SUBLINGUAL LORAZEPAM: A BETTER PREMEDICATION?

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SUMMARY

The efficacy of a sublingual preparation of lorazepam was compared with an i.m. injection of lorazepam as premedication for 150 patients undergoing minor gynaecological surgery. Anxiety, arousability and recall of auditory, visual and tactile stimuli were used as measurements of the degree and rate of onset of the effects. Anxiety scores decreased in both groups after medication. Patients who received the drug sublingually showed less recall, an earlier onset of sedation, more drowsiness and a longer recovery time than those who received the drug i.m. It is concluded that lorazepam given by the sublingual route is superior to that given i.m. because of more rapid absorption resulting in earlier drowsiness and more amnesia. An additional advantage is the absence of the discomfort of an injection.

Lorazepam (7-chloro-5(0-chlorophenyl)-1, 3-dihydro-3-hydroxy-2H-1, 4-benzodiazepine-2-one) is a newer compound of the benzodiazepine series and its use i.m. as a premedicant has been reported in two previous studies (Gale and Galloon, 1976; Galloon, Gale and Lancee, 1977). The first of these demonstrated that lorazepam decreased anxiety more than papaveretum, and produced more amnesia and less nausea and vomiting, with equal sedation in both groups. The second study compared lorazepam with diazepam, both given i.m. and showed that, although lorazepam produced more sedation and more amnesia, the recovery time was longer. However, like all parenteral benzodiazepines, lorazepam is poorly soluble in aqueous solution and is associated with pain or discomfort on injection. Also, it must be refrigerated and its shelf-life is short.

The blood supply of the oral cavity bypasses the liver and goes directly into the systemic circulation. This makes buccal administration superior to the gastric route for drugs which are unstable in the gastro-intestinal tract or which are substantially metabolized in the liver (Beckett and Triggs, 1967). Rapid sublingual absorption of lorazepam was demonstrated by Caille and colleagues (1980) who found a greater blood concentration at 30–40 min after sublingual administration than after injection i.m., although the latter route gave a greater blood concentration 1 h after the injection. Lorazepam is absorbed more rapidly from the buccal cavity than from the gastro-intestinal tract and the rate of absorption parallels that from an i.m. site.

PATIENTS AND METHODS

The present study was undertaken to compare the efficacy of lorazepam administered sublingually, and i.m., as a premedicant. One hundred and fifty healthy women (ASA I and II) admitted for dilatation and curettage were selected, and informed written consent obtained on the day before operation.

Approximately 2.5 h before operation, a trained nurse visited each patient and assessed her state of sedation and reusability (on a scale of 1 = alert, to 6 = fast asleep) and her anxiety (1 = no anxiety, to 5 = very anxious). The patient also completed a self-assessment test at this time for anxiety, hostility and depression using an adaptation of the Multiple Affect Adjective Check List (MAACL)—a self-rating scale used by the patient (Zuckerman, 1960; Was senhaar et al., 1977). Two hours before operation each patient received a sublingual tablet and an injection i.m., one of which was a placebo. The dose of lorazepam was weight-related, patients less than 40 kg received 2 mg, those 41 – 60 kg received 3 mg, and those heavier than 60 kg received 4 mg. The patient, the nurse and the anaesthetist were unaware of the route of administration of the lorazepam. The trained nurse visited the patient after premedication and reassessed anxiety and reusability at 30, 60 and

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90 min; vital signs and any adverse effects and the MAACL test were assessed at 30 and 90 min. At 60 min, the patient was shown three cards with a black and white object drawn on each, and was asked to identify each of the objects. At 90 min, the patient was told a catch phrase ("the black cat sat on the mat" or "the white mouse ran into the house") and asked to repeat it. Other items to be memorized just before anaesthesia were radio music in the operating room, the colour of the anaesthetist’s hat (green or white), and the i.v. needle. Anaesthesia was induced with thiopentone and maintained with nitrous oxide in oxygen plus intermittent injections of thiopentone. Following surgery, the progress of recovery, vital signs and adverse effects were recorded. The day after surgery, the patient was asked if she remembered the premedication needle, any of the picture cards, the catch phrase, the hat colour, the music or the needle in the operating room.

**Statistical analysis**

The data were analysed by analysis of variance techniques. In addition, likelihood ratio and chi-square statistics were generated from the frequency tables to establish significant differences between variables considered.

**RESULTS**

There were 75 patients in each group. There were no statistical differences between groups in terms of age, weight and height (table I).

**Arousalability**

Patients in both groups were drowsy at 30 min and thereafter (P > 0.002), but they were significantly more drowsy in the sublingual group at 60 min (P > 0.07) and 90 min (P > 0.03) compared with the i.m. group (fig. 1).

**Clinical assessment of anxiety**

Both groups showed significant decreases in anxiety (P > 0.002), at 30, 60 and 90 min compared with assessments before premedication, but there were no differences between the two groups (fig. 2).

