazepam lorsqu'il est administré comme de la narcotique. Les paramètres étudiés comprenaient les effets sédatifs et amnésiques ainsi que les effets subis par les systèmes cardiovasculaire et respiratoire parmi d'autres. Dans cette étude nous avons examiné l'effet des voies intramusculaires et intraveineuses sur les paramètres ci-dessus en nous servant des doses mesurant 2 mg, 3 mg, et 4 mg pour chaque voie. Les résultats avaient suggéré que les effets du sédatif et de l'amnésie étaient plus prononcés sur la voie intraveineuse, et que dans les deux voies l'incidence et la sédation ainsi que de l'amnésié dépendrait de la dose. Nous recommandrions donc l'administration par la voie intraveineuse; (étant donné les facteurs locaux) qui assurerait un démarrage plus rapide de la sédation, avant l'induction de l'anesthésie, pourvu que la surveillance soit assurée. En plus, 2 mg de lorazepam intraveineusement administrés sont plus efficaces, et avec moins d'incidence de la nausée et du vomissement couramment associée avec des doses plus larges. La pression sanguine artérielle, la pulsation et la qualité de la respiration avaient subi aussi des changements minimaux.

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Introduction

Desirable features of parenteral lorazepam administered pre-operatively include anxiolysis, sedation, and some degree of general unawareness of the operating room environment. In a previous study on the comparison of lorazepam and diazepam as oral premedicant by Magbagbeola (1974), it was observed that lorazepam 2 mg was more acceptable than diazepam 10 mg for procedures carried out under regional anaesthesia.

The object of the present paper is to report the findings on dose/response study of injectable preparation of lorazepam as the premedicant drug on patients scheduled for minor gynaecological operations under general anaesthesia.

Materials and methods

Two hundred and twenty-five adult female patients for minor gynaecological surgery participated in this study. Informed consent was obtained from all the patients. The patients were randomly placed in the two major groups, while the physician administering the drug was unaware of the dose — all doses were made up to the same volume saline. The interval between the administration of the drug and induction of anaesthesia was not less than 60 min. One group consisting of seventy-five patients received lorazepam intravenously (IV group), while 150 patients received lorazepam intramuscularly (IM group) in the upper outer corner of the buttock. The doses and subgroups are shown in Table 1.

Basic vital signs such as arterial blood pressure, pulse rate, and respiratory rate were measured prior to administration of the drug. The following observations were made 15, 30, 45 and 60 min after the injection of lorazepam. The degree of sedation was scored as shown in Table 2. Sedation was also assessed independently by one of the authors as 'good', 'fair', 'slight', or 'nil'. Patients were shown different locally familiar objects at each time of observation, and recall of these was tested for 24 h later, except at 60 min when memory of journey to the theatre and details of events in the induction room were the parameters tested for. Those who were asleep and not rousable could not obviously be shown any objects. Such patients were included among those exhibiting total lack of recall in obsevation. Memory for these events was scored as shown in Table 4. Other parameters measured during the period of observation include changes in arterial blood pressure respiratory effects such as rate, hiccough, and laryngospasm; and emetic sequelae.

Patients were also asked if they experienced any pain at the injection site.

Results

Table 1 shows that the six subgroups of patients in this study are comparable with regards to age, weight, and duration of surgery.

Table 1. Details of the patients, duration of surgery and Recovery time

Group	No. of patients	Mean age (years) (range)	Mean wt. (kg) (range)	Mean duration of surgery (min) (range)	Mean recovery time (min) (range)
Intravenous					
2 mg	25	30.16 (15–54)	61.24 (43.1–85.7)	18.4 (8–35)	21.4 (2–55)
3 mg	25	31.28 (22–46)	54.72 (42.0–65.0)	14.68 (8–25)	32.68 (2–95)
4 mg	25	30.96 (19–48)	66.2 (55–80)	15.56 (7–25)	30.8 (15–50)
Intramuscular					
2 mg	50	29.9 (21–46)	56.3 (42.5–76)	14.46 (10–30)	17.7 (5–40)
3 mg	50	30.8 (20–45)	55.82 (48–72)	14.28 (8–22)	32.0 (15–75)
4 mg	50	34.6 (21–55)	60.46 (44–74)	17.8 (7–35)	31.94 (10–101)

