Br. J. Anaesth. (1985), 57, 1107–1109

EFFECT OF DIAZEPAM ON DRUG ABSORPTION AND GASTRIC EMPTYING IN MAN

B. ADELHØJ, O. U. PETRING, J. BRYNNUM, M. IBSEN AND H. E. POULSEN

SUMMARY

Paracetamol 20 mg kg^{-1} dissolved in 200 ml of water was given by mouth to seven healthy volunteers, together with a single i.v. dose of diazepam 0.2 mg kg^{-1} or saline 0.04 ml kg^{-1}. This study demonstrated that the rate of paracetamol absorption was not significantly changed by diazepam, indicating that there was no delay in gastric emptying attributable to diazepam per se.

Diazepam decreases apprehension, excitement and autonomic responses (Dundee and Haslett, 1970), and remains one of the most widely used benzodiazepines. Although diazepam is a safe drug (Kanto, 1981), the effect on gastric emptying in man is not clear.

In the present study we determined the effect, if any, of diazepam on gastric emptying in man, using paracetamol absorption as an index of the rate of gastric emptying. Paracetamol is not absorbed to any appreciable extent from the stomach, but is readily absorbed from the upper small intestine. In this way the rate of absorption of paracetamol following oral administration is dependent on the rate of gastric emptying (Heading et al., 1973). Simultaneous measurements of paracetamol absorption and gastric emptying have confirmed that measurement of the rate of paracetamol absorption is a dependable expression of gastric emptying (Clements et al., 1978).

SUBJECTS AND METHODS

Informed consent was obtained from each subject and the experimental study was approved by the local Ethics Committee.

Seven healthy volunteers (four women) (age 23–36 yr, body weight 45–75 kg, height 155–183 cm) were each studied on two occasions in random order with an interval of at least 2 weeks between studies. Diazepam (5 mg ml^{-1}) 0.2 mg kg^{-1} i.v. or physiological saline 0.04 ml kg^{-1} i.v. was given double-blind to each volunteer. On each occasion they were investigated after an overnight fast. Fasting was continued until the end of the investigation.

The subjects remained at rest in bed in a semi-recumbent position and a slow i.v. infusion of physiological saline was established. Immediately after the injection of the test solution (over 2 min) the subjects ingested paracetamol 20 mg kg^{-1} dissolved in 200 ml of water. Venous blood samples were taken from an indwelling cannula before and 10, 20, 30, 40, 50, 60, 75, 90, 105 and 120 min after the administration of the paracetamol. Serum was separated and stored at −20 °C until measurement of serum paracetamol concentration by high pressure liquid chromatography was performed (Lo and Bye, 1979).

Paracetamol absorption was assessed from the plasma concentrations at each sampling time, the peak paracetamol concentration (C_{max}), the time to reach peak concentration (t_{max}) and the area under the plasma concentration–time curve from 0 to 120 min (AUC).

A paired Student's t test was used; P values less than 0.05 were considered statistically significant.

RESULTS

Mean plasma paracetamol concentrations at each sampling time are given in table I; the individual

BENNY ADELHØJ,* M.D.; OSCAR ULF PETRING, M.D.; Department of Anaesthesiology, Kommunehospitalet, Copenhagen, Denmark. JEANNE BRYNNUM; MERETE IBSEN; HENRIK ENGHUSEN POULSEN, M.D.; Medical Department A, Rigshospitalet (State University Hospital), Copenhagen, Denmark.

*Address for correspondence: Department of Anesthesia, Gentofte Hospital, DK-2900 Hellerup, Denmark.

