Gastric decontamination performed 5 min after the ingestion of temazepam, verapamil and moclobemide: charcoal is superior to lavage

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Aims The aim was to study the efficacy of gastric lavage and activated charcoal in preventing the absorption of temazepam, verapamil and moclobemide when gastric decontamination was performed immediately after ingestion of the drugs.

Methods Nine healthy volunteers took part in a randomized cross-over study with three phases. The subjects were administered single oral doses of 10 mg temazepam, 80 mg verapamil and 150 mg moclobemide. Five minutes later, they were assigned to one of the following treatments: 200 ml water (control), 25 g activated charcoal as a suspension in 200 ml water or gastric lavage. Plasma concentrations and the cumulative excretion into urine of the three drugs were determined up to 24 h.

Results The mean AUC(0,24 h) of temazepam, verapamil and moclobemide was reduced by 95.2% ($P<0.01$), 92.8% ($P<0.01$) and 99.7% ($P<0.01$), respectively, by activated charcoal compared with control. Gastric lavage did not reduce significantly the AUC(0,24 h) of these drugs. The 24 h cumulative excretion of temazepam, verapamil and moclobemide into urine was reduced significantly ($P<0.05$) by charcoal but not by gastric lavage. Charcoal reduced the AUC(0,24 h), C_{max} and urinary excretion of all three drugs significantly more than lavage.

Conclusions Activated charcoal is very effective and gastric lavage can be rather ineffective in preventing the absorption of temazepam, verapamil and moclobemide when the treatment is given very rapidly after ingestion of the drugs, before tablet disintegration has occurred.

Keywords: charcoal, gastric lavage, moclobemide, temazepam, verapamil

Introduction

Both activated charcoal and gastric lavage have been used to prevent absorption of drugs after their accidental or suicidal ingestion. It is generally accepted that the efficacy of these gastric decontamination methods decreases when the time interval between the ingestion and decontamination increases [1]. There seem to be only few studies on the efficacy of gastric lavage performed shortly after drug ingestion [2–4]. For example, the study of Auerbach *et al.* [2], in which patients who arrived at the hospital because of drug overdose were given thiamine in liquid form as a marker compound, showed a 90% mean recovery of thiamine when gastric lavage was performed 5 min after thiamine ingestion.

The efficacy of activated charcoal in preventing drug absorption is well documented, but there seem to be no comparative studies on the efficacy of activated charcoal and gastric lavage immediately after drug ingestion. The aim of this study was to compare the effects of gastric lavage and activated charcoal on the absorption of temazepam, verapamil and moclobemide directly after ingestion of the drugs as plain tablets or capsules.

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Methods

Subjects

Four male and five female healthy volunteers (age range, 19–33 years; weight range, 55–88 kg) participated in this

study after written informed consent. None of the subjects used any other medication during the study, except for one woman who used oral contraceptive steroids. She was instructed to take her pill at least 12 h before or after administration of charcoal. None of the subjects had any gastrointestinal, hepatic or renal disease, and the results of physical examination and routine laboratory tests before the study were normal.

The protocol was approved by the Ethics Committee of the Department of Clinical Pharmacology, University of Helsinki, and by the Finnish National Agency for Medicines.

Study design

A randomised, balanced cross-over study design with three phases was used at intervals of 1 week. The test drugs and their doses were: 10 mg temazepam (one Normison 10 mg capsule, Wyeth-Pharma, Germany), 80 mg verapamil (one Verpamil 80 mg tablet, Orion Pharma, Finland) and 150 mg moclobemide (one Aurorix 150 mg tablet, F. Hoffmann-La Roche, Switzerland). The drugs were taken simultaneously with 150 ml water at about 08.30 h after an overnight fast. Five minutes after taking the drugs, the subjects were assigned to one of the following treatments: 200 ml water (control), 25 g activated charcoal (Carbomix, Leiras, Finland) as a suspension in 200 ml water or gastric lavage. Gastric lavage was performed with the subject in the sitting position, using a standard large-bore orogastric tube. The length of the tube was 80 cm, the inner diameter was 8 mm and the outer diameter was 10 mm. Gastric lavage was performed by two nurses with a long experience in performing gastric lavage of intoxicated patients. For lavage, 2 l of warm tap water in repeated 200 ml aliquots were used. A standard meal was served 3 h and a snack 7 h after drug administration.

