THE EFFECT OF INTRAVENOUS PREMEDICATION WITH LORAZEPAM (ATIVAN), PENTOBARBITONE OR DIAZEPAM ON RECALL

DAVID V. HEISTERKAMP AND PETER J. COHEN

SUMMARY
Sixty-nine patients undergoing regional anaesthesia were premedicated with either lorazepam (1, 2, 3 or 5 mg), diazepam (5 or 10 mg), pentobarbitone (50 mg) or placebo given i.v., on a double-blind, randomized basis. A simple yet rigorous protocol was used to test the effect of these drugs on anterograde recall. Lorazepam 3 and 5 mg was found to affect anterograde recall significantly. None of the other drugs tested affected recall.

Lorazepam, a newer compound in the benzodiazepine series has been shown to have a dose-related anti-anxiety and hypnotic sedative action (Norris and Wallace, 1971; Paymaster, 1973; Elliott et al., 1971). In addition, Wilson and Ellis (1973) found that oral premedication with this drug provided significant anterograde amnesia. We undertook a study to determine the ability of lorazepam given intravenously in the preoperative period to affect a patient's recall of specific events while undergoing regional anaesthesia. The ability of diazepam, pentobarbitone, or placebo to affect anterograde memory was also investigated.

METHODS
A total of 69 patients between the ages of 21 and 63 in good general health were studied. All patients were visited the evening prior to surgery and their consent obtained. Each patient was brought to the operating room without premedication approximately 45 min before surgery and received an i.v. dose of premedicant drug (see below) on a double-blind randomized basis. Exactly 30 min later, the patient was shown a “memory card” (a picture of a large one-dollar bill) and asked to identify the picture. Exactly 15 and again 30 min following the exposure to the “memory card”, he was asked if he remembered being shown a picture and, if so, what it was. If the patient did not recall seeing the “memory card”, he was not prompted in any way. Each patient received regional anaesthesia for surgery. During the procedure, if supplemental medication was needed, fentanyl 1–2 ml i.v. was used. No patient received any supplementary medication before his exposure to the “memory card”. Twenty-four hours later, each patient was again questioned with respect to the “memory card”. At this time, if he could not remember being shown a picture, he was shown a large composite that contained the “memory card” together with seven other photographs and he was asked if this helped recall of the original “memory card”. At this time he was also asked to evaluate the premedication. On the day of surgery, the observer scored the effect of the premedicant as “satisfactory” or “unsatisfactory”.

Three groups of patients were studied:

Group I.
Ten patients. Five of the patients in this group received lorazepam 5 mg and five received a placebo (benzyl alcohol vehicle).

Group II.
Nineteen patients. The patients received either pentobarbitone 50 mg (five patients), diazepam 5 mg (nine patients) or diazepam 10 mg (five patients).

Group III.
Forty patients. Ten patients each received 1, 2 or 3 mg of lorazepam or diazepam 10 mg. All doses were randomized in a double-blind fashion. All drugs were given intravenously over a 2-min period by a person not directly involved in the study.

RESULTS

Group I.
No patient who received lorazepam was able to recall the “memory card” at 15 or 30 min or after

David V. Heisterkamp, M.D., Peter J. Cohen, M.D., Department of Anesthesia, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver, Colorado 80220.
24 hours. No patient was able to identify the “memory card” when shown the composite plate. All patients who received placebo were able to recall the “memory card” when asked at 15 and 30 min and 24 hours. All patients felt that lorazepam was a satisfactory premedication. Two patients requested lorazepam as premedication for future surgery. Three patients who received a placebo felt that the premedication was unsatisfactory because of inadequate sedation. In the physician’s evaluation, all patients receiving placebo were rated as having unsatisfactory premedication because they were not sedated adequately. In those patients receiving lorazepam, two were judged as having unsatisfactory premedication. One patient was agitated during the performance of the spinal anaesthetic and the second was confused for 17 hours after receiving the drug.

**Group II.**

All patients in this group were able to recall the “memory card” at all time intervals. A majority of patients and physicians felt that the premedication was satisfactory in all groups.

**Group III.**

Results for the assessment of recall are shown in figure 1. Table I shows the results of using the composite plate to stimulate recall in the group of patients who, initially, could not recall seeing the “memory card”. Chi-square analysis revealed significant differences between the four groups (P<0.02). Diazepam 10 mg had the same effect as lorazepam 1 mg.

Except for the group who received the 1-mg dose of lorazepam, patient and physician satisfaction was 80% and 100%. In the lorazepam 1-mg group, 40% of the patients felt that they were inadequately sedated. Physician satisfaction with this group was 90%.

**DISCUSSION**

There has been increasing interest in drugs that affect anterograde memory (Pandit, Dundee and Keilty, 1971; Dundee and Pandit, 1972). Both lorazepam and diazepam have been alleged to possess this property (Wilson and Ellis, 1973; Dundee and Pandit, 1972; Clarke et al., 1970). We sought to compare these drugs using a rigorous but simple memory protocol and also to avoid whatever effect may be introduced by using general anaesthesia.

