

Further Studies of the Anti-recall Effect of Lorazepam:

A Dose-Time-Effect Relationship

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The time of onset and duration of the anti-recall action of lorazepam were assessed under clinical conditions by measuring recall and recognition of visual stimuli 24 hours after intravenous administration of lorazepam. The visual stimuli were first presented 5-240 minutes after 2 mg and 5-360 minutes after 4 mg lorazepam. Retrograde amnesia was not produced. Lorazepam, 2 mg, produced a short anti-recall effect (anterograde amnesia) in 50 per cent of the cases, with a latency of 30 minutes and a duration of less than half an hour. Duration and frequency of the anti-recall effect were greater after 4 mg, while the latency was shorter. More than 70 per cent of the individuals tested were amnesic for the visual stimuli 15 minutes to 4 hours after 4 mg lorazepam. Sedation was satisfactory and long-lasting following both doses of lorazepam, but was not related to the anti-recall effect. (Key words: Hypnotics, benzodiazepines, lorazepam; Premedication, lorazepam; Memory, lorazepam.)

AMONG THE MYRIAD premedicant drugs that have been used during the history of clinical anesthesia, only two, scopolamine and diazepam, have been shown to impair human memory.¹⁻⁴ In addition to their soporific effects, these two drugs seem to be able to depress selectively those parts of the brain concerned with the registration and consolidation mechanism of human memory. Heisterkamp and Cohen⁵ recently reported that a new benzodiazepine derivative, lorazepam,

can also significantly impair memory in human subjects. Lorazepam in doses of 3 and 5 mg given intravenously was found to be a significantly better amnesic agent than placebo, pentobarbital, or diazepam (5 and 10 mg) for events occurring 30 minutes after drug administration. However, the dose-time-effect relationships of the amnesic effects of scopolamine and diazepam vary enormously.⁶ For this reason, it was decided to study the anterograde and retrograde anti-recall effects of lorazepam at two dose levels to determine their time-effect relationship.

Method

Subjects of the study were 50 healthy adult patients of either sex (ASA Class I or II) scheduled for elective surgery. All patients were assessed during a routine preanesthetic visit, using the usual methods of preanesthetic interrogation; no special test was performed. All were found to be of reasonable intelligence with negative psychological histories, and none had received any tranquilizer or central nervous system depressant drug during the previous week. Informed consent was given by each patient. It was clearly explained to the patient that the premedication he was to receive might affect memory of events immediately before and after operation, and that to test this he would be shown a few simple pictures (as memory cards) while waiting for the operation and would be interrogated about these the next day. Lorazepam was administered intravenously in the patient's hospital room sufficiently in advance of operation to allow time to study its effects over the next 5 minutes to six hours. The patient was not moved from his room until the last memory card had been shown to him.

Three memory cards were shown to each patient, one at a time, at three predetermined

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times after drug administration. The memory cards consisted of the pictures of (1) horses, (2) flowers, and (3) a large dollar bill. The sequence of the three memory cards was kept constant.

There were ten groups of patients (five patients in each group), arranged according to the time of the exposure to the three memory cards (Tables 1 and 2). Since previous investigations had demonstrated an unsatisfactory response (agitation and confusion) in two of five patients receiving 5 mg lorazepam, we elected to evaluate a 2 mg dose and a 4 mg dose. Twenty-five patients (five groups) received 2 mg lorazepam and the other 25 received 4 mg. Thus, the total number of observations was 150, with 75 in each dose level. The groups deliberately overlapped at one or both ends with their adjacent groups. Since the sequence of the memory cards was constant, overlapping of the groups gave randomization of the memory cards shown to the patient at each point of observation.

