RANITIDINE INFLUENCES THE UPTAKE OF ORAL MIDAZOLAM

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In a randomised crossover study in volunteers plasma midazolam levels were estimated for 24 h following 15 mg by mouth, either preceded by no medication or following 24 h therapy with ranitidine. Administration of the H₂-receptor blocker significantly increased bioavailability of the benzodiazepine and resulted in higher plasma levels for the first 6 h after taking midazolam. This was accompanied by a greater soporific effect.

Introduction

H₂-receptor antagonist therapy has become increasingly popular since the introduction of cimetidine in 1976 and the more specific ranitidine in 1981. Alteration of gastric pH may influence the uptake of drugs from the upper gastrointestinal tract, particularly the stomach, and especially drugs with a low pK_a value. This may be of clinical importance, particularly to anaesthetists, because of the widespread therapeutic use of cimetidine, the possible use of H₂-receptor antagonism as prophylaxis against pulmonary acid aspiration syndrome in obstetrics (Johnston *et al.*, 1982), and the increasing popularity of oral pre-anaesthetic medications, especially benzodiazepines. McGowan & Dundee (1982) reported an increased uptake of diazepam from tablets, but not capsules, in patients who had received 400 mg of intravenous cimetidine 30 min prior to oral pre-anaesthetic medication.

The water-soluble imidazo benzodiazepine, midazolam, has been investigated as an intravenous sedative (Dundee *et al.*, 1980) and induction agent (Conner *et al.*, 1978; Fragen *et al.*, 1978). It is currently undergoing investigation as an oral hypnotic (Sjovall *et al.*, 1982) and premedicant (Elwood *et al.*, 1983). We report here the influence of 24 h ranitidine therapy on plasma levels of midazolam following its oral administration.

Methods

Five fit male members of departmental staff, receiving no concomitant medication, and fully aware of the implications of this investigation, volunteered for a randomised crossover study.

Each received 15 mg midazolam orally with 30 ml water which had been preceded by either 150 mg

ranitidine 2.5 h earlier and at 10.00 and 22.00 h on the previous day, or no pretreatment. Blood samples were drawn at 0, 15, 30, 45, 60, 90, 120, 150, 180 min and 4, 5, 6, 7, 8, 9, 12 and 24 h after midazolam administration via a 16 swg teflon cannula inserted into a large forearm vein at the beginning of the investigation. Patency was maintained by flushing with 2 ml of heparinised saline.

Three weeks later the cross-over study was carried out under the same conditions: two subjects received ranitidine first and three had no medication. Since this was essentially an objective study of plasma levels there was no reason why subjects should not know what drugs they would take, although it was noted whether the subjects fell asleep following midazolam. Plasma midazolam levels were estimated by high performance liquid chromatography (Dundee *et al.*, 1980).

Results

Figure 1 shows the mean plasma midazolam concentrations ($\pm$ s.e. mean) in the two groups. This was consistently higher when the subjects were pretreated with ranitidine, the difference being statistically significant at 2 and 2.5 h ($P < 0.01$) and 3, 6 and 7 h ($P < 0.05$). The mean peak concentration was 92 ± 9 ng/ml following pre-treatment with ranitidine compared with 60 ± 9 ng/ml in the control study; these differ significantly at the 1% level. Although there was no difference in mean time to peak concentration in the two series, midazolam was present in the plasma at 15 min in two of the five volunteers pretreated with ranitidine as compared with none of the non-treated group. Subjectively each volunteer was much more sleepy on the occasion when he received ranitidine

Figure 1 Mean plasma levels $\pm$ s.e. mean (ng/ml) in five subjects following 15 mg midazolam by mouth, preceded by either 24 h ranitidine therapy (O—O) or no therapy (●—●).

pre-treatment, although recovery did not appear to be affected.

The bioavailability of midazolam appears to be increased in those subjects who were given ranitidine. This is confirmed by the area under the curve (AUC) which averages 187 ± 20 ng ml⁻¹ h for the control and 310 ± 25 ng ml⁻¹ h for those pre-treated with ranitidine. These differ significantly ($t = 3.816$; $P < 0.01$). Relative bioavailability (F_{rel}) was 1.686 ± 0.105 in the ranitidine group compared with unity in the control series. This calculation assumes that clearance is constant in each subject on both administrations. If F_{rel} is calculated for AUC, $0.693/t_{1/2}$ (where $t_{1/2}$ is the terminal half-life), which assumes that volume of distribution remains constant, F_{rel} is 1.693 ± 0.20 in the ranitidine group compared with unity in the controls. The terminal half-life was similar in both series.

Discussion

This controlled crossover study shows a greater clinical effect for oral midazolam following pre-treatment with ranitidine as compared with a control series. This is accompanied by higher plasma concentrations of the benzodiazepine. These findings must be related to the influence of gastric pH on the uptake of the drug. Midazolam has a water-soluble, open ring structure, which closes at pH levels above 4.0 resulting in a lipid soluble preparation which may be more absorbed from the stomach.

Many patients are prescribed both H₂-receptor blockers and benzodiazepines. If these findings apply to all benzodiazepines there may be an indication for reduction in dosage in patients on long-term H₂-receptor blocker therapy.

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References

- CONNER, J.T., KATZ, R.L., PAGANO, R.R. & GRAHAM, C.W. (1978). Ro 21-3981 for intravenous surgical premedication and induction of anesthesia. *Anesth. Analg. (Cleve.)*, **57**, 1-5.
- DUNDEE, J.W., SAMUEL, I.O., TONER, W. & HOWARD, P.J. (1980). Midazolam: a water-soluble benzodiazepine. Studies in volunteers. *Anaesthesia*, **35**, 454-458.
- ELWOOD, R.J., KAWAR, P., HILDEBRAND, P.J. & DUNDEE, J.W. (1981). Midazolam: a water-soluble benzodiazepine. *Anaesthesia*, **36**, 454-458.

- J.W. (1983). Hypnotic and sedative effect of oral temazepam and midazolam compared with diazepam. *Br. J. clin. Pharmac.*, **15**, 586P.
- FRAGEN, R.J., GAHL, F. & CALDWELL, N. (1978). A water-soluble benzodiazepine Ro 21-3981, for induction of anesthesia. *Anesthesiology*, **49**, 41-43.
- GAMBLE, J.A.S., KAWAR, P., DUNDEE, J.W., MOORE, J. & BRIGGS, L.P. (1981). Evaluation of midazolam as an intravenous induction agent. *Anaesthesia*, **36**, 868-873.
- JOHNSTON, J.W., McCAUGHEY, W., MOORE, J. & DUNDEE, J.W. (1982). Cimetidine as an oral antacid before elective Caesarean section. *Anaesthesia*, **37**, 26-32.
- McGOWAN, W.A.W. & DUNDEE, J.W. (1982). The effect of intravenous cimetidine on the absorption of orally administered diazepam and lorazepam. *Br. J. clin. Pharmac.*, **14**, 207-211.
- SJOVALL, S., KANTO, J., KANGAS, L. & PAKKANEN, A. (1982). Comparison of midazolam and flunitrazepam for night sedation. *Anaesthesia*, **37**, 924-928.

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