Blood and urine sampling and assay of drugs

A forearm vein of each subject was cannulated with a plastic cannula and kept patent with an obturator. Timed blood samples (10 ml each) were collected before administration of the drugs and 0.5, 1, 1.5, 2, 3, 5, 7, 10 and 24 h afterwards into tubes that contained ethylenediaminetetra-acetic acid (EDTA). Plasma was separated within 30 min. Urine was collected cumulatively in fractions of 0–10 h and 10–24 h. The samples were stored at -20°C until analysed.

The concentrations of temazepam, verapamil and moclobemide in plasma and urine were determined by high-performance liquid chromatography [5–8]. The between-day coefficients of variation in plasma were $<10\%$ at relevant concentrations.

Pharmacokinetics

The absorption of temazepam, verapamil and moclobemide was characterized by the area under the plasma concentration-time curve from 0 to 24 h [AUC(0, 24 h)], calculated with the linear trapezoidal method, the peak plasma concentration (C_{max}), time to peak (t_{max}) and the cumulative excretion into urine over 24 h.

Statistical analysis

The results are expressed as mean values $\pm$s.d. or, in case of t_{max}, as median and range. 95% confidence intervals (CI) on selected variables were calculated for the main comparisons. One-way analysis of variance (ANOVA), with the Tukey test used for *post hoc* comparisons, was used for statistical analysis of the results. Differences were regarded as statistically significant when P values were <0.05.

Results

Temazepam

Activated charcoal was superior to gastric lavage in preventing the absorption of temazepam. The AUC(0, 24 h) of temazepam was reduced by 95.2% ($P<0.01$) by charcoal and by 25.6% ($P=$ns) by gastric lavage compared with the control (Table 1, Figure 1), the difference between the treatments (-1584 ng ml^{-1} h; 95% CI -2543, -626) being significant ($P<0.01$). The C_{max} of temazepam was reduced by 94.8% ($P<0.01$) by charcoal and by 42.7% ($P<0.01$) by gastric lavage, with a significant ($P<0.01$) difference (-220 ng ml^{-1}; 95% CI -329, -109) between the treatments.

Activated charcoal reduced the 24 h cumulative excretion of temazepam into urine by 71.4% ($P<0.05$), whereas the effect of gastric lavage (14.3%) was not significant. The mean difference between the treatments was -12.3 μg (95% CI -24.1, -0.5, $P<0.05$).

Verapamil

Activated charcoal was very effective in preventing the absorption of verapamil, while gastric lavage had little effect. The AUC(0,24 h) of verapamil was reduced by 92.8% ($P<0.01$) by charcoal and by 4.0% ($P=$NS) by gastric lavage compared with control (Table 1, Figure 1). The difference between the charcoal and lavage phases (-198 ng ml^{-1} h; 95% CI -282, -114) was significant ($P<0.01$). The reduction of C_{max} was significant in the charcoal phase (94.1%, $P<0.01$) but not in the gastric lavage phase (7.7%, $P=$NS), with a significant difference ($P<0.01$) between the treatments (-33.3 ng ml^{-1}; 95% CI -47.7, -18.9).

