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Peptic ulcer and non-steroidal anti-inflammatory agents

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SUMMARY Aspirin is generally regarded as a cause of gastric ulcer but the role of non-steroidal anti-inflammatory agents and paracetamol in the aetiology of peptic ulcer is unclear. To investigate this we conducted a case control study of 180 matched pairs of peptic ulcer patients and controls obtained from surgical and dermatology outpatient clinics. There were 95 gastric ulcer and 85 duodenal ulcer patients. A statistically and clinically significant association (relative risk=5) was found between the regular use of non-steroidal anti-inflammatory agents and gastric ulcer. There was also evidence of positive associations between gastric ulcer and aspirin containing preparations with or without non-steroidal anti-inflammatory agents. By contrast, duodenal ulcer was unrelated to these drugs. Too few patients used paracetamol for any conclusion to be drawn on its role.

Although aspirin use is widely regarded as related to chronic gastric ulcer,[1] the role of the non-steroidal anti-inflammatory agents (NSAIA) and paracetamol in peptic ulcer, particularly duodenal ulcer, is unclear.[2–6] Recent studies have shown an association of gastric ulcer with aspirin and the other NSAIAs[7] and of perforated ulcer, both duodenal and gastric, with aspirin and the NSAIAs.[8] To clarify this issue we conducted a case control study of gastric ulcer and duodenal ulcer patients and controls, comparing their consumption of these drugs.

Methods

PATIENTS

CASES

These were all the patients presenting for the first time to the Gastroenterology Unit of the Royal Newcastle Hospital from March 1980 to April 1981 who were diagnosed at endoscopy as having duodenal ulcer or gastric ulcer, but not both. Presenting features were abdominal pain (43%), acute bleeding (42%), and other symptoms (15%).

CONTROLS

These were recruited from patients attending surgical and dermatology clinics for the first time at the same hospital during the same period with the exclusion of patients with known peptic ulcer or abdominal pain. The controls were drawn from two different clinic populations in order to reduce selection bias.[9]

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DATA COLLECTION

A questionnaire was administered to patients and controls by the same trained interviewer seeking information relating to demographic characteristics and use of drugs containing aspirin, paracetamol, and other NSAIAs. Social class was defined by occupation into categories[10] with 1 the highest status and 5 the lowest. Those not employed, mainly housewives and pensioners, were allocated to an additional category. Respondents were asked about the frequency, quantity, and duration of use of each drug. Regular drug use was defined as two or more doses of the drug taken weekly in the last three months. Drug use was classified into six categories: aspirin taken alone or as a compound preparation containing aspirin and caffeine; NSAIAs alone; NSAIAs and aspirin or aspirin and caffeine; paracetamol alone; 'other' comprising patients with irregular drug consumption patterns and non-respondents to these questions; and less than two doses of these drugs per week. Aspirin abuse was defined as the use of one dose per day of an analgesic containing aspirin for 10 years, or two doses per day for five years, and so on, to 10 doses

per day for one year. At the time of the study naproxen, ibuprofen, and indomethacin would have constituted the majority of NSAIAs used. Data on smoking behaviour classified as 'current smoker', 'never smoked', and 'ex smoker', were only available for ulcer patients.

MATCHING

The consumption of analgesics is related to age, sex, and social class and because these are thought to be risk factors for peptic ulcer[1] they were regarded as confounders.[11] Accordingly each patient was matched with one control of the same sex and as nearly as possible on the other two factors.

Table 1 *Demographic characteristics of peptic ulcer patients and matched controls (nos)*

	Gastric ulcer		*Duodenal ulcer*	
	Cases	*Controls*	*Cases*	*Controls*
Sex				
Men	54	54	65	65
Women	41	41	20	20
Age (years)				
<50	20	19	33	33
50–69	53	55	42	42
>70	22	21	10	10
Social class				
1 or 2	11	17	10	9
3	27	28	32	37
4	13	18	14	14
5	11	6	13	11
other	33	26	16	14
Total	95	95	85	85

STATISTICAL METHODS

For comparisons between cases and controls, conventional analyses for matched pairs were used. The relative risk was estimated by the odds ratio – that is, the ratio of the off-diagonal cell frequencies in 2×2 tables with the lowest category of drug use taken as the baseline. Each other level of the variable was compared with this baseline level in turn and confidence intervals for odds ratios were calculated using exact probabilities.[12 13] Significance levels were also calculated by exact methods[13] and two tailed tests were used throughout.

