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RELATIVE AMNESIC ACTIONS OF DIAZEPAM, FLUNITRAZEPAM AND LORAZEPAM IN MAN

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1 Ten postcards were shown to groups of ten to twenty patients over 60, 90 or 270 min after intravenous injection of saline, diazepam (10 and 20 mg), flunitrazepam (1 and 2 mg) and lorazepam (4 mg).

2 Incidence of amnesia was estimated by the patients' ability to recall or recognize these cards and to recall various other incidents in the para-anaesthetic period.

3 The use of a dummy confirmed the reliability of the method of testing for amnesia in man.

4 Flunitrazepam produced a dose-related incidence of amnesia slightly longer than with the equivalent (1 x 10) dose of diazepam.

5 The onset of amnesia was slower with lorazepam (4 mg) but appeared to last for up to four hours.

6 This amnesic action of lorazepam was paralleled by a useful sedative effect but there was no similar correlation for diazepam and flunitrazepam.

7 With three drugs of different duration of action it should be possible to produce amnesia for any required clinical situation.

Introduction

The benzodiazepines appear to have specific amnesia-producing properties especially when given intravenously. Dundee & Pandit (1972) have fully investigated this in the case of diazepam. Lorazepam, a newer compound in the benzodiazepine series, has been shown to have a dose-related anti-anxiety and hypnotic action (Elliott, Nomof, Navarro, Ruelius, Knowles & Comer, 1971; Norris & Wallace, 1971; Paymaster, 1973). In addition, Wilson & Ellis (1973) found that oral premedication with this drug provided significant anterograde amnesia. More recently Heisterkamp & Cohen (1975) showed 30-60% incidence of amnesia at 15 and 30 min after lorazepam (3 mg).

Flunitrazepam (Ro 5-4200), another benzodiazepine compound, has been investigated as an intravenous induction agent and found to have an action similar to that of diazepam (Vega, 1971; Stovner, Endresen & Österud, 1973; Ungerer & Erasmus, 1973). Although its value for induction of anaesthesia may be in doubt we have attempted to study its effect on memory when used as a premedicant in low doses.

This paper describes a comparative study of the amnesic action of these two new compounds and of diazepam in man. Their formulae are given in Figure 1. The generally accepted tranquillizing or premedicant doses of these drugs were studied but, except in the case of diazepam, it is too early to be sure of the correctness of the chosen doses.

Method

The studies were carried out on healthy women, scheduled for minor gynaecological operations, to whom the test drugs were given as preanaesthetic medication. Patients who were receiving any long term tranquillizers or those who had been given a hypnotic on the night before operation were excluded.

The period of observation varied with the drug and dose used, the studies being designed to cover the expected duration of action of the compound under study. As shown in Table 1, these fall into three groups. With the short and intermediate studies the observations were all made and operations carried out in the morning, whereas with the long studies the test drugs were given at 09.00 h and the operations carried out in the early afternoon. The plan of the study is shown in Figure 2. Its nature was first explained to the patients and their cooperation requested. They were then brought to a quiet room at the appropriate time and remained there, under

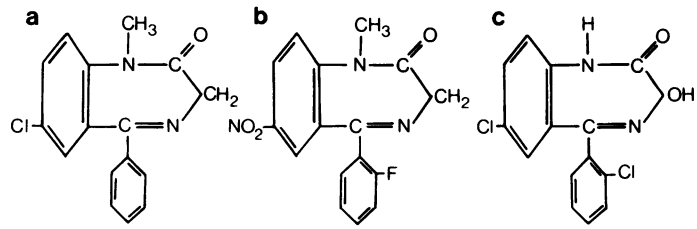

Figure 1 Formulae of a) diazepam, b) flunitrazepam and c) lorazepam.

observation, until they were taken to the operating theatre. Before administering the test drug, a familiar object such as a pen or pencil was shown to each patient, who was asked to identify it. The test drugs were given intravenously over a period of 1 min.

A series of ten cards was shown to each patient over a period of either 60, 90 or 270 min (Table 1). On each occasion the patient was asked to identify the card. The degree of drowsiness was noted in each patient—at 20, 40, 60 and 90 min after administration or at all observation times in the long study—according to the scheme described by Dundee, Moore & Nicholl (1962a). If at any time during the study patients were too drowsy to recognize the test object they were excluded from further participation in the study. The total number of patients in Table 2 indicates complete uncomplicated studies.

