INFLUENCE OF ORAL ATROPINE OR HYOSCINE ON THE ABSORPTION OF ORAL DIAZEPAM

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SUMMARY

The influence of oral atropine or hyoscine on the absorption of oral diazepam administered at the same time was studied in eight volunteers using a three-way crossover randomized double-blind design. No difference was found in the timing of sedation or in the degree of sedation after diazepam alone or in combination with the anticholinergics. Diazepam serum concentrations were not significantly different after the three regimens. It is concluded that the anticholinergics can be given with diazepam for oral premedication without interfering with diazepam absorption.

Diazepam is an effective oral premedicant (Brandt and Oakes, 1965; Moore and Hollis, 1968; Murray, Bechtoldt and Berman, 1968). At times an anticholinergic drug may be required for premedication; indeed this is often a routine practice (Mirakhur et al., 1978). Since both atropine and hyoscine are well absorbed from the gastrointestinal tract, oral administration of the anticholinergic and diazepam together would be convenient. However, anticholinergic compounds may slow the rate of absorption of another drug given orally, by delaying gastric emptying (Nimmo, 1976; Gamble et al., 1976). Delayed absorption could delay the onset of action and this could be detrimental when an immediate effect is required, as when diazepam is given for sedation before the operation.

This study was designed to assess the effects of oral atropine and hyoscine, in doses effective for anticholinergic premedication (Murrin, 1973; Mirakhur, 1978), on the absorption and the clinical effects of oral diazepam.

METHODS

The study was conducted in eight healthy volunteers, five female and three male, who gave informed consent. Their mean age was 22.7 ± 1.5 yr, body weight 67.4 ± 15.4 kg, and height 1.74 ± 0.14 m. Three of them were smokers who abstained during the experiments and two women were taking oral contraceptives.

The volunteers fasted from midnight for the duration of the experiment. On three occasions, each subject was given orally, with 40 ml of water, one capsule containing diazepam 10 mg, diazepam 10 mg with atropine sulphate 1 mg, or diazepam 10 mg with hyoscine hydrobromide 1 mg. The capsules were prepared to B.P. specifications by our pharmacy. An in vitro dissolution test (British Pharmacopoeia 1980, vol. II, appendix XII D) did not show any difference in the dissolution rate of diazepam either alone or mixed with the anticholinergics, complete dissolution occurring within 10 min.

The order of drug administration was randomized. The tests were performed always at 8.30 a.m. and a minimum interval of 1 week separated consecutive tests on each subject. The subjects were studied by a single observer (S.M.G.) for 2.5 h after drug administration. During this time the subjects either sat or lay down according to their preference. Sedation was assessed every 15 min following drug administration, using an arbitrary score from 0 (no sedation) to 3 (asleep when left undisturbed), based on both the subject's and observer's evaluation. Other symptoms like dizziness, mouth dryness and blurred vision were also assessed. Neither the subject nor the observer was aware of the nature of the capsule that had been taken.

Venous blood samples for determination of diazepam concentration were taken from an indwelling i.v. cannula before and at 30, 45, 60, 75, 90, 120 and 150 min after drug administration. The serum, separated by centrifugation after clotting, was deep-
frozen until analysed. Diazepam concentration was determined by high-pressure liquid chromatography according to a general method described elsewhere (van Dijk and Uges, 1980).

The coefficient of variation of the method for diazepam was 4% ($C = 400 \mu\text{g litre}^{-1}, n = 10$). The correlation coefficient of the calibration curve ($C = 50-1000 \mu\text{g litre}^{-1}$) was more than 0.999 on each day. Results reported are the mean of duplicate determinations.

Differences were tested using the Wilcoxon matched pairs signed-ranks test and Student’s paired $t$ test and considered to be significant when $P < 0.05$.

RESULTS
No difference was found in the time of onset of sedation or in the time of maximum sedation (respectively about 30 min and 60 min) after oral administration of the three preparations. After 60 min, and throughout the observation period, the subjects were more sedated after diazepam and hyoscine than after diazepam alone or with atropine (which were undistinguishable in their effects), although these differences were not statistically significant (fig. 1). Diazepam serum concentrations were not significantly different after diazepam alone or combined with the anticholinergics (fig. 2). All the subjects experienced a dry mouth after the anticholinergics, but none after diazepam alone. This symptom was noted at 60 min, was most marked at 75–90 min, and persisted until the end of the study. No difference was detected between atropine and hyoscine. One subject complained of dizziness during all three tests. No other side-effect was detected. No volunteer judged the subjective feelings after the drug(s) as unpleasant.