Table 2. Incidence and degree of sedation (%) number of subjects given IV drug = 25, IM = 50

	Time after injection (min)																					
	15						30						45						60			
	IV (mg)			IM (mg)			IV (mg)			IM (mg)			IV (mg)			IM (mg)			IV (mg)			IM (mg)		
Group	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
Fully awake	48	40	32	94	90	88	16	4	0	56	60	62	8	4	0	22	18	16	0	0	0	12	8	8
Drowsy	48	48	56	6	10	10	48	16	24	34	36	22	20	8	0	46	56	40	20	12	0	38	56	30
Asleep but rousable	4	12	12	0	0	2	28	76	60	10	4	12	60	52	52	28	26	34	60	52	40	46	36	44
Asleep not rousable	0	0	0	0	0	0	8	4	16	0	0	4	12	36	48	4	0	10	20	36	60	4	0	18

The incidence and degree of sedation are outlined in Table 2. It shows that 60 min after the intravenous administration of lorazepam, all patients were either drowsy or asleep, 89.2% of them being actually asleep. On the other hand, only 49.3% of patients in the IM group were asleep 60 min after the injection.

An assumption that the ideal state of a premedicated patient is that of being asleep but rousable, this state was selected as ideal state of sedation in this study. It thus can be seen that in the intravenous group, 40% of the subjects were asleep but rousable for the 4 mg dose, 52% for the 3 mg dose, and 60% for the 2 mg dose, 60 min after injection. However, the rate of onset of sedation was faster with the larger dose. In the IM group, a similar trend occurs as regards the rate of onset sedation with 44% of patients who received 4 mg, 36% of those who received 3 mg and 46% of those who received 2 mg being asleep but rousable 60 minutes after injection.

Table 3 shows a comparison of the route of administration and the state of sedation at periods of observation. Forty-five min after injection of lorazepam, more patients were asleep but rousable in the intravenous groups (41/75) than in the intramuscular groups (44/150). Applying the Normal Distribution Test this difference is statistically significant (SND = 3.69; $P<0.01$). Similarly at 30 min the difference is highly statistically significant (SND = 7.73; $P<0.001$). However at 60 min, 38 out of 75 subjects in the IV group and 63 out of 150 subjects in the IM group were asleep but rousable. Using the same statistical analysis, this difference is not significant (SND = 1.23; $P>0.2$), as more patients in the IV group are now completely asleep.

Table 4 shows the percentage incidence of amnesia. A greater percentage of patients in the IM group retained clear memory of events and objects compared to the intravenous group of whom more patients had hazy or no recall of events or objects shown.

There were no significant changes in arteral blood pressure, pulse rate or respiratory parameters.

Eight patients (10.6%) in the IV group experienced nausea within the first 6 h post-operatively while four patients actually vomited. In the IM group, seven patients (4.6%) experienced nausea while only two patients vomited. These patients received 4 mg lorazepam each.

The recovery time (Table 2) was taken as

Table 3. Comparison of route of administration and state of sedation

	Time of observation (min)							
	15		30		45		60	
Group	IV	IM	IV	IM	IV	IM	IV	IM
Fully awake	30	136	5	89	3	28	0	14
Drowsy	38	13	22	46	7	71	8	62
Asleep but rousable	7	1	41	13	41	44	38	63
Asleep not rousable	0	0	7	2	24	7	29	11
Total	75	150	75	150	75	150	75	150