Patients were taken to the operating theatre and anaesthetized with methohexitone-nitrous oxide-oxygen for operations which lasted between 5-10 min. The course of anaesthesia was documented as described by Dundee, Moore & Nicholl (1962b). No patient received any supplemental analgesic drug following operation.

Table 1 Times after drug administration at which objects were shown to patients, in the three types of amnesia studies

Study	*Observation time (min)*									
Short	1	2	3	4	5	7	10	20	40	60
Intermediate	5	10	20	30	40	50	60	70	80	90
Long	20	40	60	90	120	150	180	210	240	270

Table 2 Numbers of patients studied at different parts of this investigation, together with numbers taken from paper of Dundee & Pandit (1972) which were included in final analysis

Type of study	*Drug*	*This study*				*Cases from Dundee & Pandit (1972)*	*Total analysed*
		Pilot	*Blind*	*Open*	*Total*		
Short (1-60 min)	Saline		5		5	20	25
	Diazepam (10 mg)		10		10	40	50
	Diazepam (20 mg)		10		10		10
	Flunitrazepam (1 mg)	5	10	5	20		20
	Flunitrazepam (2 mg)	5	10		15		15
	Lorazepam (2 mg)	5					
	Lorazepam (4 mg)	5					
Intermediate (5-90 min)	Saline		15		15	10	25
	Diazepam (20 mg)		10		10		10
	Flunitrazepam (2 mg)	5	10		15		15
	Lorazepam (4 mg)	5	10	5	20		20
Long (20-270 min)	Lorazepam (4 mg)	5		15	20		20

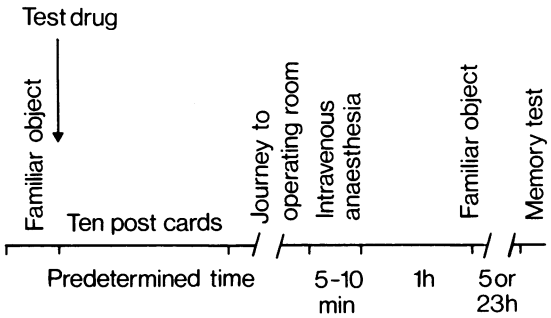

Figure 2 Plan of investigation.

One hour after recovery patients were shown a further familiar object, again making sure that they recognized it.

Each patient was visited at 6 h after operation and asked if she remembered the pictures shown to her. At first she was asked to recall the pictures, not necessarily in the order shown (recollection) and then to pick the ten out of a bundle of twenty cards (recognition). On each occasion memory for the object or event was recorded as clear, hazy or nil. Memory of the objects shown before administration of the test drug (retrograde amnesia) and 1 h after operation and for the journey to the operating room and intravenous injection (anterograde amnesia) was also tested.

Flunitrazepam and lorazepam being relatively new drugs, short and intermediate pilot studies were carried out with two doses of each of these, in which the nature of the drugs was known to the observer. There were five patients in each of these pilot studies. The short studies with lorazepam (2 and 4 mg) were not continued beyond this stage and their findings are not reported here.

Following this, two 'double-blind' studies (short and intermediate duration) were carried out (in ninety patients) with ten receiving each test drug and with sufficient saline ampoules to bring the final total with the placebo to twenty-five observations in each series. Thereafter five additional 'open' studies with the two most promising compounds brought the number of observations to the total shown in Table 2.

The time required to carry out a long study was such as to limit it to one drug and no placebo was included in this study.

In the final assessment of amnesia, the number of patients who failed to recognize or recall an object or specific event was noted. Complete amnesia signifies no memory at all for the particular event.

There was no difference between the findings in the open and blind studies, nor between the findings with saline and diazepam (10 mg) in this study and in that of Dundee & Pandit (1972) and in presenting the findings, data from all these sources are pooled.

