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EFFECT OF ORAL BENZODIAZEPINES ON MEMORY

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SUMMARY

The effects of the oral administration of diazepam 5, 10 and 20 mg, flunitrazepam 0.5 and 1 mg and lorazepam 1, 2 and 4 mg on memory were studied in groups of healthy patients before surgery. The degree of sedation was noted also. A dose-related amnesic effect was produced by all the drugs, but this was not significant with diazepam 5 mg and lorazepam 1 mg. Larger doses of diazepam (10 and 20 mg) produced brief amnesia comparable to equivalent doses of flunitrazepam (0.5 and 1 mg). There was the same delay in the onset of amnesia after oral lorazepam 4 mg as when it was given i.v. and its effect lasted for at least 90 min after administration. In contrast to the effect of the same drugs given i.v., drowsiness and failure of recognition follow a similar time course.

Shortly after its introduction it was noted that i.v. diazepam caused anterograde amnesia (Brandt and Oakes, 1965; Haslett and Dundee, 1968). This property has since been investigated in a number of clinical studies. The amnesic action is more marked when diazepam is given i.v. than after i.m. injection (Pandit and Dundee, 1970; Pandit, Dundee and Keilty, 1971). The latter authors found that narcotic analgesics given alone produced a negligible frequency of amnesia, but caused more drowsiness after operation than combinations of diazepam or hyoscine and suggested a specific amnesic action of diazepam. Dundee and Pandit (1972) found that diazepam 10 mg i.v. caused significantly more amnesia than hyoscine 0.4 mg or 0.6 mg, the peak effect of diazepam occurring 2–3 min after administration and lasting 20–30 min. Frumin, Herekar and Jarvik (1976) also found diazepam to be more effective than hyoscine, although their stimuli were not presented until 15 min after i.v. injection.

Clarke and others (1970), in a detailed volunteer study, confirmed that i.v. diazepam, in clinical doses, caused anterograde amnesia maximal in the first 10 min after administration and that this was not accompanied by a serious reduction in the level of consciousness. They concluded that the drug acts upon the process of consolidation in memory formation rather than registration (input) or retrieval (output) (fig. 1). This was also the finding of Grove-White and Kelman (1971) and of Gregg, Ryan and Levin (1974). These latter authors also noted, in patients undergoing oral surgery under local anaesthesia and i.v. diazepam, that "strong" operative stimuli were recalled more frequently than experimental stimuli, and that these two responses paralleled each other. Ghoneim and Mewaldt (1975) reached similar conclusions on the mode of action of both diazepam and hyoscine and suggested that a central anticholinergic action might be involved in both cases.

Amnesic properties have also been attributed to the more recently introduced benzodiazepine, lorazepam, even when given by mouth (Wilson and Ellis, 1973; Harry and Richards, 1972). With the i.v. route, Heisterkamp and Cohen (1975), using a single stimulus presented 30 min after injection, found a dose-related amnesic effect with lorazepam, but no significant amnesia with diazepam or pentobarbitone. Other authors have also found marked amnesia with i.v. lorazepam (Blitt et al., 1976; Taub and Eisenberg, 1976; George and Dundee, 1977; Brown et al., 1978). Flunitrazepam (R05 4200; Rohypnol) also causes anterograde amnesia (Dundee et al., 1976), comparable in effect, in terms of both the extent and duration of action, to that of equivalent doses of diazepam (George and Dundee, 1977).

It appears to be a consistent finding that, in adequate doses, i.v. diazepam causes rapid onset (2–3 min), short-lasting (20–30 min) anterograde amnesia. Increasing the dose affects the duration rather than the degree of amnesia (Gregg, Ryan and Levin, 1974; Dundee, 1979). In contrast, lorazepam has an amnesic action after both oral and i.v. administration; with both routes there is a

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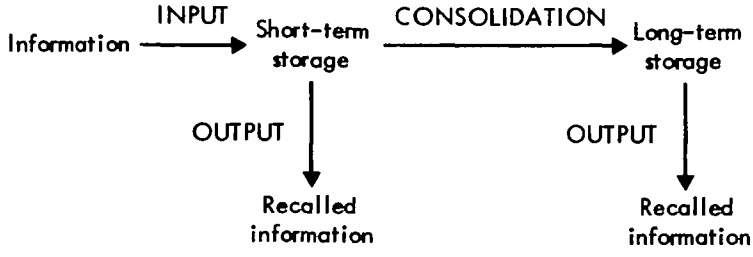

FIG. 1. Suggested model of memory processes (Cherkin and Harroun, 1971).

delay in onset (30–40 min) and prolonged amnesia (up to 270 min). The findings for oral diazepam are less consistent, however. Several authors did not find amnesia (Dundee and Keilty, 1969; Harry and Richards, 1972; Wilson and Ellis, 1973), although it was reported in volunteers by Baird and Hailey (1972).

