The Effect of Gastrin on Gastric Ulceration in Pigs after Bile Duct Ligation

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SUMMARY

Pigs develop gastric ulceration spontaneously and after bile duct ligation. Despite increased basal acid secretion, serum gastrin levels are not elevated, and a possible 'protective' role of gastrin was proposed. Continuous intravenous infusion of synthetic human gastrin did not protect from gastric ulceration, but was associated with simultaneous duodenal ulceration. Another ulcerogenic mechanism must be invoked.


Bile duct ligation has been shown to result in a 100% incidence of gastric ulceration in the pig. These ulcers occur in the pars oesophagea, a tongue of squamous epithelium which projects from the oesophagus into the stomach, and they may be prevented by highly selective vagotomy, partial gastrectomy, or gastro-enterostomy. It has also previously been found that while bile duct ligation in the pig is associated with a rise in basal acid secretion, there is a fall in serum gastrin. Since gastrin has a trophic effect upon the stomach, this study was designed to investigate its 'protective' effects on the stomach of the bile duct-ligated (BDL) pig.

MATERIALS AND METHODS

Four groups of young pigs, Landrace X Large White breed, weighing 18 - 24 kg and of either sex, were prepared with (i) bile duct ligation; (ii) bile duct ligation plus gastrin infusion; (iii) sham operation; and (iv) sham operation plus gastrin infusion. Synthetic human gastrin (ICI) was given intravenously as a constant infusion in the dose of 0.25 µg/kg/h. After simple bile duct ligation and division, or sham operation, the pigs were kept in specially designed cages with a continuous intravenous infusion of gastrin in normal saline or saline alone with human albumin added to a final concentration of 0.25%. Arterial blood samples were taken at 24-hour intervals and the animals were fed only after such samples had been taken. Three animals were prepared simultaneously on any occasion in order that they might be group-fed postoperatively, so that the smallest amount of food eaten by any one animal would be given to the others the following day. This was done because bile duct ligation generally impaired appetite. Arterial blood samples were analysed for gastrin and for serum glutamic oxalo-acetic acid transaminase (SGOT), bilirubin and alkaline phosphatase. Statistical analyses were done using McNemar's test. After death a full postmortem examination was performed and the entire stomach and duodenum were removed and washed out. Histological sections were taken from sites which appeared to be ulcerated. When the BDL animals of a triplet had died, the others were sacrificed in order to determine the state of the gastro-oesophageal mucosa at comparable times.

RESULTS

Survival

Most of the BDL or BDL plus gastrin-infused animals died between the 3rd and 4th postoperative days. The mortality and morbidity figures are shown in Table 1. Fifty per cent of pigs that had undergone bile duct ligation and 80% of BDL plus gastrin-infused pigs died from gastrointestinal haemorrhage. In the sham-operated groups only one animal in each group died of unrelated causes.

Incidence of Ulceration (Table 1)

All 6 animals in both the BDL and BDL gastrin-treated groups had large pars oesophageal ulcers (total erosion of the pars oesophageal mucosa, as has previously been described). Two of 6 in each group had gastric ulcers elsewhere in the stomach, and 4 and 5 of 6 respectively had duodenal ulcers. In the gastrin-treated BDL group, in all 4 pigs with duodenal lesions, the ulcers were multiple, while only 1 non-gastrin-treated BDL pig had multiple ulcers (P<0.05). In 3 of the 6 BDL gastrin-treated pigs perforation of the ulcers had occurred. In sham-operated pigs, 2 had hyperkeratosis of the pars oesophagea, but when gastrin was given to sham-operated pigs, 2 developed small linear pars oesophageal ulcers, and 4 had hyperkeratosis.

Serum Gastrin

The mean ± SE of the serum gastrin level is shown in Fig. 1. There was a significant rise in the serum gastrin levels of sham-operated animals in the first 2 postoperative days, but gastrin levels in BDL animals did not change. Administration of gastrin to sham-operated animals resulted in very high values for 2 days, which then fell over the 3rd and 4th days, rose again on the 6th day,
and fell again on the 7th day. This pattern was similar in the animals with bile duct ligation which were given gastrin, although the magnitude of the rise was not nearly as great.

Liver Function Tests

Serum bilirubin and alkaline phosphatase levels rose in both groups of BDL pigs and fell marginally in sham-operated pigs. There was a marginal elevation of SGOT in BDL pigs.

DISCUSSION

It has previously been shown that bile duct ligation induced pars oesophageal ulceration in the pig which was associated with lower levels of serum gastrin than in sham-operated animals. This was indeed the case in this study, and at no time during this study was the gastrin level in the BDL group higher than that in the sham-operated group. The gastrin levels achieved by infusion of gastrin in sham-operated animals were very high for 2 days, and fell thereafter, despite continued infusion of gastrin. A similar pattern, although of lesser magnitude, was noted in the BDL group. There was no protective effect of gastrin administration upon the gastric ulceration of BDL pigs. Indeed, the incidence of gastric ulceration away from the pars oesophagea and duodenal ulceration, particularly with perforation, was higher in the BDL animals which received gastrin. It has been confirmed (unpublished observations) that bilirubin in the serum does not interfere with the measurement of gastrin levels, and thus the different values of gastrin obtained in BDL and sham-operated animals given identical doses of gastrin are of great interest, for it suggests that the BDL group had some alternative means of disposal of gastrin which would account for the lower levels achieved both with and without gastrin infusion. In both instances the fall in serum gastrin levels after the 3rd day with almost normal values on the 5th and 7th days is also difficult to explain.

