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Buprenorphine Delays Drug Absorption and Gastric Emptying in Man

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The aim of the present study was to investigate the effects of buprenorphine on drug absorption and gastric emptying in man, using paracetamol absorption as an index of gastric emptying rate. Paracetamol was given to eight healthy volunteers p.o. together with or without a single i.v. dose of buprenorphine 4 μg kg^{-1} body weight. Nausea occurred in five of the subjects, four subjects vomited and one was excluded due to vomiting during the study period. The mean peak serum paracetamol concentration (C_{max}) was significantly ($P<0.0002$) lowered by a factor 3 by buprenorphine, the mean time from administration of paracetamol to its peak concentration (T_{max}) was significantly ($P<0.03$) prolonged by a factor 6, and the area under the plasma concentration-time curve from 0 to 120 min was significantly ($P<0.00006$) reduced by a factor 3. This demonstrates a marked inhibition of the rate of paracetamol absorption, indicating a clinically important reduction of gastric emptying following administration of buprenorphine.

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Buprenorphine (Temgesic®) is a synthetic opiate analgesic with mixed agonist-antagonist properties (1) that in most cases produces analgesia for 6–10 h or more (2–9). Only limited pharmacokinetic data are available, but the elimination half-life of buprenorphine seems to be long, which is probably the basis for its long-acting analgesic effect after i.v. administration (2, 10).

Buprenorphine has insignificant respiratory (2, 5, 11, 12) and cardiovascular effects (5, 8, 12, 13) and seems to have a low psychotomimetic profile and an absence of dysphoria. The most frequent side-effects are drowsiness and sleep (12, 14). The incidence of sweating and dizziness seems quite low, and it appears that the drug has a minimal dependence potential (12).

A varying effect of buprenorphine on gastrointestinal motility has been reported. One study indicates postoperative bowel motility to be somewhat slower after buprenorphine than after morphine (9), but absence of constipation has also been reported (15). It has been demonstrated in a study that buprenorphine slows down the passage of a charcoal meal in rats (16). Some investigators have reported the incidence of nausea and vomiting to be as high as 70% (5, 9, 17), whereas others have found a low incidence (7, 15), and compared with morphine no difference was observed (2, 3, 6, 8, 11, 13).

The aim of the present study was to investigate the effects of buprenorphine on drug absorption and gastric emptying in man using paracetamol absorption as an index of the gastric emptying rate. Paracetamol is not normally absorbed to any appreciable extent from the stomach, but is easily absorbed from the upper small intestine. In this way, the rate of absorption of paracetamol administered orally indicates the rate of gastric emptying. Simultaneous measurements of paracetamol absorption and gastric emptying have confirmed measurements of the rate of paracetamol administered orally as a dependable expression of gastric emptying (18, 19).

PATIENTS AND METHODS

This study was approved by the regional ethics committee, and informed consent was obtained from each volunteer.

Eight healthy volunteers, six men and two women, with no history of gastrointestinal, hepatic, respiratory, cardiac or renal disease (age 21–39 years, weight 45–105 kg, height 155–190 cm) were studied on two occasions at least 2 weeks apart.

After an overnight fast the subjects lay in bed in a half-supine position, and were given buprenorphine (Temgesic®) 4 $\mu g \cdot kg^{-1}$ i.v. One hour later, each subject ingested paracetamol solution 20 $mg \cdot kg^{-1}$ and 200 ml of water. Venous blood samples were taken from an indwelling cannula before and 20, 40, 60, 75, 90, 105, 120, 150, 180, 240, 300, 360, 420, and 480 min after paracetamol administration. The serum was stored at −20°C until measurement of unchanged serum paracetamol concentrations by high performance liquid chromatography (20). No food, fluid or tobacco was allowed throughout the study, but 1000 ml 5% glucose was given slowly i.v.

Symptoms of vomiting, nausea, dizziness, sweating, dys- or euphoria were recorded for each patient. The pulse rate and blood pressure were observed every 15 min.

The study was repeated without buprenorphine administration after an interval of 14–28 days. Venous blood samples were taken before and 20, 40, 60, 75, 90, 105, and 120 min after paracetamol administration, and recordings were made as described above.

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

Statistics

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

RESULTS

Nausea occurred in five of the subjects, and four vomited after the end of the study. One subject was excluded due to vomiting during the study period.