Although the amnesic properties of i.v. benzodiazepines are important, clinically, the popularity of the drugs in routine premedication depends largely on the ease and convenience of their oral administration. Evidence on their amnesic action by this route is conflicting. The present study was carried out in an attempt to quantify this using the method of Dundee and Pandit (1972), Dundee and George (1976) and George and Dundee (1977) as described for i.v. drugs. In addition, an attempt was made to investigate any relationship between amnesia and sedation and to ascertain to what extent these properties are separate entities.

PATIENTS AND METHODS

The investigations were carried out on healthy adult women, weighing between 45 and 75 kg, about to undergo minor gynaecological operations. They were not receiving any regular medication and had not been given any drugs on the night before surgery. Each drug or combination of drugs was studied in not less than 10 patients (table I).

TABLE I. *Details and numbers of patients in the various groups studied*

Drug	Dose (mg)	Mean age (yr)	Mean weight (kg)	*n*
Diazepam	5	31	61	10
Diazepam	10	31	60	20
Diazepam	20	29	59	20
Flunitrazepam	0.5	33	59	20
Flunitrazepam	1	30	58	20
Lorazepam	1	29	62	20
Lorazepam	2	31	58	10
Lorazepam	4	29	58	20
Lorazepam + hyoscine	2 1	32	58	10
Lorazepam + hyoscine	4 1	33	63	10
Inert		30	57	40

A simplified, standard explanation of the nature and purpose of the study was given to each patient and verbal permission to participate was obtained. The patient was shown a familiar object such as a pen, and asked to identify it and the test drug was administered (fig. 2).

Five minutes after administration the patient was shown a picture postcard of a familiar scene and asked to identify it without prompting or correction. A second card was shown 5 min later

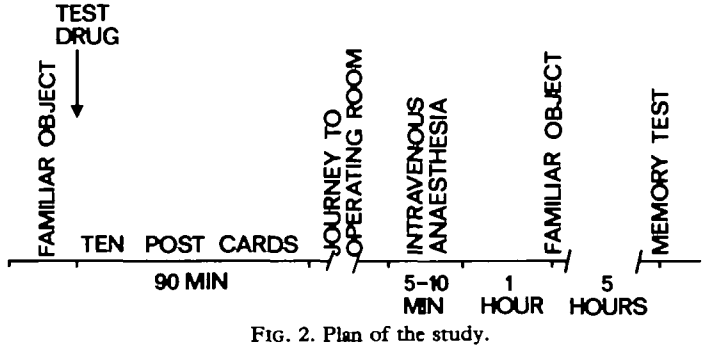

FIG. 2. Plan of the study.

and thereafter a card was shown every 10 min up to a total of 10. The contents of these were emotionally neutral and they were chosen so that no two could be confused readily with each other. The sequence used was the same in all patients.

At each visit the condition of the patient was assessed with regard to the efficacy of the drug as a premedicant, using the method described by Dundee, Moore and Nicholl (1962). A "score" was allotted ranging from 1 (awake, apprehensive and restless) to 5 (lightly asleep) as each card was presented. If the patient was asleep she was roused and asked to identify the card.

After 90 min the patient was brought to the operating theatre, where anaesthesia was induced with 2% methohexitone 1.6 mg kg^{-1} and maintained with 75% nitrous oxide in oxygen, supplemented by additional methohexitone as required.

One hour after recovery from anaesthesia the patient was shown a second familiar object and asked to identify it. Six hours after her operation each patient was visited again. Patients were asked first: "Did I show you anything before you had your tablet?" and second "Did I show you anything after your operation?" Each patient was then asked whether she remembered the journey from the ward to the operating theatre and the i.v. injection.

At the 6-h visit the patient was asked to recall, in any order, as many of the postcards as she could (recall). She was then presented with a sequence of 20 cards in random order, consisting of the 10 seen already and 10 "dummies". (It was explained that some, but not all, of these cards had been seen previously and that the patient had to select those seen previously (recognition).)

Performance on unaided recall and on recognition was scored for each postcard as clear, hazy or nil. Several indices are available by means of which the degree of amnesia might be quantified. In the "control" studies the frequency of complete or partial failure of recognition was very low indeed, occurring in only seven of 400 presentations and this parameter is used in most of the results shown. In addition, the overall frequency of amnesia was calculated as described by Dundee and Pandit (1972). Complete amnesia required failure of recall and recognition, while absence of amnesia indicated complete clarity of recall and recognition. Intermediate grades were classed as partial amnesia. The statistical significance of the findings was calculated on absolute numbers by the χ^2 method with $P<0.05$ as the lower level of significance.

RESULTS

A total of 160 drug observations were made, as well as 40 observations on patients who were given an inert preparation. The groups of patients were broadly comparable with regard to average age and weight (table I).