Br. J. Anaesth. (1985), 57, 1107–1109

EFFECT OF DIAZEPAM ON DRUG ABSORPTION AND GASTRIC EMPTYING IN MAN

B. ADELHØJ, O. U. PETRING, J. BRYNNUM, M. IBSEN AND H. E. POULSEN

SUMMARY

Paracetamol 20 mg kg^{-1} dissolved in 200 ml of water was given by mouth to seven healthy volunteers, together with a single i.v. dose of diazepam 0.2 mg kg^{-1} or saline 0.04 ml kg^{-1}. This study demonstrated that the rate of paracetamol absorption was not significantly changed by diazepam, indicating that there was no delay in gastric emptying attributable to diazepam per se.

Diazepam decreases apprehension, excitement and autonomic responses (Dundee and Haslett, 1970), and remains one of the most widely used benzodiazepines. Although diazepam is a safe drug (Kanto, 1981), the effect on gastric emptying in man is not clear.

In the present study we determined the effect, if any, of diazepam on gastric emptying in man, using paracetamol absorption as an index of the rate of gastric emptying. Paracetamol is not absorbed to any appreciable extent from the stomach, but is readily absorbed from the upper small intestine. In this way the rate of absorption of paracetamol following oral administration is dependent on the rate of gastric emptying (Heading et al., 1973). Simultaneous measurements of paracetamol absorption and gastric emptying have confirmed that measurement of the rate of paracetamol absorption is a dependable expression of gastric emptying (Clements et al., 1978).

SUBJECTS AND METHODS

Informed consent was obtained from each subject and the experimental study was approved by the local Ethics Committee.

Seven healthy volunteers (four women) (age 23–36 yr, body weight 45–75 kg, height 155–183 cm) were each studied on two occasions in random order with an interval of at least 2 weeks between studies. Diazepam (5 mg ml^{-1}) 0.2 mg kg^{-1} i.v. or physiological saline 0.04 ml kg^{-1} i.v. was given double-blind to each volunteer. On each occasion they were investigated after an overnight fast. Fasting was continued until the end of the investigation.

The subjects remained at rest in bed in a semi-recumbent position and a slow i.v. infusion of physiological saline was established. Immediately after the injection of the test solution (over 2 min) the subjects ingested paracetamol 20 mg kg^{-1} dissolved in 200 ml of water. Venous blood samples were taken from an indwelling cannula before and 10, 20, 30, 40, 50, 60, 75, 90, 105 and 120 min after the administration of the paracetamol. Serum was separated and stored at −20 °C until measurement of serum paracetamol concentration by high pressure liquid chromatography was performed (Lo and Bye, 1979).

Paracetamol absorption was assessed from the plasma concentrations at each sampling time, the peak paracetamol concentration (C_{max}), the time to reach peak concentration (t_{max}) and the area under the plasma concentration–time curve from 0 to 120 min (AUC).

A paired Student's t test was used; P values less than 0.05 were considered statistically significant.

RESULTS

Mean plasma paracetamol concentrations at each sampling time are given in table I; the individual

BENNY ADELHØJ,* M.D.; OSCAR ULF PETRING, M.D.; Department of Anaesthesiology, Kommunehospitalet, Copenhagen, Denmark. JEANNE BRYNNUM; MERETE IBSEN; HENRIK ENGHUSEN POULSEN, M.D.; Medical Department A, Rigshospitalet (State University Hospital), Copenhagen, Denmark.

*Address for correspondence: Department of Anesthesia, Gentofte Hospital, DK-2900 Hellerup, Denmark.

TABLE I. *Mean plasma paracetamol concentrations (± SEM) and P values (Student's t test) at each sampling time with and without diazepam. Patients received paracetamol 20 mg kg/body weight dissolved in 200 ml water*

	Mean plasma paracetamol concentrations (μg ml^{-1})									
	10 min	20 min	30 min	40 min	50 min	60 min	75 min	90 min	105 min	120 min
Saline ($n = 7$)	6.2±6.2	14.9±8.0	13.9±5.8	14.0±3.2	14.0±3.5	13.9±3.1	11.9±2.6	11.0±2.9	10.3±2.7	10.2±2.2
Diazepam ($n = 7$)	4.3±5.2	9.5±6.5	10.8±5.2	12.4±3.2	11.8±2.7	13.3±3.8	12.4±4.4	11.9±4.0	10.9±4.0	10.4±3.9
P	0.39	0.24	0.38	0.20	0.18	0.71	0.78	0.64	0.70	0.85