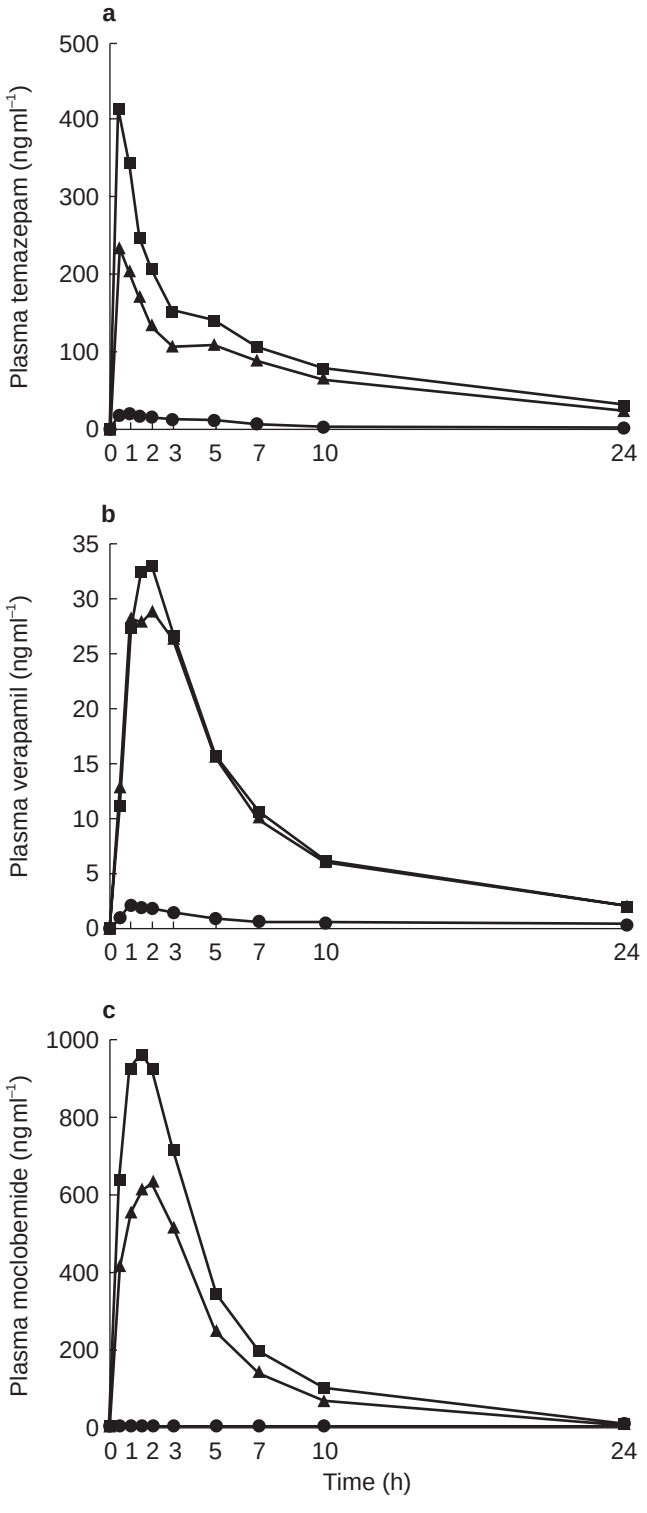

Figure 1 Mean plasma concentrations of 10 mg temazepam (a), 80 mg verapamil (b) and 150 mg moclobemide (c) in nine healthy volunteers following water (control; ■) 25 g activated charcoal (●) or gastric lavage (▲). For the clarity, only mean values are given.

The 24 h cumulative excretion of verapamil into urine was reduced by 94.2% ($P<0.01$) by activated charcoal, whereas the effect of gastric lavage (a reduction of 6.0%) was not significant. The mean difference between the treatments was −457 μg (95% CI −754, −160, $P<0.01$).

Moclobemide

Activated charcoal prevented the absorption of moclobemide almost completely. The reduction of the AUC(0,24 h) in the charcoal phase was 99.7% ($P<0.01$) compared with control (Table 1, Figure 1). Gastric lavage reduced the AUC(0,24 h) of moclobemide by 32.3% (P=NS). The difference between these two treatments (−3406 ng ml^{-1} h; 95% CI −5371, −1440) was significant ($P<0.05$). The C_{max} of moclobemide was reduced by 99.5% ($P<0.01$) with charcoal but not significantly (by 34.6%) with gastric lavage, the difference between the treatments (−719 ng ml^{-1}; 95% CI −1006, −431) being significant ($P<0.01$).

The 24 h cumulative excretion of moclobemide into urine was reduced by 99.8% ($P<0.05$) by activated charcoal and by 26.7% (P=NS) by gastric lavage, and the difference between the treatments (−952 μg; 95% CI −1909, 4.8) was statistically significant ($P=0.05$; $P<0.01$ after log transformation).

Discussion

In this study, when the gastric decontamination procedures were applied 5 min after the ingestion of two tablets and one capsule, activated charcoal was superior to gastric lavage in preventing the absorption of temazepam, verapamil and moclobemide. The reductions of the AUC(0,24 h) of temazepam, verapamil and moclobemide caused by activated charcoal (95.2%, 92.8% and 99.7%, respectively) were significantly greater than the (non-significant) reductions after gastric lavage (25.6%, 4.0% and 32.3%, respectively). The results regarding the effects of activated charcoal and gastric lavage on the excretion of these drugs into urine were in good agreement with the AUC(0,24 h) data, confirming the better efficacy of activated charcoal compared with gastric lavage.