The frequencies of complete or partial failure of recognition in each group are shown in table II. This gives the percentage frequency of amnesia for the object shown before drug administration

TABLE II. *Percentage frequency of failure of recognition at the times shown following the administration of the various drugs (or combinations). R = memory of object shown before administration of drug (retrograde); J = memory of journey to operating theatre; I = memory of i.v. injection; O = memory of object shown 6 h following administration of drug*

Drug	Dose (mg)	Time after administration (min) R	5	10	20	30	40	50	60	70	80	90	J	I	O
Diazepam	5	0	0	0	0	10	0	0	0	0	10	0	0	0	0
Diazepam	10	5	5	0	0	25	40	25	40	10	15	25	5	0	15
Diazepam	20	0	0	0	10	25	30	25	25	30	50	35	10	0	5
Flunitrazepam	0.5	5	0	5	0	25	30	20	25	15	25	10	5	0	5
Flunitrazepam	1	10	5	5	20	55	50	35	65	30	55	50	5	15	15
Lorazepam	1	0	0	0	0	0	0	0	5	10	10	10	0	0	0
Lorazepam	2	10	0	0	0	0	10	10	20	20	10	30	10	10	70
Lorazepam	4	0	0	0	5	5	25	35	50	45	55	70	65	70	40
Lorazepam + hyoscine	2 1	0	0	0	0	0	10	20	30	30	50	60	20	20	40
Lorazepam + hyoscine	4 1	20	0	0	0	30	20	30	50	50	70	60	80	80	90
Inert	—	2.5	0	0	0	0	2.5	5	0	5	2.5	0	0	0	2.5

(retrograde amnesia), the journey to the operating theatre, the i.v. injection and the object shown 1 h after operation. There was a dose-related amnesic effect for all three benzodiazepines.

Diazepam 5 mg caused no greater impairment of recognition than an inert preparation. A significant amnesic effect occurred with 10 mg and 20 mg beginning 20–30 min after administration and persisting for at least 90 min. The effect of the two larger doses did not differ until 70 min after administration, at which time 20 mg produced a significantly greater frequency of failure of recognition (fig. 3).

Both doses of flunitrazepam caused appreciable failure of recognition beginning at 20–30 min (fig. 4); 1 mg had a significantly greater amnesic effect than 0.5 mg.

The amnesic action of lorazepam was clearly dose-related (fig. 5). The effect of 1 mg did not differ significantly from that of placebo. At all observation times 4 mg produced a significantly greater frequency of failure of recognition than

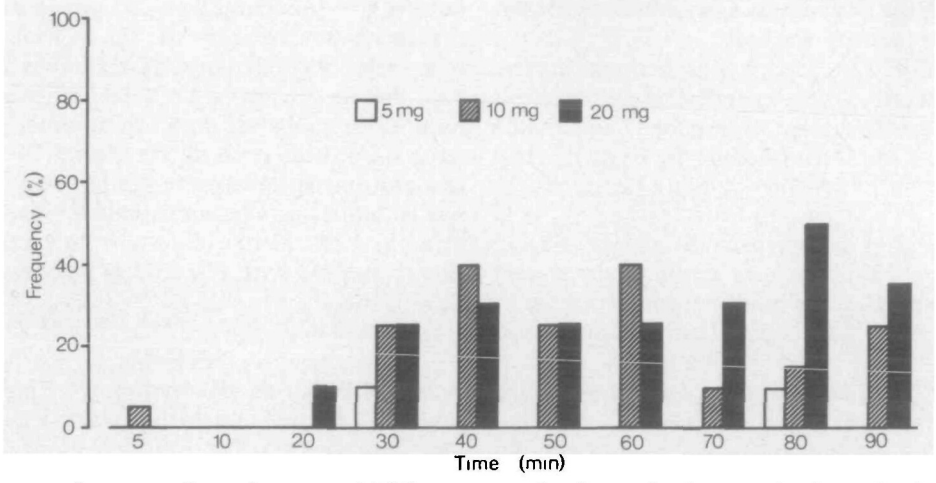

FIG. 3. Percentage frequency of complete or partial failure to recognize the previously seen stimulus at the times shown after the oral administration of diazepam 5 mg, 10 mg and 20 mg.

