EFFECT OF ORAL DIAZEPAM ON LOWER OESOPHAGEAL SPHINCTER PRESSURE

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SUMMARY

The effect of diazepam 10 mg orally was investigated on lower oesophageal sphincter pressure in a random double-blind study of nine healthy volunteers. Barrier pressure decreased to a small but statistically significant extent. The reduction in barrier pressure was not related to the level of drowsiness.

The tendency to regurgitate is related to the barrier pressure (BP) which is the difference in pressure between gastric (GP) and the lower oesophageal sphincter (LOS) or high pressure zone (HPZ). Any drug which decreases BP may increase the risk of reflux from stomach to the oesophagus.

In an uncontrolled study in humans and monkeys diazepam decreased BP and increased gastro-oesophageal reflux as indicated by oesophageal pH testing (Hall et al., 1975). Only a single measurement at an unspecified time interval was made following the i.v. injection of diazepam 2.5-10 mg. In a double-blind study diazepam 5 or 10 mg i.v. in healthy volunteers had no effect on BP, but 20 mg produced a significant increase in BP (Weiruch et al., 1979); measurements were made at 10-min intervals for 2 h. In view of these conflicting data we have undertaken a study of the effects of oral diazepam on LOS in healthy volunteers.

METHODS

Informed consent to this study was obtained from nine healthy volunteers (ages 23-29 yr) with no history of gastrointestinal, respiratory or cardiovascular disease, and not receiving any drug therapy. Four subjects were male and five female, and none was a tobacco smoker. All subjects had fasted for at least 6 h before the study.

Each volunteer attended on two occasions, separated by at least 1 week. After a control sample of venous blood had been taken from the antecubital fossa for measurement of plasma diazepam concentration, the subject swallowed either diazepam 10 mg contained in two capsules or two identical capsules containing an inert placebo. The pairs of capsules were distributed in a double-blind random manner.

Thirty minutes later the subject swallowed a silastic nasogastric tube (3 mm o.d.) into which were embedded three subminiature strain gauge pressure transducers at 5, 10 and 15 cm from the distal tip (Gaeltec Ltd). This was connected via a pre-amplifier to a chart recorder (Linearorder Mk III). Each transducer was calibrated by immersion in a column of water at 37 °C. The tube was swallowed until all the transducers were in the stomach and a period of 15 min allowed to elapse to enable gastric motility to settle.

Measurements of gastric (GP) and high pressure zone (HPZ) pressures were made by withdrawal of the tube from the stomach, 0.5 cm at a time with pauses for a few seconds, through the HPZ until all the transducers were in the oesophagus. Pressure changes produced by swallowing were evident on the oesophageal trace and recognized as described previously (Smith, Dalling and Williams, 1978). Our techniques have been described in detail previously (Cotton and Smith, 1981).

Measurements were commenced 45 min after ingestion of the capsules and at 5-min intervals for a further 30 min. Each volunteer acted as his or her own control. At the end of recording, the tube was removed and the zero baseline and calibration reassessed. On all occasions zero drift and changes in calibration were minimal. A further sample of venous blood was then taken for measurement of plasma diazepam concentration. During the course of the study, the investigator (unaware of
the nature of the contents of capsules) graded the condition of the subject as follows:

- = awake and alert
+ = slightly drowsy
++ = definitely drowsy
+++ = asleep but easily rousable
++++ = asleep but barely rousable

All results were subjected to analysis of variance with replications and also by Student's t test.

Plasma concentrations of diazepam were measured by high performance liquid chromatography following benzene extraction according to the technique of Coder, Puglisi and Gustafson (1981), modified slightly by using saturated potassium chloride solution as the carrier vehicle.

RESULTS

Figure 1 shows that the barrier pressure was reduced slightly following the administration of diazepam and that this decrease persisted for 30 min until the end of recording. Unpaired Student's t test applied to values at various sample times revealed a significant difference \((P < 0.05)\) between placebo and diazepam only at 50 min following administration.