At the predetermined interval after drug ad-

ministration, each patient was visited by the same observer (S.K.P.) and the level of sedation was recorded according to the following scheme:

- Grade 1: No sedation
- Grade 2: Calm but not asleep
- Grade 3: Asleep but easily arousable
- Grade 4: Asleep and not easily arousable
- Grade 5: Unable to communicate

The patient was then awakened (if necessary), interrogated for a few moments until he became lucid (*i.e.*, he could answer questions regarding his well-being, location, and the time) and then was shown the selected memory card. The patient was asked to identify the picture and his interpretation of the card was recorded. One patient in the 4-mg group was profoundly sedated 2 and 3 hours after drug administration and was unable to communicate (Grade 5). She was presumed to be totally amnesic (no registration). All the other patients were lucid enough to communicate and to interpret the memory cards correctly.

TABLE 1. Case Distribution by Time Memory Cards* Were Shown after Lorazepam, 2 mg, iv

	Number of Patients per Group	Time in Minutes								Number of Observations per Group	
		5	15	30	45	60	90	120	180		240
Group I	5	H	F	D							15
Group II	5		H	F							15
Group III	5			D	H	F	D				15
Group IV	5					H	F	D			15
Group V	5							H	F	D	15
Total number of observations		5	10	10	10	10	10	10	5	5	75

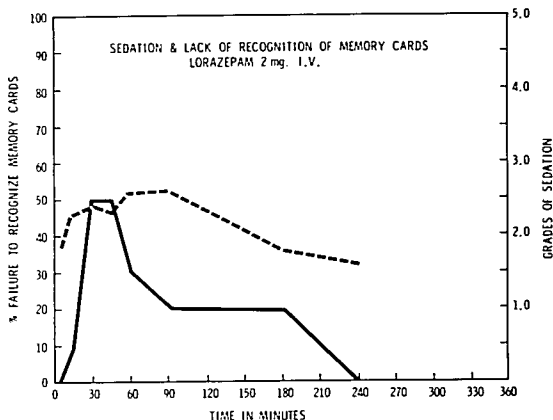
* Memory cards: H = horse picture; F = flower picture; D = dollar bill.

TABLE 2. Case Distribution by Time Memory Cards* Were Shown after Lorazepam, 4 mg, iv

	Number of Patients per Group	Time in Minutes								Number of Observations per Group	
		5	15	30	60	120	180	240	300		360
Group I	5	H	F	D							15
Group II	5			H	F						15
Group III	5					D	H	F	D		15
Group IV	5							H	F	D	15
Group V	5								F	D	15
Total number of observations		5	5	10	5	10	10	15	10	5	75

* Memory cards: H = horse picture; F = flower picture; D = dollar bill.

FIG. 1. Relationship between sedation (---) and the lack of recognition (—) of memory cards from composite pictures after lorazepam, 2 mg, iv.



All patients (except three whose operations were cancelled for surgical reasons after they received premedication) were given general, regional, or local-infiltration anesthesia and underwent uneventful operations. Almost all patients spent a few hours after operation in the recovery room or surgical intensive therapy unit before returning to their own rooms.

POSTOPERATIVE QUESTIONNAIRE

Each patient was visited 24 hours after the operation by the same observer (S.K.P.) and was interrogated for several minutes. After a period of casual conversation, the patient was asked whether he remembered the observer and the administration of the pre-

FIG. 2. Relationship between sedation (---) and the lack of recognition (—) of memory cards from composite pictures after lorazepam, 4 mg, iv.

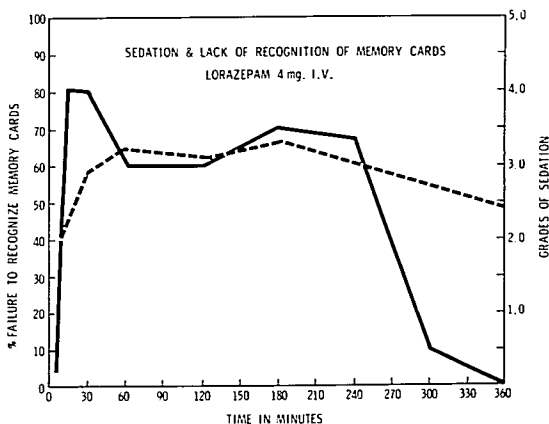


TABLE 3. Incidence of Anti-recall Effect and Grades of Sedation with Lorazepam, 2 mg, iv