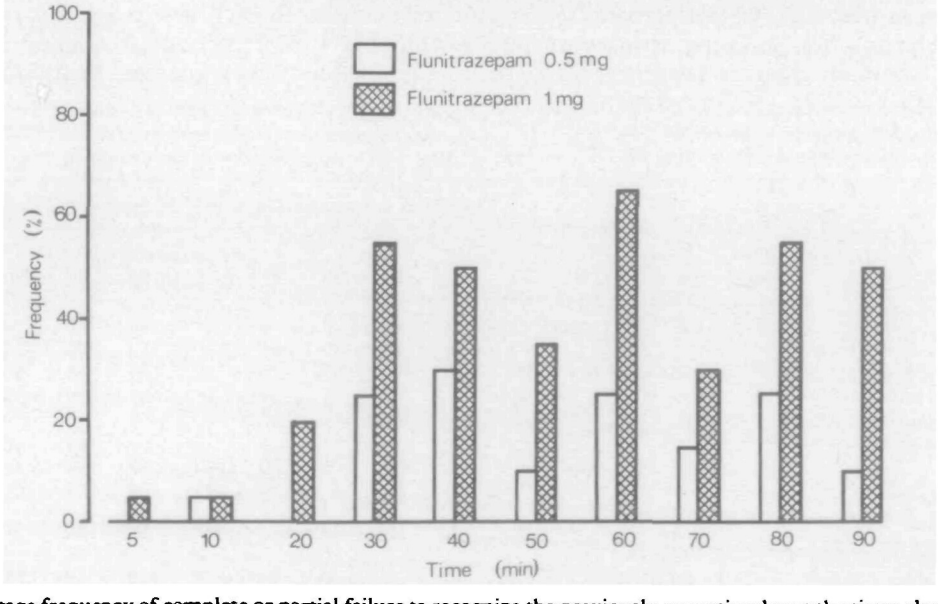

FIG. 4. Percentage frequency of complete or partial failure to recognize the previously seen stimulus at the times shown after the oral administration of flunitrazepam 0.5 and 1 mg.

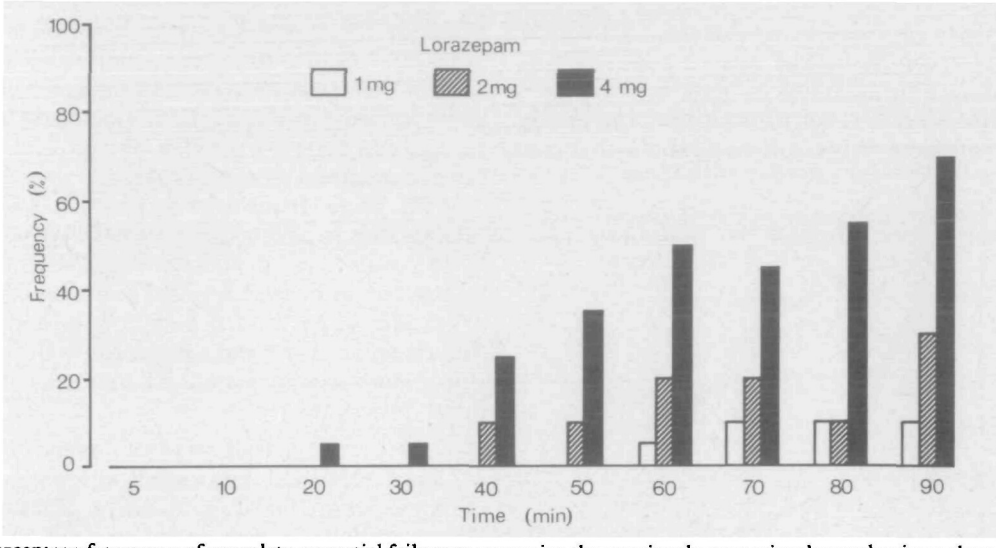

FIG. 5. Percentage frequency of complete or partial failure to recognize the previously seen stimulus at the times shown after the oral administration of lorazepam 1 mg, 2 mg and 4 mg.

2 mg, but even with the greater dose the onset of action did not occur until 40 min after administration.

Flunitrazepam 1 mg and diazepam 20 mg appeared to have a similar potency and time course of action. In contrast lorazepam 4 mg had a more delayed onset of effect and a higher frequency of failure of recognition, and its amnesic effect showed no sign of diminishing at 90 min.

The addition of hyoscine 1 mg to lorazepam 2 mg increased the failure of recognition at 80 and 90 min but this did not occur with the 4-mg dose. Some patients receiving hyoscine complained of dry mouth, dizziness and restlessness, while others who received it in combination with lorazepam 4 mg were more deeply sedated than was considered safe or desirable. The addition of hyoscine did not hasten the onset of amnesia in either case.

The frequency of retrograde amnesia (as measured by failure to remember the object seen before administration of the drug) was negligible in all series (table II). There was also a low frequency of amnesia for the journey to the operating theatre and the i.v. injection, except with lorazepam 4 mg (with or without hyoscine). Persistence of amnesia until 1 h after operation was seen only with lorazepam.

Table III gives the data for failure of recall.

TABLE III. *Percentage frequency of failure of recall at the times shown following the administration of the various drugs (or combinations)*

Drug	Dose (mg)	Time after administration (min)									
		5	10	20	30	40	50	60	70	80	90
Diazepam	5	0	10	0	20	0	10	10	10	10	0
Diazepam	10	10	10	45	50	60	55	85	50	75	40
Diazepam	20	10	5	40	35	50	55	80	65	70	70
Flunitrazepam	0.5	5	15	45	60	50	40	80	50	60	30
Flunitrazepam	1	15	5	60	60	60	45	80	60	75	55
Lorazepam	1	0	5	15	15	0	30	30	30	35	30
Lorazepam	2	0	0	0	0	20	40	50	70	70	80
Lorazepam	4	0	5	15	15	55	55	75	90	75	90
Lorazepam + hyoscine	2 + 1	10	0	0	10	50	40	80	40	80	90
Lorazepam + hyoscine	4 + 1	10	10	15	50	50	70	80	70	80	100
Inert	—	12.5	20	17.5	10	10	22.5	12.5	27.5	10	7.5