TABLE II. *The individual values of the peak serum paracetamol concentration (C_{max}), the time from administration of paracetamol to its peak concentration (t_{max}), the area under the plasma concentration–time curve from 0 to 120 min (AUC) and P values with and without diazepam*

	C_{max} (μg ml^{-1})		t_{max} (min)		AUC (μg min^{-1} ml^{-1})	
Subject	Saline	Diazepam	Saline	Diazepam	Saline	Diazepam
1	14.9	17.8	40	30	1458	1732
2	16.0	20.7	40	30	1182	1461
3	16.5	15.9	20	60	1440	992
4	18.6	20.3	60	75	1355	1573
5	28.3	17.9	20	40	1971	881
6	12.0	10.3	40	40	905	870
7	20.5	18.9	20	20	1448	1429
Mean ± SEM	18.1±2.0	16.5±1.5	34.3±5.7	42.1±7.2	1394±122	1277±134
P	0.57		0.30		0.56	

values of C_{max}, t_{max} and AUC are presented in table II.

At no sampling time did the mean paracetamol concentration after the administration of diazepam differ significantly from the mean concentration after saline ($P > 0.05$).

After the administration of the saline, mean C_{max} was 18.1 ± 2.0 μg ml^{-1} (mean of 7 values ± SEM), mean t_{max} was 34.3 ± 5.7 min and mean AUC was 1394 ± 122 μg min^{-1} ml^{-1}. After diazepam, mean C_{max} was 16.5 ± 1.5 μg ml^{-1}, mean t_{max} 42.1 ± 7.2 min and mean AUC was 1277 ± 134 μg min^{-1} ml^{-1}. None of these values was significantly different from control ($P > 0.05$).

The respective 95% confidence limits for the differences between the peak paracetamol concentration and the time to peak paracetamol concentration were −3.0 to 8.0 μg ml^{-1} and −12.2 to 27.8 min, respectively.

DISCUSSION

In the present study paracetamol absorption was used as an index of gastric emptying. This method has been demonstrated to correlate well with other methods used to estimate gastric emptying (Clements et al., 1978).

The study demonstrated that the absorption of paracetamol was not altered significantly by a single i.v. dose of diazepam 0.2 mg kg^{-1}, and would indicate that gastric emptying was not changed significantly by diazepam.

The patterns of gastric emptying were similar in the seven subjects. After both diazepam and placebo, the absorption of the paracetamol seemed to follow a first-order process and gastric emptying was either type 1 or type 2 as classified by Clements and colleagues (1978). However, gastric emptying was delayed slightly in two subjects (No. 3 and No. 5) after diazepam i.v., and this may reflect small individual variations in the rate of gastric emptying produced by diazepam.

Paracetamol absorption was rapid in seven patients awaiting elective general anaesthesia who received diazepam 10 mg i.m. as premedication (Todd and Nimmo, 1983) and paracetamol concentrations from 15 to 90 min after diazepam administration were almost identical to those obtained in eight healthy volunteers who were not receiving diazepam after the same dose of paracetamol (Nimmo and Prescott, 1978). Parace-