	Time in Minutes								
	5	15	30	45	60	90	120	180	240
Number of observations	5	10	10	10	10	10	10	5	5
Average grade of sedation (\pm SD)	1.8 \pm 0.45	2.3 \pm 0.82	2.4 \pm 0.7	2.3 \pm 0.95	2.6 \pm 0.7	2.6 \pm 0.7	2.3 \pm 0.67	1.8 \pm 0.84	1.6 \pm 0.55
Incidence of anti-recall effect (in percentage of total)	0	10	50	50	30	20	20	20	0

TABLE 4. Incidence of Anti-recall Effect and Grades of Sedation with Lorazepam, 4 mg, iv

	Time in Minutes								
	5	15	30	60	120	180	240	300	360
Number of observations	5	5	10	5	10	10	15	10	5
Average grade of sedation (\pm SD)	1.8 \pm 0.45	2.2 \pm 0.84	2.9 \pm 0.99	3.2 \pm 0.45	3.1 \pm 0.88	3.3 \pm 0.82	3.0 \pm 0.53	2.7 \pm 0.48	2.4 \pm 0.55
Incidence of anti-recall effect (in percentage of total)	0	80	80	60	60	70	67	10	0

medicant drug in the hospital room. Failure to recollect these would have been interpreted as "retrograde amnesia."

The patient was then asked to recall the pictures shown to him the previous day. If he could not spontaneously recall one or more of the memory cards, these were shown to him in three composites, each composite containing one of the memory cards and three or more other picture cards of the same size. The patient was asked to identify the ones he had seen the previous day (recognition). The failure of both recollection and recognition of the memory card was considered to be a definite anti-recall effect of lorazepam ("anterograde amnesia").

Results

All groups and subgroups of patients were homogeneous in respect to age, height and weight.

All patients remembered the observer and the administration of lorazepam in the hospital room. Thus, neither dose of lorazepam produced retrograde amnesia.

Figures 1 and 2 and tables 3 and 4 indicate both the degree of sedation and the frequency of anterograde anti-recall action for the 2-mg and 4-mg lorazepam groups, respectively, during the period of study. It is obvious that the degree of sedation and the incidence of amnesia did not coincide in either group. Good sedation was achieved with 2 mg lorazepam for a period of three hours after drug administration after a latency of 5 minutes. The period during which the anti-recall effect was evident lasted only half an hour and had a latency of 30 minutes. Significant amnesia was present in only 50 per cent of the cases. With 4 mg lorazepam, good sedation persisted until the end of the study after a latency of 5 minutes, and the onset of the anti-recall effect occurred 15 minutes after drug

administration, the frequency was very high (70–80 per cent) and duration was longer (4 hours). The incidence of amnesia at five hours was 15 per cent, and that at six hours, 0.

Discussion

Lorazepam has already been proven to be a long-acting, safe, effective premedicant drug with good patient acceptance.⁷⁻⁹ The present study confirms this. Particularly noteworthy in this context is the long duration of sedation.

Retrograde amnesia was totally absent in the present series. This is not a surprising finding in man. Although drugs that depress the central nervous system, including general anesthetics, have been shown to produce retrograde amnesia (inhibition of the consolidation of a learning process) in lower forms of animals,¹⁰⁻¹² several researchers have been unable to demonstrate this in man after the administration of various premedicant drugs or intravenous and inhalational anesthetic agents.¹³⁻¹⁵ The absence of retrograde amnesia with lorazepam reconfirms in man that once a learning process is registered properly, the consolidation process takes place rather quickly or is continued even under the influence of depressant drugs.