Clearly there is a difference between failure of recall and recognition, the latter occurring less frequently. The difference between the two frequencies decreased consistently with increasing dosage of all three drugs. Figure 6 expresses this as

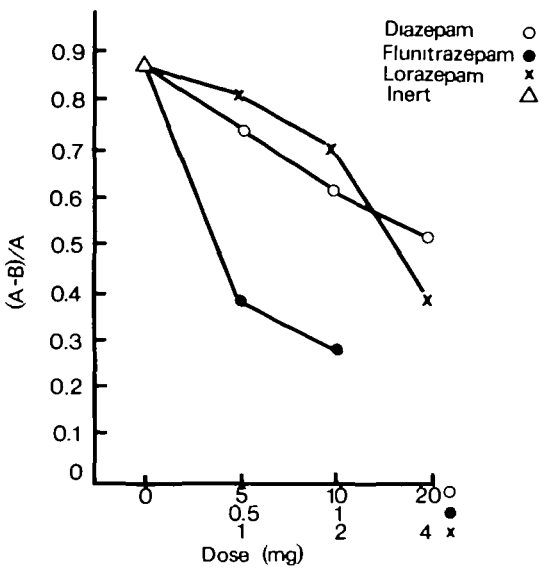

FIG. 6. The relationship between the difference between percentage failure of recall (A) and percentage failure of recognition (B) expressed as a ratio of the former and dose for the three benzodiazepines studied.

the difference in the frequency of recall (A) and recognition (B) divided by the frequency of recall.

Drowsiness and amnesia

Table IV shows the percentage frequency of marked drowsiness or sleep (efficacy score of 4 or 5) for each series. The relationship between this index and failure of recognition with two doses each of diazepam (fig. 7) and lorazepam (fig. 8) is shown clearly; increasing drowsiness and failure of recognition follow a similar time course and are not independent of each other.

With some drugs it was possible to show a relationship between the total number of failures of recognition of postcards and the cumulative "sedation" score in individual patients. Figure 9 is a typical positive finding based on the results with flunitrazepam 1 mg and substantiates the relationship between amnesia and drowsiness with oral benzodiazepines.

Comparison of the oral and i.v. routes

Using published data based on identical methodology from the same centre (Dundee and Pandit, 1972; George and Dundee, 1977) it is possible to compare the effect of diazepam 10 and 20 mg, lorazepam 4 mg and flunitrazepam 1 mg given by the oral and i.v. routes. Table V shows the percentage frequency of any degree of failure of recognition of cards with the same drug given by different routes. Lorazepam 4 mg produced a similar impairment of recognition by both routes, with a more delayed onset of action when taken by mouth. In contrast, the time course of action of both diazepam and flunitrazepam was very different when given by mouth as compared with i.v. administration.

This difference is illustrated in figure 10, which is based on data for diazepam 10 mg and shows that the amnesic effect of the i.v. drug is waning, while that of the oral drug has not yet reached its maximum. This applies also to flunitrazepam.

TABLE IV. *Percentage frequency of marked drowsiness or sleep at the time of the stimulus in various groups*

Drug	Dose (mg)	Time after administration (min)									
		5	10	20	30	40	50	60	70	80	90
Diazepam	10	0	0	15	25	45	40	60	50	50	60
Diazepam	20	0	0	10	25	40	40	55	80	80	80
Flunitrazepam	0.5	0	0	25	40	40	40	65	60	55	45
Flunitrazepam	1	0	0	20	65	60	70	70	70	65	55
Lorazepam	2	0	0	0	40	40	50	50	70	60	70
Lorazepam	4	0	—	0	—	35	—	90	—	—	90
Lorazepam + hyoscine	2 + 1	0	0	10	10	20	40	50	60	70	90
Lorazepam + hyoscine	4 + 1	0	0	10	30	60	60	60	70	70	70

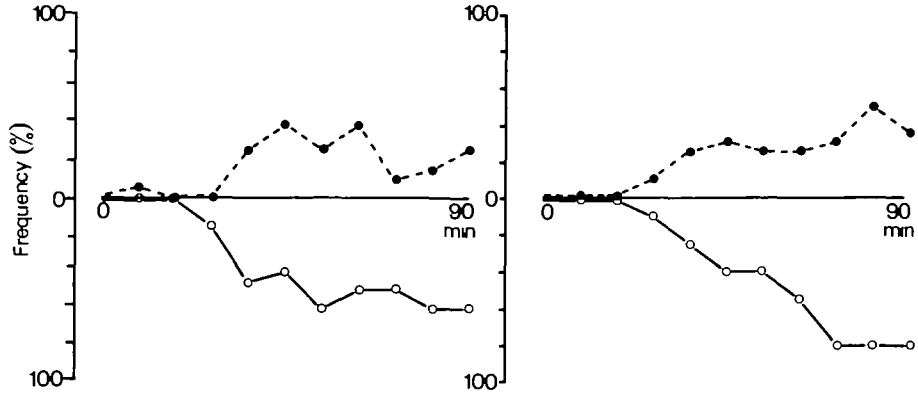

FIG. 7. The relationship between failure of recognition (●---●) and marked drowsiness (○——○) after the oral administration of diazepam 10 mg (left) and 20 mg (right).