The results of these studies suggest that gastrin is not the only ulcerogenic factor in BDL pigs. However, it may act in conjunction with other ulcerogenic factors or gastric acid secretagogues. It has been shown that despite lower gastrin levels, acid secretion increases after bile duct ligation. Other factors in the serum or gastrointestinal lumen might be responsible for acid hypersecretion. Rather than a trophic effect, the administration of gastrin to BDL pigs resulted in a greater incidence of perforation than previously seen. Even in sham-operated animals, the administration of gastrin resulted in mild hyperkeratosis of the pars oesophageal area, which is thought by some authors to be pre-ulcerogenic.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean survival (h)</th>
<th>Mortality</th>
<th>Pars oesophageal ulcer</th>
<th>Gastric ulcer</th>
<th>Duodenal ulcer</th>
<th>Additional information</th>
</tr>
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<tr>
<td>I</td>
<td>BDL + gastrin</td>
<td>113 ± 8</td>
<td>5/6</td>
<td>6/6</td>
<td>2/6</td>
<td>4/6</td>
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<tr>
<td></td>
<td>BDL</td>
<td>125 ± 5</td>
<td>3/6</td>
<td>6/6</td>
<td>2/6</td>
<td>5/6</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Sham operation sacrificed</td>
<td>1/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Sham operation + gastrin sacrificed</td>
<td>*1/6</td>
<td>12/6</td>
<td>4/6</td>
<td>0/6</td>
</tr>
</tbody>
</table>

* Cannula bleed
* Small linear ulcer

Table 1. Mortality Rate and Findings at Autopsy or Sacrifice

Bile duct-ligated + gastrin v. sham-operated or sham-operated + gastrin (P<0.05).
It seems, therefore, that in these large doses of gastrin which raise levels to the Zollinger-Ellison syndrome range, the gastrin is not trophic, but increases the risk of perforation of ulcers. The effect is probably acid-mediated, but may be related to other effects of gastrin on the mucosa, as suggested by Emas and Grossman.  

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REFERENCES


Fractures of the Tibial Shaft

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SUMMARY

The closed treatment of fractures of the tibial shaft will usually result in bony union within a period of 4 months. Early weight-bearing in a suitable cast or cast brace is advised.

Infection following open reduction is often undetected until months or even years have elapsed. When infection occurs, union is delayed on average for 4 years, and amputation is not infrequently the end-result.


Fractures of the tibia and fibula are common, their treatment is controversial and the failures of open reduction are disastrous. To those who never advise open operation, and to those who treat nearly all fractures by primary open reduction and internal fixation, I should like to bring to mind the words of Sandy McPherson, who said: 'Moderation is aye best . . . Yea!'

NicolI, in a series of 674 cases treated conservatively with plaster immobilization, reported union and healing in 96% within 16 weeks. Those few fractures in which treatment failed were so comminuted or mangled that the patients could have been regarded as candidates for amputation.

Dehne et al. treated over 400 consecutive cases by means of immediate ambulation in plaster and achieved union and healing in 100% within 14.5 weeks. Sarmiento has virtually eliminated the need for open reduction by the simple rule of cast brace ambulation at the earliest possible moment. In a series of 482 patients, 89% received the functional brace within 4 weeks and in these the healing time averaged 14.5 weeks, the same as in Dehne et al.'s series. Sarmiento, at a meeting in Copenhagen in 1975, declared: 'I have not had the opportunity to do internal fixation (of the tibia) for a very long time, and it's not that I don't have the ability or the facilities. There has not been one case during the past few years . . .

Charnley warns that 'the failures of operative treatment and the failures of conservative treatment are not equally salvageable', and Dehne offers an arresting report on complications in fractures of the lower extremity: 'The relation . . . complications to treatment becomes apparent under two circumstances: (i) end-result studies — preferably by independent observers; (ii) large concentrations of problem cases in specialized centres (war surgery). He continues: 'The past World War II period afforded such opportunity. Most of the 1 900 orthopaedic inpatients at Oliver General Hospital had infected compound fractures in which conventional methods had failed. Only half of these patients were battle casualties; the others, fractures infected after open reduction.'

Dehne continues: 'The answer to this problem was quite simple: to seek non-surgical methods even if full reduction should not always be achieved. The answer to the problem of infection, however, was slower in forthcoming but then quite startling.

'In a frantic attempt to solve the problems of patients anxious to return to their previous occupations they were subjected to serial surgical procedures: first, to clear up infection; then, to re-establish sound skin coverage to finally ready them for reconstructive surgery. Of those in whom the repeated debridement led to bone defects,