The results of this study concerning the efficacy of activated charcoal in preventing drug absorption conform well with earlier studies where charcoal was given 5 min after the ingestion of different drugs [9–11]. There is, however, an apparent discrepancy between our findings and some of the earlier studies regarding the ability of gastric lavage to reduce drug absorption when performed immediately or within 20 min after dosing [2–4]. In the study of Auerbach *et al.* [2], the recovery of thiamine, used as a marker of recovery in gastric samples, was 90% by gastric lavage. In that study, patients with an intentional overdose were given 100 mg liquid thiamine through a nasogastric or orogastric tube, and gastric lavage was performed 5 min later. Tandberg *et al.* [3] performed

Table 1 Effect of activated charcoal (25 g) and gastric lavage on the absorption of temazepam, verapamil and moclobemide. Gastric decontamination was performed 5 min after ingestion of the drugs.

	AUC (0,24 h)		C_{max}		t_{max}	*Excretion in urine over 24 h*	
	(ng ml^{-1} h)	*(% of control)*	*(ng ml^{-1})*	*(% of control)*	*(h)*	*(μg)*	*(% of control)*
Temazepam 10 mg							
+ water (control)	2280 ± 1030	100	421 ± 120	100	0.5 (0.5–1)	21 ± 14	100
+ activated charcoal	108 ± 117★★‡	4.8	21.9 ± 35.2★★‡	5.2	1 (0.5–3)	6.0 ± 6.2★†	28.6
+ gastric lavage	1690 ± 1290	74.4	241 ± 157★★	57.3	0.5 (0.5–1.5)	18 ± 15	85.7
Verapamil 80 mg							
+ water (control)	223 ± 118	100	38.6 ± 20.9	100	1.5 (0.5–2)	518 ± 311	100
+ activated charcoal	16.2 ± 13.4★★‡	7.2	2.3 ± 2.6★★‡	5.9	1.5 (1–3)	30 ± 48★★‡	5.8
+ gastric lavage	214 ± 107	96	35.6 ± 17.7	92.3	1.5 (0.5–3)	487 ± 395	94.0
Moclobemide 150 mg							
+ water (control)	5050 ± 3230	100	1110 ± 417	100	1 (0.5–2)	1300 ± 822	100
+ activated charcoal	13.5 ± 19.2★★†	0.3	5.9 ± 8.2★★‡	0.5	1 (0–2)	2.3 ± 3.2★‡	0.2
+ gastric lavage	3420 ± 2550	67.7	725 ± 370	65.4	1.5 (0.5–3)	954 ± 1240	73.3

Data are mean values ± s.d. for nine subjects; t_{max} is given as median with range
★Significantly ($P<0.05$) different from control, ★★Significantly ($P<0.01$) different from control
†Significantly ($P<0.05$) different from gastric lavage, ‡Significantly ($P<0.01$) different from gastric lavage.

gastric lavage 10 min after administration of cyanocobalamin to 18 healthy volunteers; the mean recovery of cyanocobalamin was 45% (range 19–68%). In the study of Young & Bivins [4], 17 volunteers ingested gelatine capsules containing a nonabsorbable radionuclide marker, and gastric lavage was performed 9–42 min (mean 19 min) later; the mean tracer recovery was 30%. In our study, the efficacy of gastric lavage in preventing the absorption of temazepam and moclobemide was roughly similar to that in the two last mentioned studies [3, 4]. However, the reduction in the absorption of verapamil achieved by gastric lavage in our study was very small.

It is probable that incomplete disintegration of the tablets and the capsule in the stomach within 5 min of their ingestion is the main reason why gastric lavage was surprisingly ineffective in our study. *In vitro* in 0.1N HCl, the disintegration time of temazepam capsules was about 9–10 min and that of verapamil and moclobemide tablets about 20–25 min. The length of the temazepam capsule and the moclobemide and verapamil tablets used is 11 mm, 16 mm and 9 mm, respectively. Therefore, if not disintegrated, they may not be easily washed out from the stomach through an orogastric tube (inner diameter 8 mm) but can stay in the stomach in spite of proper lavage.

The antidotal effect of activated charcoal is the better the shorter the lag time in its administration is, but with gastric lavage the situation is more complex as discussed above. The optimal time for performing lavage is probably immediately after the disintegration of the tablets. However, the disintegration times of different formulations vary and depend, e.g. on the contents of the stomach and the amount of tablets ingested. We are well aware that most of the patients with an intentional overdose present at the hospital only several hours after ingestion [12]. There are, however, sometimes situations where a patient has ingested an overdose and it is possible to start treatment immediately after the ingestion. Our findings clearly support the use of activated charcoal instead of gastric lavage in such cases. In any case, further studies on the effect of lag time on the antidotal efficacy of activated charcoal and gastric lavage are needed.

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