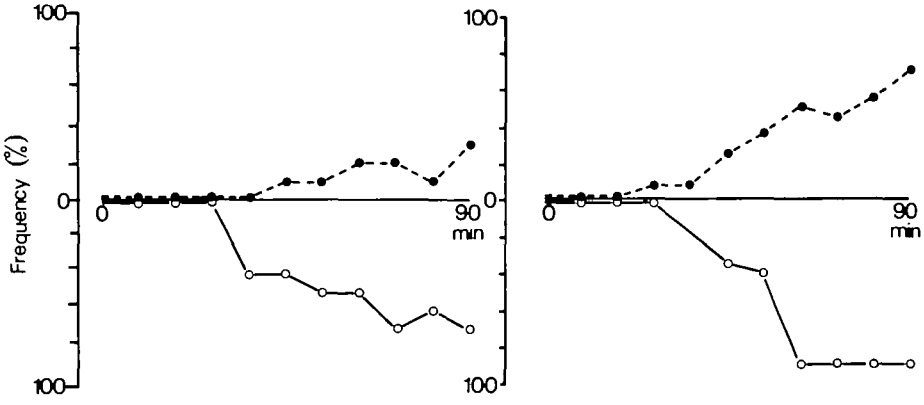

FIG. 8. The relationship between failure of recognition (●---●) and marked drowsiness (○——○) after the oral administration of lorazepam 2 mg (left) and 4 mg (right).

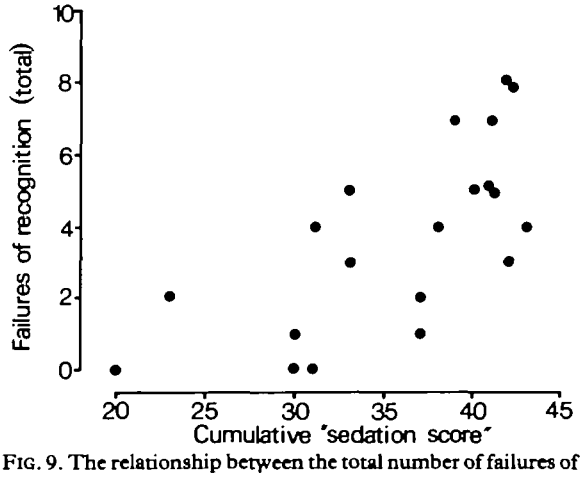

FIG. 9. The relationship between the total number of failures of recognition and the cumulative "sedation score" over 90 min in individual cases after the administration of flunitrazepam 1 mg.

DISCUSSION

The three benzodiazepines, when given orally in doses used normally for premedication, produced dose-related anterograde amnesia. This paralleled closely, both in extent and duration, their soporific action. However, no detectable degree of amnesia was found with minimal tranquillizing doses of diazepam (5 mg) or lorazepam (1 mg).

The ability of premedicant doses of these agents to produce amnesia by the oral route may be a useful adjunct to their anxiolytic and soporific effects. Amnesia for the experimental stimuli (postcards) was much greater than for the emotionally significant experiences of being taken to the operating theatre and being given an i.v. injection. This occurred soon after the 90-min postcard was shown, so that the difference (table II) cannot be

TABLE V. *Percentage frequency of complete and partial failure of recognition with the same drug given by the i.v. and oral routes. (Data on i.v. administration taken from Dundee and Pandit (1972) and George and Dundee (1977))*

Drug	Dose (mg)	Route	Time after administration (min)									
			5	10	20	30	40	50	60	70	80	90
Diazepam	10	i.v.	60	37	17	—	7	—	3	—	—	—
		oral	5	0	0	—	40	—	40	—	—	—
Diazepam	20	i.v.	60	30	30	20	40	40	40	30	20	0
		oral	0	0	10	25	30	25	25	30	50	35
Lorazepam	4	i.v.	15	50	55	70	65	80	60	80	70	75
		oral	0	0	5	5	25	35	50	45	55	70
Flunitrazepam	1	i.v.	65	65	40	—	15	—	10	—	—	—
		oral	5	5	20	—	50	—	65	—	—	—