**The Multiple Affect Adjective Check List**

There were no significant differences between the two groups with this test (fig. 3). Both groups showed decreases in anxiety and depression (P > 0.001) as well as hostility (P > 0.03) 30 min

| TABLE I. Characteristics of the subjects (mean ± SEM) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Dose group      | Age (yr)        | Weight (kg)     | Height (cm)     | Sample size     |
| Sublingual      | 23.85 ± 0.63    | 57.99 ± 0.96    | 163.33 ± 0.69   | 75              |
| I.m.            | 23.91 ± 0.54    | 59.16 ± 1.13    | 162.45 ± 0.75   | 75              |
after medication. The decrease continued from 30 to 90 min for anxiety (P > 0.006) and depression (P > 0.01).

Memory

Figure 4 shows the effects on recall 24–48 h after surgery. Recall was significantly less in the sublingual group for two out of three cards (P > 0.01), the catch phrase (P > 0.001), the colour of the hat (P > 0.01), the music (P > 0.01) and the needle (P > 0.0001).

Patients with a lack of recall for the individual picture cards were shown a composite picture, which resulted in recognition of more cards in the i.m. than the sublingual group. Failure of recognition occurred in 25% of patients receiving the sublingual preparation but in only 9% of patients who received i.m. medication (P > 0.01).

Haemodynamic and respiratory effects

The haemodynamic changes were significant statistically but not clinically. In both groups the heart rate decreased 5 beat min⁻¹ (P > 0.001) 30 min after medication and then increased again at 90 min.

![Figure 3](image)

**Fig. 3.** Effect of lorazepam on the results of the Multiple Affect Adjective Check List Test.

![Figure 4](image)

**Fig. 4.** Effect on recall 24–48 h after surgery. Open columns = i.m. group; black columns = sublingual group.
Changes in arterial pressure and respiration following premedication were minimal.

**Side-effects**

The frequency of nausea, vomiting, dizziness, blurred vision and headache was low following premedication and before induction (<4%). The frequency of nausea and vomiting (about 29%) in the period after operation was in keeping with that after anaesthesia (Dundee, Nicholl and Moore, 1962), and the frequencies with the sublingual tablet and the i.m. injection did not differ.

**Recovery after operation**

Response to a nasal catheter was assessed on arrival in the recovery room and at intervals of 15 min, until the patients responded to the catheter. There was a significant difference between the groups, sublingual medication being associated with a delayed response. The time to opening the eyes, which was used as a sign of awakening, was the same in both groups.

**DISCUSSION**

The effects of sublingual and i.m. preparations of lorazepam as premedicants were compared. Anxiety, arousability and recall of audio, visual and tactile stimuli were used as measurements of the degree, and rate of onset, of the effects. The measurement of anxiety by clinical observation alone is questionable (Wassenaar et al., 1977), but the combination of clinical observation (nurse-observer ratings) with the MAACL results (Zuckerman, 1960) (patient self-evaluation) overcomes this problem, as has been shown in two previous studies (Gale and Galloon, 1976; Galloon, Gale and Lancee, 1977).

In the present study, the results of the MAACL testing and the observations of the trained nurse showed a similar and clinically significant decrease in anxiety in both groups.

Sedation occurred in both groups, but this commenced earlier with the sublingual administration. Many patients fell asleep but were easily aroused at 90 and 120 min at question and stimulation times. As in our previous studies of lorazepam, the recovery period was prolonged with a delayed response to the insertion of a nasal catheter and opening of the eyes on command. However, the response to the nasal catheter was more delayed in the sublingual group and, since both groups had the same average amount of thiopentone per kg body weight, it is concluded that the delayed response was attributable to the sublingual route of administration of lorazepam. Waking time, as judged by opening of the eyes, although prolonged, was the same in both groups.

Earlier studies (Clarke et al., 1970; Duarte, 1976; Gale and Galloon, 1976; Galloon, Gale and Lancee, 1977) have shown impaired recall after lorazepam i.m. at a dose of approximately 0.05 mg kg⁻¹. This was found to be a true effect on recall and not on recognition because it was found that, when a composite of the picture cards was presented to a patient with no apparent recall of having seen cards 24 h before, recognition of the pictures was equal in both groups. Clarke and colleagues (1970) considered that the effect of diazepam on recall was the result of impairment of memory input on the consolidation process as both recall and recognition were affected equally. Our results (Gale and Galloon, 1976; Galloon, Gale and Lancee, 1977) have consistently suggested that lorazepam impairs retrieval of information rather than input and consolidation.

By presenting varying auditory, visual and tactile stimuli at precise times after the administration of the premedication dose, we attempted to define the time of onset of the lack of recall. Lack of recall was significantly greater with the sublingual medication as early as 60 min after administration and extended throughout the period before the induction of anaesthesia (fig. 4). This suggests that sublingual administration is associated with more clinically useful lack of recall for those patients who might otherwise have unpleasant memories of the period before operation. For example, 50% of patients who received the drug sublingually did not remember the pain of the induction needle, while only 12% of the patients who had the same dose of lorazepam i.m. did not remember the pain.