The evaluation of the effect of any drug on memory is made difficult for several reasons. If the investigator asks a patient a series of general recall questions, he is faced with the fact that there is a large difference among patients concerning the emotional impact of the surgical experience. If one uses the very sophisticated methods of Clarke et al. (1970), one has to deal with individual difference in intelligence as well as sedation effect. Further, one needs an unusually well-motivated group of patients in order to have comparable data.

The group of patients who received lorazepam 5 mg had a profound loss of anterograde memory. However, at this dose, 40% of the patients were subject to either prolonged (17 hours) disorientation or agitation. Thus, it was felt that 5 mg was too large a dose for routine clinical use. Diazepam was investigated because of the claim in the literature that this drug can affect recall. Pentobarbital was added to the protocol to determine what effect

| Table I |
|-----------------|---|---|---|---|
| Patient group | Lorazepam | Diazepam |  |
| 1 mg | 2 mg | 3 mg | 10 mg |
| Number of patients not able to recall “memory card” initially | 2 | 3 | 6 | 2 |
| Number of patients correctly identifying “memory card” after seeing composites | 2 | 1* | 0 | 1 |

*One patient who did not remember the “memory card” could not be shown the composite.

![Fig. 1. Results of recall for patients in group III.](image-url)
sedation would have on our method of measuring recall.

Several other investigators (Harry and Richards, 1972; Wilson and Ellis, 1973) have studied and compared the effects of lorazepam as well as diazepam and a barbiturate on anterograde memory. Harry and Richards (1972) used oral doses of 2 and 4 mg of lorazepam and 10 and 20 mg of diazepam and found diazepam did not affect memory significantly. Lorazepam 4 mg did significantly decrease recall. Wilson and Ellis (1973), again using oral premedication, found that lorazepam 3 mg produced "poor recall" in 52.6% of the patients tested while diazepam 10 mg had no effect and heptobarbitone 400 mg caused 8.6% of the patients to have poor recall.

Our results using i.v. medication agree in most respects with these investigators. Six out of ten patients receiving lorazepam 3 mg could not recall seeing the "memory card". Patients who received pentobarbitone or diazepam suffered no effect on their ability to recall.

The fact that diazepam did not significantly affect recall in our study probably reflects the rather short period of action on recall (between 10 and 20 min) which has been noted by other investigators (Dundee and Pandit, 1972).

Patient acceptance of lorazepam was very good. Even those patients judged by the physician to have unsatisfactory premedication and to be disorientated judged the drug to be excellent in the follow-up interview. Two of these people requested the drug for a second operation.

REFERENCES


LES EFFETS D'UNE PREMEDICATION INTRAVEINEUSE AVEC LORAZEPAM, PENTOBARBITONE ARTIVAN OU DIAZEPAM SUR LE RAPPEL

RESUME
Soixante-neuf patients subissant une anesthésie régionale ont reçu à titre de médicament préalable soit du lorazepam (1, 2, 3 ou 5 mg), du diazepam (5 ou 10 mg), du pentobarbitone (50 mg) ou un placebo donni intraveineusement sur une base aléatoire avec double cache. Une procédure simple mais strict a été employée pour vérifier l'effet de ces médicaments sur le rappel de l'état antérieur. On a découvert que le lorazepam 3 et 5 mg affectait de manière appreciable le rappel de l'état antérieur. Aucun des autres médicaments essayés n'affectait le rappel.

DIE AUSWIRKUNGEN INTRAVENÖSER VORBEHANDLUNG MIT LORAZEPAM, ARTIVAN PENTOBARBITON ODER DIAZEPAM

ZUSAMMENFASSUNG
69 Patienten unter Lokalanästhesie erhielten vorbereitend entweder Lorazepam (1, 2, 3 oder 5 mg), Diazepam (5 oder 10 mg), Pentobarbital (50 mg) oder Placebo in beliebiger Verteilung auf Doppelblind-Basis. Ein einfaches, aber rigoros eingehaltenes Protokoll wurde verwendet, um die Wirkung dieser Drogen auf anterogrades Wiederherstellen zu prüfen. Lorazepam 3 und 5 mg hatte eine starke diesbezügliche Wirkung, die anderen Drogen nicht.

LOS EFECTOS DE LA PREMEDICACION INTRAVENOSA CON LORAZEPAM ARTIVAN PENTOBARBITON O EFECTOS SECUNDARIOS PROVOCADOS POR DIAZEPAM

SUMARIO
Sesenta y nueve pacientes a quienes se aplicó anestesia local fueron tratados previamente bien con lorazepam (1, 2, 3 o 5 mg), diazepam (5 o 10 mg), pentobarbitón (50 mg) o placebo, administrado i.v., sobre una base aleatorizada de doble pantalla. Se empleó un protocolo sencillo aunque riguroso para probar el efecto de estas drogas sobre una deposición anterográda. Se encontró que el lorazepam afecta significativamente la deposición anterograda. Ninguna de las otras drogas ensayadas afectó a la deposición.