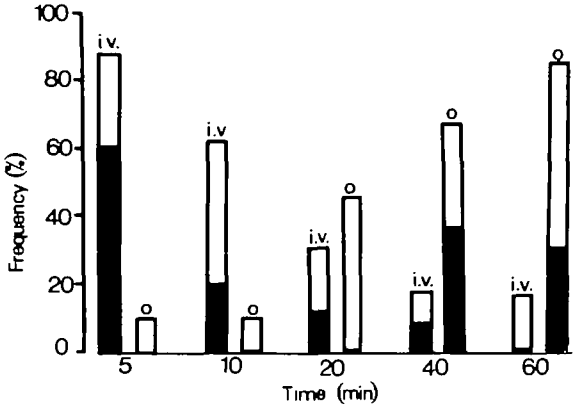

FIG. 10. Percentage frequency of complete (solid) and partial (clear) failure of recognition at the times shown following the i.v. and oral (o) administration of diazepam 10 mg.

explained solely on the basis of time after administration of the drug. It would appear unwise to handle a patient who has had an oral benzodiazepine in any way differently from those having other premedicants on the assumption that they may not remember the events. With lorazepam 4 mg, however, the frequency of amnesia for the journey to the theatre and the injection was similar to that for the postcards and did not differ greatly from that found with the i.v. route.

The difference between lorazepam and the other two drugs with regard to the effect of the emotional significance of the memory stimulus may be a result of the difference in duration of action; the plasma concentrations following 4 mg orally and i.v. are similar 90 min after administration (Dundee et al., 1978), and the frequency of amnesia with oral lorazepam eventually reaches that following i.v. injection. This does not apply to diazepam or flunitrazepam.

To claim a specific amnesic action for a drug it is clearly necessary to demonstrate that the subject was sufficiently awake at and around the time of the stimulus to be able to register it, and to show that subsequent amnesia is not related to a depressed level of consciousness. In several studies using benzodiazepines administered i.v. a method for assessing registration of information was either contained within the experimental design (Clarke et al., 1970; Frumin, Herekar and Jarvik, 1976) or applied clinically (Dundee and Pandit, 1972, Gregg, Ryan and Levin, 1974; George and Dundee, 1977). A striking feature in all of these studies was that amnesia occurred in subjects who appeared conscious and co-operative at the time of the stimulus. No definite correlation between significant drowsiness and amnesia was found by George and Dundee (1977) for i.v. diazepam and flunitrazepam.

In contrast, these two effects were related in the present study when drugs were given orally. Where patients were conscious and co-operative, amnesia was less likely. Thus, the attribution of a specific amnesic action to diazepam and flunitrazepam, which has resulted from the findings in i.v. studies would be difficult to justify from these present studies.

The differences in the time-courses of the amnesic actions of diazepam and flunitrazepam paralleled the plasma concentrations of these two drugs. However, it is not possible to explain the delay in onset of lorazepam on these grounds.

The specific amnesic action after the i.v. but not the oral route of administration of diazepam and flunitrazepam might be a result of the difference in plasma concentrations achieved with the two

routes, or perhaps be related to the more rapid increase in plasma concentration following i.v. administration.

Are the amnesic and sedative actions of the drug separate entities, or do they simply reflect progressive steps in cerebral depression? In the case of lorazepam, the only difference between the oral and i.v. routes, as regards amnesia, was the delay in the former attributable to absorption. With both the i.v. (George and Dundee, 1977) and oral routes amnesia correlated closely with drowsiness. The degree of amnesia found with each route was approximately the same after time was allowed for absorption. After oral lorazepam, amnesia occured for emotionally significant as well as for neutral stimuli. While lorazepam amnesia is not separated from sedation, it is of a different and more profound character from that of diazepam or flunitrazepam. For this reason it may be the preferred drug for premedication, particularly on the night before operation.

In this study, retrograde amnesia was a sporadic occurrence which was neither drug- nor dose-related. This is in agreement with previous results (Dundee and Pandit, 1972) which suggested that retrograde amnesia associated with drug action occurred only where sedation had been sufficiently deep to cause some degree of cerebral hypoxia. The administration of diazepam following a strong stimulus would not be expected to suppress the memory of this event; thus it cannot be recommended for this purpose in obstetric anaesthesia (Marshall Barr et al., 1977; Dundee and McKay, 1978). It is important to appreciate that the terms anterograde and retrograde have been confused in the literature (Suri, 1978).

Many studies have shown that hyoscine has an amnesic action, both alone and in combination with diazepam (Hardy and Wakely, 1962; Dundee and Pandit, 1972). Our results suggest that oral hyoscine may slightly increase the amnesic effect of lorazepam, but will not cause a more rapid onset of action. It should not be given with large doses of benzodiazepines.

Our findings agree with those of other workers who concluded that benzodiazepines act upon the early consolidation phase of memory processing, although in a clinical study such as this it was not possible to separate this from an effect on registration.

Both Clarke and colleagues (1970) and Gregg, Ryan and Levin (1974) found that, while impairment of unaided recall by benzodiazepines was, as might be expected, always greater than impairment of recognition, the difference between these two features did not change from control values despite increasing dose. This is interpreted as evidence that benzodiazepine amnesia is not the result of an effect on retrieval of information; this latter type is associated with organic brain disorder and is characterized by an increased difference between recall and recognition performances (Williams and Zangwill, 1952; Victor, 1969); it is interesting that in the present study the difference between impairment of recall and of recognition, taken as a ratio to the former (fig. 6) consistently decreased with increasing dose of each drug, being greatest in the inert group. This is further evidence that benzodiazepine amnesia does not result from an effect on retrieval.