DISCUSSION
In this study, atropine and hyoscine administered with diazepam did not affect the time course of clinical effects or the serum concentrations of diazepam, suggesting that the former drugs did not influence the absorption of the latter. These results contrast with the reduced rate of gastrointestinal absorption of drugs associated with atropine administration reported by previous authors (Gibbons and Lant, 1975; Gamble et al., 1976). Different routes of administration of atropine or different time.
intervals between the administration of atropine and
the other drug may explain this discrepancy.

Atropine inhibits gastric motility rapidly after
parenteral administration. After an oral dose of
atropine the inhibitory effects on gastrointestinal
motility develop more slowly and become maximal
at 75 min from the start of administration (Chap-
man, Rowlands and Jones, 1950). This is probably
because atropine has to reach the small bowel to be
absorbed, as no absorption takes place in the
stomach (Beermann, Hellström and Rosén, 1971).
No detailed information is available on the effects of
hyoscine on gastrointestinal motility.

The speed of effect of parenteral atropine on
gastric motility may explain the reduced rate of
absorption of diazepam found by Gamble and others
(1976) when diazepam was given orally at the same
time as parenteral atropine. The reduced absorption
of alcohol reported by Gibbons and Lant (1975) may
be explained by the fact that the alcohol meal was
given 2 h after oral atropine, when stomach motility
would be markedly inhibited (Bromster et al.,
1969).

In the present study, when the two drugs were
administered orally at the same time, both would
leave the stomach and reach the absorption sites in
the small bowel before any slowing of gastric empty-
ing by atropine might interfere with the transit and
hence the absorption of diazepam. It is conceivable
that several other drugs with an absorption pattern
similar to diazepam could be administered with an
anticholinergic without effect on the rate of absorp-
tion, provided both drugs are administered orally at
the same time. The satisfactory results of combining
a sedative-hypnotic drug with an anticholinergic as
oral premedication in children (Joseph and Vale,
support this view. However, drug interactions in
gastrointestinal absorption may be very complex,
involving several mechanisms, so that the results of
this study should be extended to other drugs with
cautions.

We conclude that, when the use of an an-
ticholinergic is desirable in premedication, atropine
or hyoscine can be conveniently administered orally
with diazepam (and, probably, similar drugs) with-
out a delay or reduction in its effect.

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INFLUENCE DE L'ATROPINE OU
DE LA HYOSCINE PER OS SUR L'ABSORPTION DE
DIAZEPAM PER OS

RESUME

L'influence de l'atropine ou de la hyoscine per os, sur l'absorption
du diazepam administré par voie orale en même temps, a été
étudiée chez huit volontaires en utilisant un protocole randomisé
en double aveugle avec triple croisement. Il n'a pas été trouvé de
différences dans la sédation en fonction du temps ni dans le degré
de sédation après diazepam seul ou en association avec les
anticholinergiques. Les concentrations sériques de diazepam
n'étaient pas significativement différentes dans les trois pro-
tocolcs Nous en concluons que les anticholinergiques peuvent être administrés avec le diazépam pour une prémédication orale sans interférer avec l’absorption du diazépam.

DER EINFLUß VON ATROPIN ODER HYOSZYMIN ORAL AUF DIE ABSORPTION VON ORALEM DIAZEPAM

ZUSAMMENFASSUNG
Der Einfluß von Atropin oder Hyoszyamin oder Atropin oral auf die Absorption von gleichzeitig verabreichtem oralen Diazepam wurde an acht Freiwilligen untersucht. Das Design war eine dreifach gekreuzte Doppelstudie. Es bestand kein Unterschied im Zeitpunkt der Sedierung oder im Grad der Sedierung nach Diazepam alleine oder zusammen mit den Anticholinergika. Die Diazepam-Serumkonzentrationen unterschieden sich nicht signifikant nach den drei Anwendungsarten. Daraus wird geschlos-

INFLUENCIA DE LA ATROPINA O HIOSCINA ORAL EN LA ABSORCIÓN DE DIAZEPAN ORAL

SUMARIO
Se procedió al estudio de la influencia de la atropina o hioscina oral sobre la absorción del diazepan oral administrados al mismo tiempo en ocho voluntarios mediante el método doble-ciego al azar cruzado y de triple sentido. No se observó diferencia alguna entre el ritmo de sedación o el grado de sedación después de la administración del diazepan sólo o combinado con los anticolinérgicos. Las concentraciones de diazepan en el suero no variaban de manera significante después de los tres regímenes. Se concluye que pueden administrarse los anticolinérgicos con el diazepan como premedicación oral sin que interfieran con la absorción del diazepan.