It is possible that in the sublingual group some of the lorazepam was dissolved and then swallowed, leading to gastric absorption. However, the nurse who gave the premedication stayed with the patient for 15 min to ensure that it was not swallowed. There is no reason to think that swallowing occurred with sublingual lorazepam any more than it does with other drugs that are used sublingually, such as nitroglycerine.

It is concluded that lorazepam given by the sublingual route is superior to that given i.m. because of more rapid absorption, resulting in more drowsiness and amnesia. An additional advantage of the sublingual route is the absence of the discomfort of an injection.
ACKNOWLEDGEMENTS

We would like to thank Dr. A. A. Scott, Chairman of the Department of Anaesthesia, University of Toronto, for his constant support and help throughout the study. Special thanks to B. Madonik, B.N., B.Sc., for her competent and professional command of the various tests on the patients; to the Pharmacy Department of the Toronto General Hospital for preparing the double-blind medications and to the nurses on the Gynaecological Wards for their cooperation. We are most grateful to the Medical Directors of Wyeth (Canada) Ltd for their constant support and help throughout the study, and to Wyeth (Canada) Ltd for supplying the lorazepam and for their financial support.

REFERENCES


LE LORAZEPAM PAR VOIE SUBLINGUALE: UNE MEILLEURE PREMEDICATION?

RESUME

L'efficacité d'une préparation sublinguale de lorazepam a été comparée à celle d'une injection i.m. de lorazepam utilisé comme agent de prémédication chez 150 patientes devant subir un acte de chirurgie gynécologique mineure. L'anxiété, les possibilités de réveil et la mémoire des stimuli auditifs, visuels et tactiles ont été utilisées pour mesurer le degré et le délai d'apparition des effets. Le niveau d'anxiété s'est abaissé dans les deux groupes après administration du produit. Les patientes qui avaient reçu le produit par voie sublinguale avaient moins de souvenirs, la séduction apparaissait chez elles plus rapidement, elles étaient plus obnubilées et mettaient plus longtemps à se réveiller que celles qui avaient reçu le produit par voie i.m. Nous en concluons que le lorazepam administré par voie sublinguale est supérieur au lorazepam i.m. du fait d'une absorption plus rapide entraînant une somnolence plus rapide et une amnésie plus importante. Un avantage supplémentaire réside dans l'absence d'injection désagréable.

SUBLINGUALES LORAZEPAM: EINE BESSERE PRÄMEDIKATION?

ZUSAMMENFASSUNG

Bei 150 Patientinnen wurde die Wirksamkeit von sublingualen Lorazepam mit einer i.m.-Injektion von Lorazepam zur Prämedikation für kleine gynäkologische Eingriffe verglichen. Angst, Erregbarkeit und Erinnerung an akustische, visuelle und taktile Stimuli wurden zur Messung des Grades und der Wirkungseintrittsgeschwindigkeit benutzt. Angsterlebnisse nahmen bei beiden Gruppen nach der Medikation ab. Patienten, die Lorazepam sublingual erhalten hatten, zeigten weniger Erinnerungsvermögen, mehr Schläfrigkeit und eine längere Erholungszeit als Patienten mit i.m.-Injektion. Die sublinguale Gabe von Lorazepam ist also wegen der schnelleren Absorption mit schnellerer eintretender Schläfrigkeit und größerer Amnesie der i.m.-Gabe überlegen. Ein zusätzlicher Vorteil ist das Fehlen der lästigen Injektion.

LORAZEPAM SUBLINGUAL: ¿UNA PREMEDICACION SUPERIOR?

SUMARIO

Se comparó la eficiencia de una preparación sublingual de lorazepam con la de una inyección intramuscular del mismo medicamento, cual premedicación para 150 pacientes sometidos a intervención quirúrgica menor de carácter ginecológico. Como mediciones del grado y del régimen de tiempo previo al comienzo de los efectos, se utilizaron la ansiedad, la capacidad para despertarse y el recuerdo de estímulos auditivos, visuales y táctiles. La puntuación sobre la ansiedad disminuyó en ambos grupos después de la premedicación. Los pacientes que recibieron la droga sublingualmente mostraron una menor evocación, un periodo de tiempo más corto previo al comienzo de los efectos de la sedación, una mayor somnolencia y un periodo de tiempo de recuperación más largo que los que recibieron la droga intramuscularmente. Las conclusiones son que la administración de lorazepam sublingualmente es superior a la administración intramuscular, a causa de que el mayor ritmo de absorción produce somnolencia con mayor rapidez y una mayor amnesia. Otra ventaja es la ausencia de la molestia debida a la inyección.