Results

The age, sex, social class, and diagnosis of the patients are shown in Table 1. There were relatively more men than women with duodenal ulcer (p=0·006) but not with gastric ulcer. Also gastric ulcer patients were older than duodenal ulcer patients. The social class distribution was similar for gastric ulcer and duodenal ulcer patients and when employment status (not shown) was considered this too was similar for both groups. The matching of cases and controls was close; no case control pair differed in age by more than five years.

The occurrence of gastric ulcer was significantly associated with NSAIA intake (p=0·008) (Table 2). The consumption of aspirin preparations alone or with NSAIA, and of paracetamol on its own was much higher among gastric ulcer patients than among controls; these differences were not statistically significant but the numbers in some categories

Table 2 *Analgesic consumption in relation to location of peptic ulcer*

			Matched pairs analyses		
	Cases (no)	*Controls (no)*	*Relative risk*	*Confidence interval*	*Significance level*
Gastric ulcer					
<2 doses/wk†	39	62	1·0		
Aspirin or APC	17	6	3·0	(0·7, 21·3)	0·146
NSAIA	20	11	5·0	(1·4, 26·9)	0·008
Aspirin/APC and NSAIA	8	0	*	*	0·062
Paracetamol	6	1	*	*	0·5
Other	5	15	0·5	(0·0, 3·5)	0·687
Total	95	95			
Duodenal ulcer					
<2 doses/wk†	49	53	1·0		
Aspirin or APC	7	7	1·0	(0·1, 7·5)	1·0
NSAIA	15	10	1·1	(0·4, 3·7)	1·0
Aspirin/APC and NSAIA	1	1	*	*	*
Paracetamol	5	0	*	*	0·25
Other	8	14	1·0	(0·3, 3·7)	1·0
Total	85	85			

*Not calculable due to cell frequencies of zero.
†Baseline level.
APC—aspirin and caffeine compounds.

Table 3 *Aspirin abuse in relation to location of peptic ulcer**

Gastric ulcer						
			Control			
			No abuse	Abuse	Total	
	Case	No abuse	61	4	65	Relative risk=4·5
		Abuse	18	4	22	Confidence interval=(1·5, 18·3)
		Total	79	8	87	Significance level=0·004
Duodenal ulcer						
			Control			
			No abuse	*Abuse*	*Total*	
	Case	No abuse	59	6	65	Relative risk=1·17
		Abuse	7	1	8	Confidence interval=(0·3, 4·2)
		Total	66	7	73	Significance level=1·0

*For 8 GU and 12 DU case-control pairs there was insufficient information to determine analgesic abuse for at least one member of the pair.

Table 4 *Smoking habit*

		Current smoker	*Never smoked*	*Exsmoker or missing data*	*Total*
Duodenal ulcer (DU)	M	38	16	11	65
	F	5	15	—	20
	Total	43	31	11	85
Gastric ulcer (GU)	M	36	13	5	54
	F	14	23	4	41
	Total	50	36	9	95

Comparing DU with GU overall, by smoking habit
$\chi^2=0{\cdot}57$, df=2, $p>0{\cdot}7$.
For men $\chi^2=1{\cdot}64$, df=2, $p>0{\cdot}4$
For women $\chi^2=1{\cdot}33$, df=2, $p>0{\cdot}5$

were small. For duodenal ulcer patients there were no statistically or clinically significant associations with consumption of any of the drugs considered.

Aspirin abuse was recorded for 22 gastric ulcer patients and eight of their controls. This was highly significant (p=0·004, relative risk=4·5) (Table 3). There was no corresponding association between aspirin abuse and duodenal ulcer.

There was no significant difference in smoking habit between the ulcer sites (Table 4).

