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Liver regeneration is enhanced by omeprazole in rats following partial hepatectomy

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The effect of omeprazole on liver regeneration was studied in rats following partial (65 per cent) hepatectomy. Omeprazole 0·2 mg/kg increased the relative liver weight (weight of liver as a proportion of body-weight) and mitotic index ($P < 0·05$). There was no difference in food and water intake. The serum gastrin concentration was significantly higher in animals receiving omeprazole 0·2 mg/kg than in controls ($P < 0·05$). Omeprazole administration induced an increase in the level of serum alkaline phosphatase ($P < 0·05$) but had no effect on serum albumin, glutamic–pyruvic transaminase and total bilirubin levels. Omeprazole stimulates liver regeneration after partial hepatectomy and this regeneration may be mediated by gastrin.

Stress ulcer may occur after major hepatic resection[1,2]. To avoid ulcer formation antisecretory agents may be administered prophylactically[3]. A potent secretory inhibitor, omeprazole, has recently been developed[4,5]. By suppressing the action of the gastric proton pump this agent inhibits acid secretion and stimulates the release of gastrin[6]. Gastrin induces liver regeneration[7].

This study examined whether omeprazole influences liver regeneration in rats following partial hepatectomy.

Materials and methods

Eighteen male Wistar rats were used and allowed free access to laboratory chow and tap water throughout the experiment. Surgery was performed and daily recordings of body-weight, and food and water intake were made between 10.00 and 12.00 hours to avoid the effect of diurnal variation.

When the animals attained 180 g, partial hepatectomy was carried out as described previously[8–10], resecting the median and left lateral lobes of the liver (two-thirds of the liver mass).

The animals were randomly allocated to three groups of six. Omeprazole 0·1 or 0·2 mg/kg was dissolved in 20 per cent ethanol and injected intramuscularly once daily for 3 days following hepatectomy (groups 2 and 3). In the control group (group 1) 20 per cent ethanol was injected. The injection was administered in a volume of 0·1 ml.

The animals were anaesthetized by intraperitoneal injection of pentobarbital sodium 40 mg/kg at 10.00 hours 3 days after surgery. Blood was collected from the tail vein and the animals were killed to measure the weight of the liver remnant.

To compare the rate of liver regeneration, the relative liver weight (weight of liver as a proportion of body-weight) was used as an index[11,12]. Histological specimens from the caudate lobe were prepared and the proportion of hepatocytes in mitosis expressed as a mitotic index.

Blood was cooled immediately on ice and centrifuged at 2200 r.p.m. for 20 min. Serum was stored at −20°C until auto-analyser (Hitachi-736; Hitachi, Tokyo, Japan) measurement of albumin (bromcresol green method)[13], glutamic–pyruvic transaminase (SGPT; ultraviolet method)[14], total bilirubin (azobilirubin method)[15] and alkaline phosphatase (Bessey–Lowry method)[16]. The plasma gastrin level was determined by radioimmunoassay[17].

Statistical analysis

The significance of differences was evaluated by analysis of variance without repetition and Duncan's multiple range test. $P < 0·05$ was considered significant.

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Results

The relative weight of excised liver was no different between the three groups but administration of omeprazole 0·2 mg/kg increased both relative liver weight and mitotic index at 3 days after hepatectomy ($P < 0·05$) (*Fig. 1*). Compared with groups 1 and 2 the responses of these two parameters to omeprazole tended to be dose dependent.

On comparing the amount of food and water intake for the 3 days after hepatectomy, omeprazole produced no significant differences (*Table 1*).