tamol absorption was also rapid 2 weeks after minor surgery on the extremities in patients who had received diazepam 15 mg by mouth (Adelhøj et al., 1984; Petring et al., 1984). However, the present study differs from these studies in a number of ways. First, we gave a larger dose of diazepam than Todd and Nimmo (1983) and, furthermore, we gave the diazepam i.v. Diazepam is fairly rapidly and almost completely absorbed after oral ingestion (Bellatunono et al., 1980), but the absorption depends on gastric emptying (Gamble et al., 1976). After i.m. injection, absorption of diazepam is slow and erratic, possibly because of crystallization at the injection site, resulting in peak plasma concentrations which are lower than after oral administration (Kanto, 1975). Moolenaar and co-workers (1980) showed that a peak concentration of 375 ± 79 ng ml^{-1} was reached 95 ± 39 min after diazepam 10 mg i.m. in nine volunteers, a peak plasma concentration of 383 ± 102 ng ml^{-1} was reached 52 ± 40 min after diazepam 10 mg orally and a peak plasma concentration of 650 ± 104 ng ml^{-1} was obtained 6 ± 5 min after diazepam 10 mg i.v. Finally, our subjects served as their own control and were studied under the same circumstances with and without diazepam.

On the basis of this study and the cited data we conclude that diazepam has no important clinical effect on gastric emptying.

Consequently, diazepam *per se* does not prolong gastric emptying, and should not increase the likelihood of nausea, vomiting, or delay in the absorption of drugs or fluid, and so increase the risk of aspiration of gastric contents.

ACKNOWLEDGEMENT

Diazepam (Stesolid) was kindly supplied by Dumex A/S.

REFERENCES

Adelhøj, B., Petring, O. U., Erin-Madsen, J., Angelo, H., and Jelert, H. (1984). General anaesthesia with halothane and drug absorption. *Acta Anaesthesiol. Scand.*, **28**, 390.

Bellatunono, C., Reggi, V., Tognoni, G., and Garattini, S. (1980). Benzodiazepines: Clinical pharmacology and therapeutic use. *Drugs*, **19**, 195.

Clements, J. A., Heading, R. C., Nimmo, W. S., and Prescott, L. F. (1978). Kinetics of acetaminophen absorption and gastric emptying in man. *Clin. Pharmacol. Ther.*, **24**, 420.

Dundee, J. W., and Haslett, W. H. K. (1970). The benzodiazepines: A review of their actions and uses relative to anaesthetic practise. *Br. J. Anaesth.*, **42**, 217.

Gamble, J. A. S., Gaston, J. H., Nair, S. G., and Dundee, J. W. (1976). Some pharmacological factors influencing the absorption of diazepam following oral administration. *Br. J. Anaesth.*, **48**, 1181.

Heading, R. C., Nimmo, J., Prescott, L. F., and Tothill, P. (1973). The dependence of paracetamol absorption on the rate of gastric emptying. *Br. J. Pharmacol.*, **47**, 415.

Kanto, J. (1975). Plasma concentrations of diazepam and its metabolites after peroral, intramuscular, and rectal administration. Correlation between plasma concentration and sedatory effect of diazepam. *Int. J. Clin. Pharmacol.*, **12**, 419.

—— (1981). Benzodiazepines as oral premedicants. *Br. J. Anaesth.*, **53**, 1179.

Lo, L., and Bye, A. (1979). Rapid determination of paracetamol in plasma by reversed-phase high performance liquid chromatography. *J. Chromatogr.*, **173**, 198.

Moolenaar, F., Bakker, S., Visser, J., and Huizinga, T. (1980). Biopharmaceutics of rectal administration of drugs in man. IX. Comparative biopharmaceutics of diazepam after single rectal, oral, intramuscular and intravenous administration in man. *Int. J. Pharmaceut.*, **5**, 127.

Nimmo, W. S., and Prescott, L. F. (1978). The influence of posture on paracetamol absorption. *Br. J. Clin. Pharmacol.*, **5**, 348.

Petring, O. U., Adelhøj, B., Erin-Madsen, J., Angelo, H., and Jelert, H. (1984). Epidural anaesthesia does not delay early postoperative gastric emptying in man. *Acta Anaesthesiol. Scand.*, **28**, 393.

Todd, J. G., and Nimmo, W. S. (1983). Effect of premedication on drug absorption and gastric emptying. *Br. J. Anaesth.*, **55**, 1189.