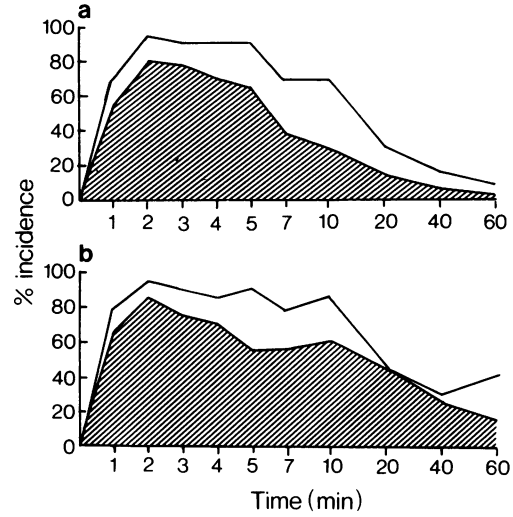

Figure 3 Percentage incidence of complete (▨) or partial (□) amnesia during the first 60 min following the intravenous injection of a) diazepam (10 mg) or b) flunitrazepam (1 mg).

Complete anterograde amnesia was not found in any of the 210 patients in this study.

Table 3 gives the findings in the fifty patients given saline. This shows the reliability of the method of study, since complete amnesia was only found in three patients during the study period and in only one did it persist for 20 min, although some impairment of memory was more common. This occurred mostly with 'recall' rather than with 'recognition' of objects.

The incidence of complete and partial amnesia found during the first hour after diazepam (10 mg) and flunitrazepam (1 mg) is very similar (Figure 3), although in these doses the effect of the latter appears to last slightly longer. Both drugs have a very transient amnesic action but doubling the dose slightly prolonged this and as seen in Table 4 the higher doses had a very marked soporific action.

Table 4 is an attempt to correlate the soporific and amnesic action of diazepam and flunitrazepam. Even when one considers partial and complete amnesia together there is only a very rough correlation between these two facets of drug action. With the lower doses of these two drugs, the incidence of patients classified as drowsy who had concomitant amnesia was 50% at 20 min, 25% at 40 min and 20% at 60 min; the corresponding

Table 3 Incidence of complete, or partial, amnesia for object shown at the times specified following administration of intravenous saline in two series, each consisting of twenty-five patients

		Time after saline (min)																
	R	*1*	*2*	*3*	*4*	*5*	*7*	*10*	*20*	*30*	*40*	*50*	*60*	*70*	*80*	*90*	*J*	*PO*
Amnesia																		
Complete	0	1	1	1	1	0	1	3	1		0		0				0	0
Partial	0	4	4	8	7	7	6	6	8		5		4				0	0
Complete	0							0	0	0	0	0	0	0	0	0	0	0
Partial	1					2		5	5	4	4	4	4	6	1	3	0	0

R = Retrograde amnesia; J = Memory of journey to operating theatre; PO = Memory of object shown 1 h postoperatively

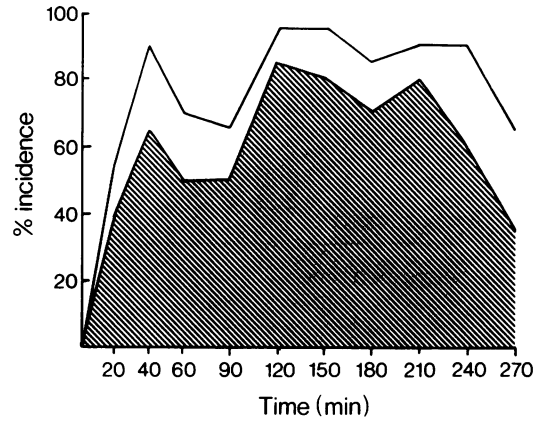

Figure 4 % incidence of complete (■) or partial (□) amnesia during the first 270 min following intravenous injection of lorazepam (4 mg).

figures for the larger doses were 60%, 40% and 38% respectively. It is obvious that some patients who appear to be drowsy can be readily aroused and can later recall events occurring during this period. It is also obvious that the amnesic action of these two drugs is much shorter than their soporific effects.

In contrast with diazepam and flunitrazepam the amnesic action of lorazepam (4 mg) was much slower in onset and lasted for up to 4 h (Figure 4; Table 5). The correlation between the amnesic and soporific action of the drugs is obvious in this study.