Table 4. % Incidence of amnesia following injection of lorazepam

	Time after injection (min)																					
	15						30						45						60			
	IV (mg)			IM (mg)			IV (mg)			IM (mg)			IV (mg)			IM (mg)			IV (mg)			IM (mg)		
Group	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
Clear (C)	72	36	8	94	98	90	40	12	0	76	68	60	56	24	0	76	54	28	24	8	0	60	24	18
Hazy (H)	12	16	52	6	2	8	40	24	20	22	30	30	24	8	12	20	44	40	24	4	4	22	40	44
No recall (N)	16	48	40	0	0	2	20	64	80	2	2	10	20	68	88	4	2	32	52	88	96	18	36	38

interval between the end of anaesthesia and the time the patient could respond appropriately to verbal commands. The differences in the recovery times for the 3 mg and 4 mg groups were not statistically significant ($P>0.05$) irrespective of route of administration. However, the recovery times for the 2 mg group were much shorter than for the larger dose schedules.

No patient complained of pain at either injection site nor was there any tenderness along the vein used for injection.

Discussion

The degree of the sedation as assessed by one of the authors independently correlated very well that observed by the nursing staff (Table 2). The results also indicated that the onset of

sedation was faster with the intravenous route than with the intramuscular route. Furthermore, the onset and degree of sedation appear to be dose-dependent particularly with the intravenous route.

In our environment, most premedicant drugs are administered intramuscularly. The results of this study show that with an intramuscular dose of 2 mg lorazepam, 12% of the patients remained awake 60 min after injection of drug compared to 0% for the same dose administered intravenously. We believe that the ideal state of a premedicated patient is that of being asleep but rousable, and using this criterion only 46% of the patients who received 2 mg intramuscularly fell in this category, compared to 60% of the patients who received the same dose intravenously. Thus our results may lead one to conclude that, with respect to sedation, the intramuscular route is not as effective as the intravenous route.

In assessing amnesia, we have used mainly recall of objects shown and events. Our results show that lack of recall for objects and events occurred more readily when the drug was administered intravenously. Its occurrence also appears to be dose dependent both in degree and rapidity of onset. This is in agreement with the findings of Gale and Galloon (1976) and MacKay and Dundee (1980). Although we did not specifically investigate the duration of amnesia following administration of the drug most patients recalled partially their stay in the recovery room (1 h) which would be approximately 3–4 h after premedication. Hewitt and Barr (1978), observed that 64% of patients who received 3 mg and 4 mg of lorazepam, intramuscularly exhibited complete lack of recall for 4–10 h.

The rate of onset, degree and incidence of amnesia seems to parallel those of sedation. These are more profound when the drug is administered intravenously. This confirms the findings of Pagano *et al.*, (1978), who emphasized the dose-dependent effect of lorazepam on both sedation and amnesia and that 4 mg intravenous lorazepam alone was significantly better than 2 mg intravenous lorazepam in providing good sedation.

Owing to certain inherent local difficulties, it is not always possible to time premedication strictly at 45 min – 1 h before induction of anaesthesia; hence the effect of premedication is hardly appreciated. It would therefore seem that in view of the more rapid rate of onset and degree of sedation observed with the intravenous route, this mode of administering lorazepam as a premedicant might be preferred. More important, the hazard of summation of many centrally-acting depressant drugs reaching peak action simultaneously (particularly for short painful procedures) will be minimized. However, if premedicant drugs should be administered intravenously, nursing staff should be available for constant signs, though our studies revealed no significant changes in arterial blood pressure, pulse rate, or respiratory parameters.

We observe in this study that 3 mg intramuscular lorazepam does not appear to provide consistently better results with regards to sedation and amnesia than 2 mg intramuscular lorazepam i.m. However, if the intravenous route is used lorazepam 2 mg is just as effective as 3 mg or 4 mg. Hence 2 mg would appear to be a safe and effective dose, particularly since the nausea and vomiting observed are associated with the larger doses. Furthermore, the recovery time is much shorter with the 2 mg dose than with the larger doses.

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