The anaesthetist will be interested in the frequencies of any degree of amnesia with the three benzodiazepines studied, and the findings are summarized in table VI.

TABLE VI. *Percentage frequency of any degree of amnesia at the times shown following various doses of the three benzodiazepines administered orally*

Drug	Dose (mg)	Time after administration (min)									
		5	10	20	30	40	50	60	70	80	90
Diazepam	5	0	10	0	20	0	10	10	10	20	0
	10	10	10	45	55	65	60	85	50	80	55
	20	10	5	40	35	50	60	85	70	75	75
Flunitrazepam	0.5	5	15	45	65	55	40	80	50	65	40
	1	20	10	60	60	75	55	85	60	75	70
Lorazepam	1	0	5	15	15	0	30	35	30	35	35
	2	0	0	0	0	20	40	50	70	70	80
	4	0	5	15	15	55	55	75	90	75	90
Inert	—	12.5	20	17.5	10	10	22.5	12.5	27.5	10	7.5

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EFFET DES BENZODIAZEPINES ORALES SUR LA MEMOIRE

RESUME

On a étudié les effets de l'administration orale de 5, 10 et 20 mg de diazepam, de 0,5 et 1 mg de flunitrazepam et de 1, 2 et 4 mg de lorazepam sur la mémoire de groupes de patients sains avant l'opération. On a pris également du degré de sédation. Toutes les substances ont produit un effet d'amnésie en rapport avec la dose, mais celui-ci n'était pas significatif quand on avait administré 5 mg de diazepam et 1 mg de lorazepam. Des doses plus fortes de diazepam (10 et 20 mg) ont eu pour effet une brève amnésie comparable à celle obtenue au moyen de doses équivalentes de flunitrazepam (0,5 et 1 mg). La même période s'est écoulée jusqu'au début de l'amnésie quand on a administré 4 mg de lorazepam oral ou i.v. et son effet a duré pendant 90 min au moins après administration. Contrairement à l'effet des mêmes substances administrées i.v., la perte de connaissance et la somnolence suivent la même courbe de durée.

DIE WIRKUNG VON MÜNDLICH VERABREICHTEN BENZODIAZEPINEN AUF DAS GEDÄCHTNIS

ZUSAMMENFASSUNG

Die Wirkungen von mündlich verabreichtem Diazepam 5, 10 und 20 mg, Flunitrazepam 0,5 und 1,0 mg und Lorazepam 1, 2 und 4 mg auf das Gedächtnis wurden bei Gruppen von gesunden Patienten vor der Chirurgie studiert. Das Beruhigungsgrad wurde ebenfalls notiert. Eine dosisbezogene amnesische Wirkung wurde in jedem Fall durch die verwendeten Mittel hervorgerufen, obwohl diese Wirkung bei

Diazepam 5 mg und Lorazepam 1 mg unbedeutend war Grössere Dosen von Diazepam (10 und 20 mg) verursachten eine kurzweilige Amnesie, die mit der Wirkung von äquivalenten Dosen von Flunitrazepam (5 mg und 1 mg) vergleichbar war. Bei einer mündlich verabreichten Dosis von Lorazepam 4 mg trat die amnesische Wirkung mit derselben Verzögerung wie bei der intravenösen Verabreichung ein und die Wirkung hielt mindestens 90 Minuten nach der Einnahme an. Im Gegensatz zu der Wirkung derselben Mittel bei intravenöser Verabreichung zeigen Schläfrigkeit und fehlende Wiedererkennung einen ähnlichen Zeitverlauf.

EFECTO DE LAS BENZODIAZEPINAS ORALES SOBRE LA MEMORIA

SUMARIO

Se estudiaron los efectos de la administración oral de 5, 10 y 20 mg de diazepam, de 0,5 y 1 mg de flunitrazepam así como de 1, 2 y 4 mg de lorazepam sobre la memoria de grupos de pacientes sanos antes de la cirujía. Se anotó también el grado de sedación. Todas las substancias produjeron un efecto de amnesia en relación con la dosis, pero éste no fue significante con 5 mg de diazepam ni tampoco con 1 mg de lorazepam. El diazepam en dosis mayores (10 y 20 mg) produjo una amnesia breve comparable con dosis equivalentes de flunitrazepam (0,5 y 1 mg). El plazo transcurrido hasta el inicio de la amnesia después de la administración oral de 4 mg de lorazepam fue análogo al de la administración i.v. y sus efectos se prolongaron durante 90 min por lo menos después de la administración. En contraste con los efectos de las mismas substancias administradas por vía i.v., la falta de conocimiento y modorra siguen una curva de tiempo similar.