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Acid induced duodenal ulcer pain: the influence of symptom status and the effect of an antispasmodic

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SUMMARY **The aims of this study were to determine whether the development of acid induced duodenal ulcer pain was influenced by the symptomatic status of the patient and whether the administration of an antispasmodic could abolish pain. One hundred millilitres of 0·1 N hydrochloric acid was infused onto the ulcer craters or scars of 143 duodenal ulcer patients on 168 occasions. Symptomatic patients were randomised to receive 40 mg of hyoscine intravenously before acid infusion, or to a control group. Typical ulcer pain developed in seven of 55 (13%) instances for non-symptomatic patients, 24/57 (42%) of control symptomatic patients, and 20/56 (36%) of symptomatic patients given hyoscine. (Asymptomatic group *v* control symptomatic group, $p<0·005$; control symptomatic group *v* hyoscine group, NS – 95% confidence limits 12% in favour of the control and 24% in favour of the hyoscine group). The results suggest that acid infusion seldom reproduces ulcer pain in non-symptomatic duodenal ulcer patients and that the pathogenesis of acid induced duodenal ulcer pain probably involves a mechanism other than spasm, as pain was not prevented by an anticholinergic.**

Despite recent advances in the diagnosis and treatment of duodenal ulcer disease, the pathogenesis of duodenal ulcer pain remains poorly understood. Early studies by Palmer,[1-3] as well as by Bonney and Pickering[4] showed that gastroduodenal acidification brought on ulcer pain in almost all symptomatic duodenal ulcer patients – that is, those who have experienced spontaneous pain within 24 hours of study. Subsequent workers, however, reported more equivocal results.[5-7] Non-symptomatic duodenal ulcer patients did not develop pain on gastroduodenal acidification.[1 4]

Abnormal gastroduodenal motility or spasm has also been suggested to be a factor in the pathogenesis of spontaneous as well as acid induced duodenal ulcer pain.[5] Although the administration of an antispasmodic had been reported to reduce motility and relieve pain,[5] other workers found that antispasmodics had no consistent effect on duodenal ulcer pain even though gastroduodenal motility was invariably suppressed.[2 6]

We have recently shown, in a controlled double blind study, that direct acidification of the duodenal ulcer crater in symptomatic subjects reproduced ulcer pain in one-third of cases.[8] As duodenal ulcer pain had been reported to correlate poorly with the presence of ulcer craters on endoscopy,[9] we decided to reinvestigate the effect of the symptom status on acid induced duodenal ulcer pain, taking endoscopic appearances into consideration. The effect of an antispasmodic on the production of acid induced duodenal ulcer pain was also investigated in a controlled manner.

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Methods

PATIENT SELECTION

Patients with endoscopically proven duodenal ulcer

disease, in whom abdominal pain was or had been one of the presenting symptoms were studied. Those with recent upper gastrointestinal haemorrhage or serious underlying diseases were excluded. Informed consent was given.

Patients were divided into a symptomatic group and a non-symptomatic group. The definition of a symptomatic patient was that used by Palmer[1] and also by Bonney and Pickering[4] – that is, a patient whose last episode of spontaneous ulcer pain had occurred within 24 hours of the time of study. Most patients were studied before institution of treatment but some were studied after a four to six week course of a H_2 antagonist.

STUDY DESIGN

Endoscopy was carried out under local anaesthesia using the Olympus GIFQ or Q10 gastroscope. No sedation or premedication was given. After diagnostic gastroduodenoscopy, a washing tube was passed through the biopsy channel of the gastroscope. Through this tube 100 ml 0·1 N hydrochloric acid was administered onto the duodenal ulcer crater or scar over five minutes. Symptomatic patients were randomly allocated to a hyoscine group or to a control group. Each patient in the hyoscine group received 40 mg of hyoscine N-butylbromide (Buscopan, Boehringer Ingelheim) intravenously after diagnostic endoscopy but before acid infusion. Patients in the control group did not receive hyoscine. The formulation and dosage of antispasmodic medication chosen represented what is routinely used in endoscopic work to suppress gastroduodenal motor activity.

The endoscopist periodically adjusted the position of the washing tube to maintain a good flow directed onto the ulcer crater or scar and in some cases the patients had to be repositioned. During the infusion the patient was asked to indicate by hand signals whether abdominal pain developed, exacerbated, or improved, and whether the pain was similar to ulcer pains normally experienced in terms of site and character. If ulcer pains typical for that particular patient developed or if pre-existing pain was exacerbated during acid infusion, the infusion was ceased. After the endoscopy, the patient was again asked about the occurrence or otherwise of pain and whether this pain was typical of ulcer pains normally experienced. All enquiries were made by an investigator other than the endoscopist and he was unaware of the symptomatic or treatment status of the patient, the endoscopy findings, and whether or not hyoscine had been administered. The last 51 patients in the study were also asked at the end of the procedure, and after the enquiry regarding pain development, whether they experienced any dryness of the mouth.