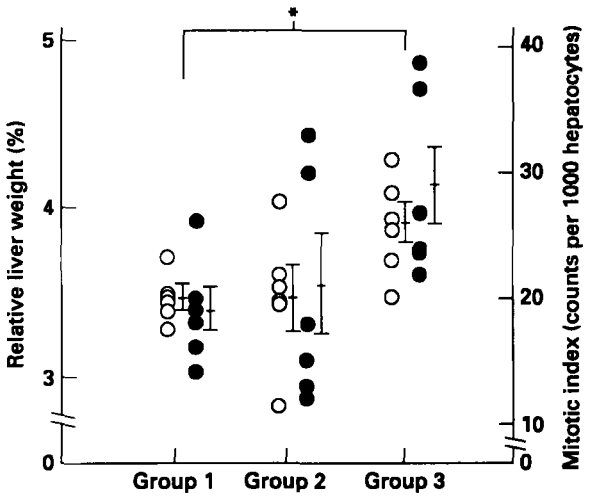

Fig. 1 Relative liver weight (○) and mitotic index (●) 3 days after hepatectomy. Bars are mean(s.e.m.). Group 1 ($n = 6$), 20 per cent ethanol (control); group 2 ($n = 6$), omeprazole 0·1 mg/kg; group 3 ($n = 6$), omeprazole 0·2 mg/kg. *$P < 0·05$ for both liver weight and mitotic index (Duncan's test)

Table 1 Intake for 3 days after administration of omeprazole

Treatment	Food intake (g)	Water intake (ml)
Group 1 ($n = 6$)	46·7(2·2)	43·5(4·1)
Group 2 ($n = 6$)	46·3(1·3)	49·0(0·4)
Group 3 ($n = 6$)	49·2(2·3)	43·3(2·2)

Values are mean(s.e.m.). There were no statistically significant differences between the groups

Table 2 Serum concentrations of gastrin, albumin, transaminase, total bilirubin and alkaline phosphatase 3 days after hepatectomy

Treatment	Gastrin (pg/ml)	Albumin (g/dl)	SGPT (units/l)	Total bilirubin (mg/dl)	Alkaline phosphatase (units/l)
Group 1 ($n=6$)	328(49)	1·6(0·0)	63(6)	0·2(0·0)	1333(136)
Group 2 ($n=6$)	291(24)	1·6(0·0)	69(9)	0·3(0·1)	1919(124)*
Group 3 ($n=6$)	492(57)*	1·7(0·0)	74(8)	0·3(0·0)	1964(148)*

Values are mean(s.e.m.). SGPT, serum glutamic–pyruvic transaminase. *$P < 0·05$ *versus* group 1 (Duncan's test)

The serum gastrin concentration was significantly increased in group 3 compared with that in group 1 3 days after hepatectomy ($P < 0·05$) (*Table 2*). Of the hepatic functional measures, the alkaline phosphatase concentration was significantly increased in groups 2 and 3 ($P < 0·05$) but no significant changes were seen in albumin, SGPT and total bilirubin levels (*Table 2*).

Discussion

This study shows that omeprazole stimulates liver regeneration in rats following partial hepatectomy. Because the responses of relative liver weight and mitotic index appeared in a dose-dependent fashion, the observed liver regenerative response seems to be specific to omeprazole.

Pharmacologically the imidazole ring, a component of drugs used in the treatment of gastric ulceration, inhibits the oxidation process in liver microsomes[3], and the ring may suppress liver regeneration[18]. A recent *in vitro* study suggested that omeprazole, a substituted benzimidazole, inhibits cytochrome P-450 mono-oxygenases[19]. Francavilla *et al.*[20], however, observed that omeprazole failed to affect rat hepatocyte proliferation *in vitro* and that repeated administration of the drug to adult male rats increased cytochrome P-450 activity[21]. The findings of the present study could therefore be interpreted as resulting from the increased activity of the cytochrome P-450 system. No cytotoxic effect on hepatocytes by omeprazole was detected.

Liver regeneration can be determined by food intake[22], but this was not affected by omeprazole.

Rasmussen *et al.*[7] found a significant rise in the serum gastrin concentration of portal venous blood after partial hepatectomy and noted an enhanced effect of administered pentagastrin on liver regeneration. They concluded that gastrin could be a hepatotrophic factor. The present study confirmed an increased serum gastrin concentration, as noted in a previous report[6]. This suggests that liver regeneration stimulated by omeprazole is mediated via a gastrin-releasing process.

Omeprazole stimulates liver regeneration after partial hepatectomy; this regeneration may be mediated by gastrin. The dose of omeprazole used is effective in inhibiting gastric acid secretion[23] and therefore following hepatectomy omeprazole may provide prophylaxis against gastric ulceration and enhancement of liver regeneration. Clinical studies of this phenomenon are awaited.

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