Lorazepam does, however, have an anterograde anti-recall effect, which is dose-dependent. Since the soporific effects and the anti-recall effects did not exactly coincide, it can be presumed that, like diazepam and scopolamine, lorazepam produces a specific depressant effect on those parts of the brain concerned with registration of memory, and that this is not necessarily related to its effect on other centers in the brain that cause sedation.

The onset of the anterograde anti-recall action of lorazepam was delayed 30 minutes after 2 mg and 15 minutes after 4 mg. This time-effect relationship of lorazepam appears to differ from those observed with diazepam (latency 2–3 minutes) and scopolamine (latency about 60 minutes).⁶ The short duration and 50 per cent incidence of anti-recall effect with 2 mg lorazepam is probably not very useful clinically. The anti-recall ef-

fect of 4 mg lorazepam, however, seems to be quite predictable and persistent. The long duration (four hours) is more comparable to the duration of the amnesic effect of scopolamine (duration about 90 minutes) than to that of diazepam (duration less than 30 minutes). However, the peak frequency of anti-recall effect with lorazepam (80 per cent) is much higher than that observed with scopolamine (50 per cent) and comparable to that seen with diazepam (90 per cent).⁶ Thus, so far as its anterograde anti-recall effects are concerned, lorazepam combines the desirable effects of diazepam (high incidence, relatively short latency) and scopolamine (long duration). This significant anti-recall action of lorazepam might prove of clinical value not only in premedication of nervous individuals and as a basal sedative during regional anesthesia, but also to prevent or reduce awareness during light anesthesia and awake endotracheal intubation, and to reduce memory in patients receiving long-term respiratory therapy.

The anti-recall effect of lorazepam was assessed in the present study only once, 24 hours after drug administration, using simple and reliable visual memory tests. A definite "amnesic" period for visual stimuli was detected, but one cannot be sure whether the patient would be amnesic to every other kind of stimulus.

It is unknown whether the anti-recall effect observed was due to a lack of registration or to interference with consolidation or retrieval mechanisms involved in memory. It is also unknown how long the anti-recall effect of lorazepam would last.

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Circulation

RENAL EFFECT OF DOPAMINE Six adult male mongrel dogs (average weight 20 kg) were anesthetized with 30 mg/kg pentobarbital and ventilated with air via an endotracheal tube. Following splenectomy the right femoral vein was cannulated for intravenous infusion and the left vein was cannulated and connected to an airless silastic reservoir for creation of hemorrhagic shock. Arterial pressure was monitored by cannulating the right femoral artery. Urinary output was monitored by Foley catheter placed in bladder. Five per cent dextrose in water (20 per cent of body weight) was given during the procedure. Shock was induced by bleeding the animal to a systolic blood pressure of 55 mm Hg. This was maintained by withdrawing more blood or by autotransfusion. Three dogs were given dopamine with infused fluid at the rate of 6 μ g/kg/min, 90 minutes after bleeding for two hours. The other three dogs did not receive dopamine in the infusion and were used as controls. The renal arteries and veins of all dogs were then cannulated and infused with heparinized physiologic

saline solution at a pressure of exactly 150 cm H₂O until the effluent from the renal vein was clear. A silicone rubber compound (MV-118) was infused through the renal artery until substance appeared in renal vein. The vessels were then tied, the animal sacrificed and the kidneys placed in a freezer for 72 hours. Sections were made following fixation. Animals that received dopamine had a urinary output of 20-60 ml/30 min, compared with 10 ml/30 min in controls. Angiomicrohistologic studies revealed markedly increased cortical perfusion and dilatation of afferent vessels in the dogs that received dopamine, in contrast to control dogs, which had markedly diminished perfusion of the cortex and vasoconstriction of afferent vessels. Cortical efferent vessels and medullary vessels did not show this striking difference. It is concluded that the site of action of dopamine is on the afferent cortical vessels. (*Nazakaue B, and others: The effect of dopamine on renal microcirculation in hemorrhagic shock in dogs. Surg Gynecol Obstet* 142: 871-874, 1976.)