Table 1 *Patient characteristics**

		Symptomatic	
	Non-symptomatic	*Hyoscine given*	*No hyoscine*
Sex (M:F)	46:9	42:14	40:17
Race (Chinese:others)	44:11	48:8	37:20
Age			
Mean yr	42	40	45
Range	18–66	18–75	18–85
Standard deviation	13	15	17
Already on treatment	34/55 (62%)	1/56 (2%)	3/57 (5%)
Active ulcer craters	35/55 (64%)	56/56 (100%)	57/57 (100%)
Duodenal erosions	13/55 (24%)	14/56 (25%)	6/57 (11%)

*The numbers given in this Table refer to studies and not patients.

STATISTICAL ANALYSIS

The Student's t test and the χ^2 test with Yate's correction were used for comparison within groups. For the symptomatic group, the question asked was whether hyoscine would prevent the development of acid induced duodenal ulcer pain. Thirty per cent of symptomatic patients were expected to develop pain with infusion of 100 ml 0·1 N hydrochloric acid.[8] The total number of subjects required to show a true reduction in the frequency of acid induced duodenal ulcer pain from 30% to 10% (α=0·05, β=0·8, one-tailed test) was approximately 116.[10] Ninety five per cent confidence limits of the difference between groups was calculated according to Wulff.[11]

Results

PATIENT CHARACTERISTICS

Altogether, 168 studies were carried out on 143 patients. One hundred and twenty two patients were studied on a single occasion each. Eighteen patients were studied on two occasions each; in eight of these the two studies were performed at pretreatment and post-treatment endoscopies during the same ulcer episode. Two patients were studied on three occasions each; for one of these patients, two of the three studies represented pretreatment and post-treatment studies during the same ulcer episode. One patient was studied on four occasions; this presented pretreatment and post-treatment studies done during two separate ulcer episodes.

There were 55 studies on non-symptomatic patients and 113 studies on symptomatic patients. For the symptomatic studies, 57 were randomised into the control group while 56 studies were randomised to the hyoscine group. The sex, age, and racial characteristics of the patients are shown in Table 1. These characteristics appear similar in the three groups.

Table 2 *Occurrence of acid induced pain*

Group	Total number	Developing pain (n)	Developing pain (%)
Non-symptomatic	55	7*	13[a]
Symptomatic hyoscine not given	57	24†	42[b]
Symptomatic hyoscine given	56	20	36[c]

a *v* b $p<0.005$; b *v* c NS; *two other patients reported atypical pain; †three other patients reported atypical pain.

Table 3 *Effect of treatment status and activity of the ulcer on pain development*

	Asymptomatic		Symptomatic	
	Treated	Untreated	Treated	Untreated
Active ulcer	4/14 (29%)	3/21 (14%)	2/4 (50%)	42/109 (39%)
Healed ulcer	0/20 (0%)	–	–	–

Number (%) developing pain.

OCCURRENCE OF PAIN (Table 2)

Seven of 55 non-symptomatic patients (13%) developed abdominal pains typical of their usual ulcer pains during acid infusion. Two others reported abdominal pains of a different nature from their usual ulcer pain. Of 57 symptomatic patients not given hyoscine, 24 (42%) stated that their usual ulcer pains were reproduced by acid infusion while three other patients reported atypical pains. Of 56 symptomatic patients given hyoscine, 20 (36%) reported typical ulcer pains during acid infusion.

COMPARISON BETWEEN GROUPS

Considering only patients with typical pains, the difference between the frequency of pain development in the non-symptomatic group and the symptomatic group, hyoscine not given, was statistically significant ($\chi^2=10.6$, $p<0.005$). There was no significant difference in the frequency of pain development in the symptomatic patients whether or not hyoscine was given. Ninety five per cent confidence limits of this difference varied from 24% in favour of the hyoscine group to 12% in favour of the no hyoscine group.

These results remained essentially unaltered even if the five patients with atypical pains were included in the analysis. The mean time taken for pain to occur was 3·3 minutes in the non-symptomatic group, 2·8 minutes in the control symptomatic group, and 2·7 minutes in the symptomatic group, hyoscine given. There is no statistically significant differences between any of these values. Twelve of 20 patients (60%) given hyoscine admitted to dryness of the mouth compared to five of 31 patients (16%) not given hyoscine.