Discussion

There is a wealth of animal data suggesting associations of most of the analgesic drugs and NSAIAs with acute gastroduodenal damage. For chronic peptic ulcer in man, however, apart from aspirin, the data are often contradictory.[5] This may be because of methodological problems in investigating the role of these drugs in peptic ulcer. Such problems include: the use of multiple drugs; the possibility of different aetiologies for acute and chronic lesions and for ulcers at different locations; and difficulties with case control studies, for example, the choice of controls and selective recall bias.

To overcome some of these difficulties in this study we considered only chronic peptic ulcer cases, distinguishing between duodenal ulcer and gastric ulcer, and compared them with outpatient controls. We investigated separately the use of various classes of drugs. The effects of using hospital based controls, who may have had higher drug use than community controls, could have led us to underestimate associations between drug use and ulcers. On the other hand two factors could have led to overestimating the effects. Firstly, the interviewer was not blinded as to whether the patient was a case or a control nor to the hypothesis being tested; nevertheless we do not believe this was a source of bias. Secondly, it is possible that cases had thought more about their history of drug use than controls, so leading to recall bias. We did not match for smoking because this was not thought to be associated with analgesic drug use (independent of age, sex and social class) and so it could have led to overmatching.[11]

For NSAIAs we found a strong association with gastric ulcer but not duodenal ulcer. This supports data from animal studies[2] and, for man, evidence of acute[4 14] and chronic[6 7 15] gastrotoxicity.

For aspirin our results suggest an association with gastric ulcer but not duodenal ulcer. These findings are consistent with other reports[1] but at variance with a recent report of an association of perforated duodenal ulcer and NSAIAs.[8] In particular, the present study showing an relative risk for gastric ulcer of three for aspirin at a level of two or more doses/week is consonant with four previous studies from the USA and Australia showing relative risks of between 3·2 and 10 for regular intakes of four to 15 doses weekly.[16] Furthermore, we found a highly

significant relationship between gastric ulcer and very high and/or prolonged aspirin use (aspirin abuse); this is important in a community where high use was widespread[17] (at least before legislative restrictions on aspirin and caffeine compounds in 1979).

The recent report[8] of an association of both perforated duodenal ulcer and gastric ulcer with the use of aspirin and other NSAIAs is difficult to explain in view of the general absence of association of duodenal ulcer and drug usage.[1] The distinction between perforated duodenal ulcer and prepyloric ulcer may be difficult at operation and it is possible that some of the ulcers labelled 'duodenal' in that series were, in fact, prepyloric for which we have suggested a strong association with aspirin use in a previous study of aspirin and perforated ulcer.[18]

There is the question of whether aspirin was taken to relieve ulcer symptoms or whether its use preceded the symptoms. Our findings, that aspirin use was associated with gastric ulcer but not duodenal ulcer and that aspirin abuse (often regular use over many years) was significant, suggest that aspirin was not taken to relieve ulcer symptoms. There is similar evidence from other studies.[19 20]

For paracetamol relatively few of our patients were users so our data provide little new information. It has been claimed, however, that this drug does not damage the gastric mucosa[21] and is probably associated, but not causally, with haematemesis.[22] On the other hand, Piper *et al*[1] reported a relative risk of 24 for gastric ulcer and paracetamol use but without considering concurrent use of other analgesics or NSAIA.

Interestingly, we found no evidence of association between duodenal ulcer and any of the drugs investigated. This too is in keeping with most previous studies which have failed to show an association of aspirin use and chronic duodenal ulcer.[16]

This study shows that the NSAIAs like aspirin, are associated with chronic gastric ulcer but not duodenal ulcer. Data on prescriptions of NSAIAs to pensioners are probably representative of prescribing patterns to other users. They show that during the study period 36% of NSAIA prescriptions were for naproxen, 29% for ibuprofen, 28% for indomethacin and far fewer for phenylbutazone and sulindac. Therefore the present study sheds no light on the ulcerogenic potential of the newer NSAIA.

The limitation of the association of both aspirin and NSAIA to gastric ulcer and not duodenal ulcer is further evidence for a different pathogenesis for thse two and supports proposals that the ulcerogenic effect of gastric ulcer are mediated by their common property of cyclo-oxygenase inhibition rather than by the Davenport mechanism.[23]

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