Serum drug concentrations after oral administration of paracetamol to patients with surgical resection of the gastrointestinal tract

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Serum concentrations of paracetamol were measured at 30, 60, 120 and 180 min after oral administration of a solution of 1500 mg paracetamol in normal subjects ($n = 32$) (Group A) and in patients with total gastrectomy (Roux-en-Y reconstruction) ($n = 5$) (Group B), distal partial gastrectomy (Billroth I reconstruction) ($n = 7$) (Group C), pylorus preserving pancreatoduodenectomy (Billroth I type reconstruction) ($n = 12$) (Group D), and short bowel syndrome ($n = 5$) (Group E). In Group B, the dose was delivered directly into the jejunum 20 cm distal to the duodenojejunal flexure. The highest serum drug concentrations were observed in the 30 min sample in Groups B and C and in the 120 min sample in Groups A, D, and E. Mean ($\pm$ s.d.) concentrations at these times were $18.90 \pm 1.55 \mu\text{g ml}^{-1}$ (Group B), $12.89 \pm 2.12 \mu\text{g ml}^{-1}$ (Group C), $11.12 \pm 3.16 \mu\text{g ml}^{-1}$ (Group A), $9.78 \pm 2.85 \mu\text{g ml}^{-1}$ (Group D), and $4.89 \pm 1.96 \mu\text{g ml}^{-1}$ (Group E), respectively. We conclude that in patients with normal intact gastrointestinal tract, most of a dose of oral paracetamol is absorbed from the jejunum distal to the duodenojejunal flexure.

Keywords paracetamol acetaminophen absorption pylorus preserving pancreatoduodenectomy short bowel syndrome

Introduction

In the rat paracetamol is absorbed from all parts of the gastrointestinal tract including the stomach and the colon, although the most efficient uptake occurs in the small intestine by a passive transport process [1]. However, comparable information is not available for man. Paracetamol is generally considered to be absorbed rapidly from the small intestine, with little or no uptake from the stomach [2–5]. To our knowledge, this has never been proven and the exact site of intestinal absorption has not been defined. We have measured serial serum concentrations of paracetamol after its oral administration to patients with total gastrectomy, distal partial gastrectomy, pylorus preserving pancreatoduodenectomy (PPPD), and short bowel syndrome, as well as in healthy subjects with normal bowels, to determine the main absorption site of paracetamol in the human gastrointestinal tract.

Methods

Thirty-two healthy subjects (Group A—13 females and 19 males, aged 24–72, mean 42 years) participated in this study along with five patients (Group B) who had undergone total gastrectomy, seven (Group C) who had undergone distal partial gastrectomy, 12 (Group D) who had undergone pylorus preserving pancreatoduodenectomy (PPPD), and five (Group E) who had a duodenostomy or jejunostomy.

All of the patients underwent gastrectomy for malignancy. In the totally gastrectomized patients, oesophagojejunostomy was constructed with the jejunum 20 cm distal from the duodenojejunal flexure (DJF) and the Roux-en-Y limb was anastomosed at 40–50 cm distal from the oesophagojejunostomy. Distal partial gastrectomies were reconstructed with Billroth I end-to-end gastroduodenostomy. PPPD was performed as follows. The duodenal bulb was transected 3 cm beyond the pylorus, and the fourth

portion of the duodenum was preserved. After completing the resection with the head of the pancreas, reconstruction was accomplished with a Billroth I type end-to-end anastomosis between the first and fourth portion of the duodenum. Pancreato-jejunosomy and choledochojejunosomy were performed as described previously [6, 7]. Short bowel syndrome patients comprised one patient (#1) with a duodenostomy 15 cm distal from the pyloric ring following a traffic accident, one patient (#2) with a jejunostomy 15 cm distal from the DJF to treat paraquat intoxication, two (#3 and 4) patients with jejunostomies 40 cm distal from the DJF to treat Crohn's disease, and one patient (#5) with a jejunostomy 60 cm distal from the DJF following generalized peritonitis.

All of the subjects had normal liver and renal function at the time of the study. They were receiving no medications known to influence gastrointestinal motility. The study was performed more than 3 months after surgery in the patients.

After an overnight fast, 200 ml of a liquid meal (YH-80, Meiji Milk Co. Ltd, Japan) mixed with 1500 mg dose of paracetamol powder (Pyrinazin, Yamanouchi Pharmaceutical Co. Ltd, Japan) was administered orally. The subjects remained supine until the end of the study. The liquid meal contained 6.2 g protein, 5.2 g fat, and 32.2 g carbohydrate. Its pH, osmolality, and total caloric value were approximately 3.9, 1000 mosm ml⁻¹, and 100 kcal ml⁻¹, respectively. No food, drink, or tobacco was permitted during the study.