EFFECT OF TREATMENT STATUS AND ACTIVITY OF THE ULCER ON PAIN DEVELOPMENT

For this analysis, shown in Table 3, patients in the buscopan group and the control group were considered together. All symptomatic patients had active ulcer craters. Treatment status did not affect the development of acid induced pain. Thus, four of 34 treated asymptomatic patients developed pain compared with three of 21 untreated asymptomatic patients (NS). Likewise, for symptomatic subjects, two of four subjects studied after a course of treatment developed pain compared with 42 of 109 untreated patients (NS). The presence of an ulcer crater appeared to be significant, however, as amongst treated asymptomatic subjects, four of 14 with active craters developed pain compared with none of 20 with healed ulcers ($p<0.05$).

Discussion

Our results indicate that while duodenal acidification reproduced ulcer pain in one-third of patients with symptomatic duodenal ulcer, patients with non-symptomatic duodenal ulcer seldom developed acid induced pain. This observation confirms the findings of earlier workers.[14] We were, however, able to accurately verify the presence or absence of ulcer craters endoscopically. Also, our study, unlike most earlier ones, was controlled and blinded.

Our results further indicate that endoscopic appearance was another determinant of the development of acid induced pain in that pain only developed in the presence of an active ulcer crater. In our patients ulcer healing was invariably associated with loss of symptoms. It would be of interest to study the group of patients who remained symptomatic despite having healed their ulcers. In some[12 13] but not in all[14] studies describing such patients it is unclear whether residual erosive duodenitis was present. Erosive duodenitis may be associated with symptoms in its own right.[15] We ourselves have seldom encountered such patients, using total re-epithelialisation as the criterion for healing.

Amongst patients who did have active ulcer craters the frequency of acid induced pain was still greater in the symptomatic group compared with the non-asymptomatic group. Treatment with H_2 blockers generally led to loss of symptoms but in itself the treatment did not reduce the frequency of acid induced pain.

Previous studies on the effect of anti-spasmodic agents on acid induced duodenal ulcer pain have

given conflicting results. Palmer found that administration of 1 mg atropine could not prevent acid induced duodenal ulcer pain even though gastroduodenal motility was abolished.[2] In the study by Smith, injections of anticholinergic agents relieved pain in five of eight patients over a period of five to 14 minutes. In three patients, pain persisted despite cessation of motility.[6] The author felt that these results were difficult to interpret. On the other hand, Texter's group found that the administration of various anticholinergics, dosage unspecified, was followed by cessation of gastroduodenal motility and pain in 25 of 26 cases.[5] The time taken for acid induced pain to subside varied from two to 13 minutes with a mean value of nine minutes. The length of time taken for acid induced ulcer pain to spontaneously subside was, however, not stated.

Our results therefore confirm the findings of Palmer[2] but not those of Texter.[5] We have the advantage of being able to verify active ulceration endoscopically, and in addition our studies are controlled and blinded. Our study, however, suffers from the disadvantage that gastroduodenal motility was not monitored. It could be argued that the dosage of hyoscine given may have been inadequate to prevent gastroduodenal spasm. This latter possibility seems unlikely because in everyday endoscopic practice, 20–40 mg hyoscine is adequate to induce gastroduodenal relaxation. Further, a substantial proportion of our patients given hyoscine reported anticholingergic side effects indicating that the dosage given was adequate. Another possibility is that the effect of the hyoscine may be so brief that it had worn off over the period of acid infusion. If this were so, however, the time taken for acid induced pain to develop would be longer for the hyoscine group, which is not the case.

The finding that an antispasmodic does not prevent acid induced duodenal ulcer pain suggests that such pain is not caused by gastroduodenal spasm. This does not exclude the possibility that abnormal motility or spasm is implicated in the pathogenesis of duodenal ulcer pain in the two-third of cases whose pain could not be reproduced by acid infusion.

Earlam[16] described the reproduction of ulcer pain by acid perfusion of the lower oesophagus in some duodenal ulcer subjects. In a few patients he could show that this pain was not prevented by simultaneous gastric perfusion with alkali. This latter finding could not, however, be reproduced by subsequent workers.[17] In the present study it is quite possible that some acid could have tracked back from the duodenum into the lower oesophagus thus contributing to pain production. Our findings on the effect of symptom status and antispasmodic administration on acid induced pain would, however, still be valid because any effect caused by acid stimulation of the lower oesophagus would occur equally in the three groups studied.

Watt *et al*[18] recently described precipitation of ulcer like pain in duodenal ulcer subjects by intravenous infusions of adenosine, suggesting that adenosine may act as a local mediator directly stimulating afferent nerves in the ulcer base. If confirmed this finding will add another dimension to our limited understanding of the pathogenesis of duodenal ulcer pain.

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