Cardiovascular upset or respiratory depression were not encountered with the doses of drugs used in this study and none of them caused a troublesome incidence of venous thrombosis.

Discussion

Table 3 confirms the reliability of the method of study to detect anterograde amnesia. It was not surprising to find that the 90 min study produced less 'false positive' readings with saline than the short study in which six objects were shown over a seven-minute period. This is undoubtedly a very rigorous test of memory.

The study was designed to compare the degree of amnesia produced by the newer benzodiazepines with that of diazepam. The intravenous route was chosen because Pandit & Dundee (1970) did not find significant anterograde amnesia with intramuscular diazepam. Even with the intravenous route there was often a considerable individual variation in response to the three

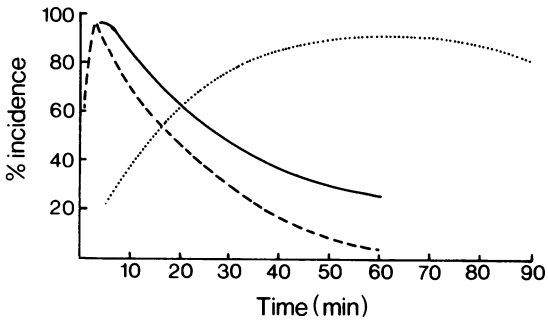

Figure 5 % incidence of any degree of amnesia at the times shown following intravenous injections of lorazepam (4 mg, ...), flunitrazepam (1 mg, ———) and diazepam (10 mg, - - - -).

benzodiazepines particularly with respect to sedation. Two patients of similar age and weight often reacted differently to the same drug given on the same day.

Our findings substantiate the view that both flunitrazepam and lorazepam appear to have a specific amnesia-producing action. A dose-related increase in incidence of amnesia and drowsiness was seen with both diazepam and flunitrazepam. At both dose levels studied flunitrazepam was slightly longer acting than the assumed equivalent dose of diazepam (Table 4). Perhaps our rates of equipotency need revision.

The present findings substantiate previous claims that lorazepam (4 mg) is capable of producing a prolonged period of amnesia. This is accompanied by an equally long soporific effect (Table 5). This confirms the findings of Heisterkamp & Cohen (1975). Although there was good correlation between amnesia and sedation with this drug, these patients were able to be aroused and they could readily identify the memory card. It appears that lorazepam (4 mg) is ideal if prolonged sedation and amnesia is required.

Figure 5 gives an overall comparison of the sedative action of the compounds studied both in relation to their duration of action and the reliability of amnesic action. Even though this is drawn freehand it gives a basis on which one could

Table 4 Incidence of notable (marked and fair) drowsiness and of complete (+) and any amnesia at 20, 40 and 60 min after the drugs shown. There were twenty patients in each series

	Time after drug (min)								
	20			*40*			*60*		
Drugs given intravenously	*Drowsiness*	*Amnesia +*	*Amnesia Any*	*Drowsiness*	*Amnesia +*	*Amnesia Any*	*Drowsiness*	*Amnesia +*	*Amnesia Any*
Diazepam 10 mg	8	3	9	7	1	4	4	1	3
20 mg	16	7	11	18	6	11	16	5	9
Flunitrazepam 1 mg	16	9	18	17	5	11	16	3	11
2 mg	19	14	20	17	9	9	16	7	11

Table 5 Incidence of amnesia and drowsiness at varying times following intravenous administration of lorazepam (4 mg)

		Time after drug (min)										
	R	*20*	*40*	*60*	*90*	*120*	*150*	*180*	*210*	*240*	*270*	*J*	*PO*
Amnesia													
Complete	0	8	13	10	10	17	16	14	16	12	7	3	1
Partial	0	3	5	4	3	2	3	3	2	6	6	6	1
Nil	20	9	2	6	7	1	1	3	2	2	7	11	18
Drowsiness													
Marked		7	11	13	14	14	14	15	12	11	9		
Moderate		9	5	4	3	4	4	4	7	7	8		
Slight		4	4	3	3	2	2	1	1	2	2		

R = Retrograde amnesia; J = Memory of journey to operating theatre; PO = Memory of object shown 1 h postoperatively

employ a specific benzodiazepine in relation to the desired duration of amnesia.

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