Venous blood samples were drawn by venepuncture and placed in glass tubes. They were collected prior to, and 30, 60, 120 and 180 min after drug dosage. The blood was centrifuged and the serum was separated and stored immediately at -20°C until assay by h.p.l.c. based on the method described by Ameer *et al.* [8].

Informed consent was obtained from all of the subjects, and the studies were carried out in accordance with the Declaration of Helsinki of 1975.

AUC(0,180 min) values were estimated using the linear trapezoidal rule. Results are given as mean $\pm$ s.d. Statistical comparisons were performed using Student's *t*-test, with *P* < 0.05 regarded as significant.

Results

Mean serum paracetamol concentrations in each group are shown in Figure 1. The highest concentrations were observed in the 30 min sample in Groups B and C and in the 120 min sample in Groups A, D and E. Mean ($\pm$ s.d.) concentrations at these times were 18.90 $\pm$ 1.55 μ g ml⁻¹ (Group B), 12.89 $\pm$ 2.12 μ g ml⁻¹ (Group C), 11.12 $\pm$ 3.16 μ g ml⁻¹ (Group A), 9.78 $\pm$ 2.85 μ g ml⁻¹ (Group D), and 4.89 $\pm$ 1.96 μ g ml⁻¹ (Group E), respectively.

AUC(0,180) values in each group were 25.31 $\pm$ 5.70 μ g ml⁻¹ h (Group A), 34.44 $\pm$ 4.66 μ g ml⁻¹ h (Group B), 30.22 $\pm$ 7.21 μ g ml⁻¹ h (Group C), 21.91 $\pm$ 5.47 μ g ml⁻¹ h (Group D), and 10.79 $\pm$ 2.92 μ g ml⁻¹ h (Group E), respectively.

Figure 1 Mean ($\pm$ s.d.) serum concentrations of paracetamol in healthy subjects and in patients with surgical resection of the gastrointestinal tract after oral administration of a solution of 1500 mg paracetamol in a liquid meal. (○—○ healthy subjects (*n* = 32); ●—● total gastrectomy (*n* = 5); □—□ distal partial gastrectomy (*n* = 7); ■—■ PPPD (*n* = 12); ▲—▲ short bowel syndrome (*n* = 5)).

The concentration at 30 min was significantly higher in Groups B and C compared with the other groups (95% confidence intervals (CI) for differences from Group A were 12.12~15.18 and 5.92~9.36, respectively). The 30 min concentrations were significantly higher in Group B compared with Group C (95% CI for difference was 3.93~8.09). The 120 min concentrations were significantly lower in Group E compared with Group A (95% CI for difference was 4.19~8.27), and the difference between Group A and D was not significant (95% CI for difference was -0.61~3.29). Significant differences were observed in AUC(0,180) between Group A and E and between Group D and E (95% CI for differences were 11.05~17.79 and 7.00~15.04, respectively). The difference between Group A and D was not significant (95% CI for difference was -0.39~7.19).

Discussion

The healthy subjects and partially gastrectomized patients had intact or partially intact stomachs and intact small intestines including the duodenum; patients after PPPD with Billroth I type reconstruction had complete gastrointestinal tracts, excluding the middle section of the duodenum; short bowel syndrome patients had intact stomachs and duodenum but limited lengths of jejunum; and totally gastrectomized patients had small intestines approximately 20 cm distal from the duodenojejunal flexure. Because of the loss of the pyloric ring, the test meal containing paracetamol entered the duodenum and the jejunum in partially gastrectomized patients, and the jejunum in totally gastrectomized patients. An early maximum serum drug concentration in patients with total gastrectomy was presumably a result of the absence of a delaying effect on absorption from the intestine of gastric emptying. Rapid gastric emptying is indicated in the partial gastrectomy group by an

early maximum serum drug concentration. A lower value of this concentration compared with the total gastrectomy group suggests slower absorption from the residual stomach and duodenum. In patients after PPPD with Billroth I type reconstruction, the serum drug concentration-time curve was similar to that in healthy subjects, suggesting that the middle section of the duodenum does not play an important role in

paracetamol absorption. In short bowel syndrome patients, the extent of absorption of paracetamol appeared to be decreased compared with absorption in healthy subjects and patients after PPPD, emphasising the role of the jejunum as an absorption site. The data indicate that the main absorption site of oral paracetamol is the jejunum distal from the duodenojejunal flexure.

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(Received 3 June 1994,
accepted 23 November 1994)