Mean serum paracetamol concentration

Time curves of paracetamol concentration with and without buprenorphine administration are shown in Figure 1.

In the control study the mean time to reach the peak paracetamol concentration was 30 ± 4 min (mean of 7 values ± s.e.mean). The mean peak serum paracetamol concentration was 18.1 ± 1.6 $\mu g \cdot ml^{-1}$ and the mean area under the serum concentration-time curve from 0 to 120 min was 1393 ± 89 $\mu g \cdot min \cdot ml^{-1}$.

When buprenorphine was administered, the mean time to reach the peak paracetamol concentrations was 204 ± 59 min, the mean peak concentration was 6.4 ± 1.4 $\mu g \cdot ml^{-1}$ and the mean area under the serum concentration-time curve from 0 to 120 min was 437 ± 133 $\mu g \cdot min \cdot ml^{-1}$.

All the mean serum paracetamol concentrations measured from 15 to 120 min after buprenorphine administered differed significantly from the mean serum paracetamol concentrations without buprenorphine ($P<0.01$). The mean time to reach the peak concentration of paracetamol after buprenorphine administration differed significantly from the mean time to reach the peak concentration of paracetamol without buprenorphine ($P<0.03$). The mean peak serum paracetamol concentration after buprenorphine administration differed significantly from the mean peak serum paracetamol concentration without buprenorphine ($P<0.0002$). The mean area under the serum paracetamol concentration-time curve from 0 to 120 min after buprenorphine administration differed significantly from the mean area under the serum concentration-time curve without buprenorphine ($P<0.00006$).

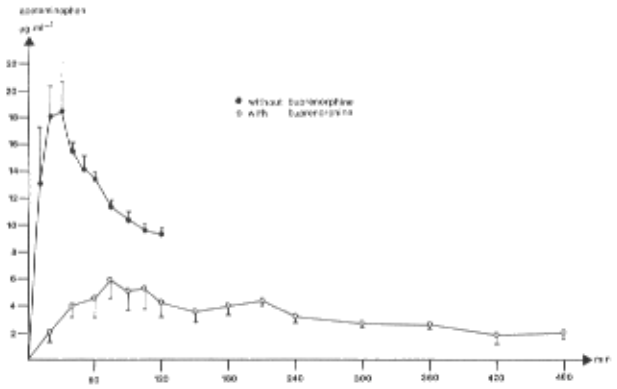

Fig. 1. Mean serum paracetamol concentration curves in seven volunteers given paracetamol 20 $mg \cdot kg^{-1}$ body weight p.o. with (○) and without (●) co-administration of buprenorphine 4 $\mu g \cdot kg^{-1}$ body weight i.v. Bars indicate s.e.mean.

DISCUSSION

This study demonstrates that buprenorphine administered as a single intravenous dose 4 $\mu g \cdot kg^{-1}$ body weight to healthy volunteers was associated with delayed paracetamol absorption, indicating a marked inhibition of gastric emptying. Gastric emptying was delayed in six volunteers and moderately delayed in one after buprenorphine administration.

In the control study paracetamol absorption followed a first order process, a type I pattern according to the classification of Clements et al. (18). After buprenorphine administration, concentration-time curves of paracetamol absorption were marked bi- or tri-phasic. The most likely explanation of the phasic curves is a biphasic gastric emptying pattern in which there are intervals of emptying, interrupted by intervals with no emptying. According to the classification of Clements et al. (18), buprenorphine induces a type III pattern of gastric emptying. Therefore the data from each patient was unsuccessfully fitted (21) to a classical two-compartment pharmacokinetic model to obtain K_a, the apparent first-order rate constant for absorption from the gastrointestinal tract. The program was not able to estimate K_a from the part of the study where buprenorphine was given, because of phasic time-concentration curves.

Side effects were frequently observed. One patient was excluded due to vomiting between administration of paracetamol and the end of the study. Five of the eight subjects had nausea or vomiting after buprenorphine administration. It is notable that nausea and vomiting were especially pronounced in the subjects who had the most prolonged paracetamol absorption from buprenorphine. This confirms the close relationship between delayed gastric emptying and the clinical symptoms relating to delayed gastric emptying.

In conclusion, as judged from the delay in paraceta-

mol absorption, buprenorphine retards gastric emptying. As a consequence anorexia, nausea, vomiting, delayed absorption of drugs and increased risk of aspiration of gastric contents to the lungs may be expected.

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