A two-way analysis of variance with replications revealed an overall significant difference in barrier pressure between placebo and diazepam \((P < 0.01)\) with no significant effect attributable to elapsed time following either drug or placebo.

Table I shows the individual results, drowsiness scores and plasma diazepam concentrations. There is no correlation between plasma diazepam concentration and the mean decrease of barrier pressure \((r = 0.07)\) or the drowsiness score \((r = 0.35)\). In addition, there is no correlation

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<th>Subject</th>
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<th>Drug</th>
<th>Barrier pressure (cm H₂O) at times (min) after drug</th>
<th>Plasma concn diazepam (ng ml⁻¹)</th>
<th>Drowsiness score</th>
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between barrier pressure and drowsiness score ($r = 0.28$).

**DISCUSSION**

Our results show that diazepam exerts an effect on LOS to decrease barrier pressure. We have shown also that this effect may persist for up to 1 h following administration, but there is considerable variation in this action during such a period of time.

Diazepam 10 mg orally is in the dose range used for anaesthetic premedication. Peak plasma concentrations occur at about 60 min following ingestion, and a decrease in plasma concentrations occurs after about 90 min (Gamble, Dundee and Assaf, 1975). Our measurements were made at 45–75 min after ingestion and should have encompassed the period of peak plasma concentrations.

The central mechanisms of action of diazepam are obscure and at the moment there are two main theories. The first suggests that the sedative and anticonvulsant effects of diazepam are related to an enhanced inhibitory neurotransmission mediated by gamma-aminobutyric acid (GABA) (Costa and Guidotti, 1979). The second states that the muscle relaxation and anti-anxiety properties produced by diazepam results from an enhanced inhibitory neurotransmission mediated by glycine (Snyder, Enna and Young, 1977). Both theories involve central actions; there is no evidence for either glycine or GABA receptors in the region of the LOS.

There was marked individual variation in response to diazepam in respect of drowsiness and effect on LOS. This variation was not related to plasma concentrations and this is in agreement with previous findings with regard to sedation (Mandelli, Tognoni and Garattini, 1978).

We do not feel confident in recommending oral diazepam in this dosage as a safe premedicant with regard to lack of risk of regurgitation. Although one subject (table I, No. 5) exhibited an increase in barrier pressure, those subjects with the highest drowsiness score (Nos 7 and 9) had the greatest decreases in BP, but there was considerable variation in response among our subjects. The difficulty in predicting responses to diazepam in individuals both in terms of development of drowsiness and decrease in LOS pressure suggests that care must be exercised in the use of this drug. Some patients may exhibit a considerable decrease in BP and suffer increased risk of regurgitation.

**REFERENCES**


**ACKNOWLEDGEMENTS**

We are grateful to Roche Products Ltd for supplies of matching capsules of diazepam and placebo.

**REFERENCES**


**EFFET DU DIAZEPAM ADMINISTRE PAR VOIE BUCCALE SUR LA PRESSION EXERCEE SUR LE SPHINCTER OESOPHAGIEN INFERIEUR**

**RESUME**

L'effet de 10 mg de diazépam administré par voie buccale, sur la pression exercée sur le sphincter oesophagien a fait l'objet de recherches au cours d'une étude à double inconnue effectuée au hasard sur neuf volontaires en bonne santé. La pression sur la barrière a diminué dans une petite mesure qui a toutefois eu une importance statistique significative. La réduction de la pression sur la barrière n'a pas été liée au niveau de somnolence.

**DIE AUSWIRKUNG DER PERORALEN VERABREICHUNG VON DIAZEPAM AUF DEN NIEDEREN SPEISEROHRENSCHLIESSENMUSKELDRUCK**

**ZUSAMMENFASSUNG**

SUMARIO
Se investigó el efecto de 10 mg de diazepam oralmente administrados, en relación a la presión del esfínter inferior del esófago, siguiendo un estudio aleatorio de doble anonimato efectuado en nueve voluntarios sanos. La presión obstáculo disminuyó ligeramente, pero alcanzando un grado estadístico significativo. La reducción de dicha presión no vino relacionada con el nivel de somnolencia.