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Aspirin, paracetamol, and haematemesis and melaena

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SUMMARY Aspirin and paracetamol consumption have been compared in 346 matched pairs of patients with haematemesis and melaena, and control individuals in the general community. Both aspirin and paracetamol intake were more common in patients than in controls, but the association for aspirin was stronger and was apparent with both recent and habitual intake, whereas for paracetamol the association was not detectable for habitual intake. The results for paracetamol suggest that patients with bleeding take analgesic drugs in part because of symptoms associated with bleeding, and such intake is not necessarily causal of bleeding. Failure to control investigations to take account of this point has exaggerated the possible risks of aspirin consumption.

Previous studies have consistently demonstrated an association between recent aspirin intake and major upper gastrointestinal haemorrhage, but the strength and significance of this relationship have been contested.[1] The evidence is derived exclusively from retrospective case-control investigations, in all of which the choice of controls can be criticised. In particular all studies to date have used hospital patients as controls, whereas a control group taken from the community would seem more appropriate, as most patients admitted with haematemesis and melaena are presenting to hospital for the first time. Furthermore, the existence of an association between salicylates and haemorrhage does not necessarily imply that salicylates cause haemorrhage. It is possible that a proportion of patients who bleed take aspirin to relieve indigestion or other symptoms associated with the onset of their haemorrhage. If this is so, a similar association should be found for other analgesics such as paracetamol which are not thought to cause bleeding. We have therefore compared the recent drug exposure of patients suffering from acute upper gastrointestinal haemorrhage with that of community controls, looking particularly for any differences between aspirin and paracetamol.

Methods

Patients admitted to the City Hospital, Nottingham, with haematemesis and melaena between November 1976 and February 1980 were included in the study. Patients whose bleeding was considered clinically trivial or where the evidence that bleeding had actually occurred was doubtful were excluded, as were a small number who died soon after admission or who were considered too confused to co-operate. Age- and sex-matched controls were selected from the lists of two local general practices, one in a middle-class neighbourhood and the other in a relatively poor area. Patients with white collar occupations were paired with controls from the first practice, while controls from manual workers were taken from the second. The controls were not necessarily attending their general practitioner at the time, but were selected by taking the next individual of the same age (to within two years) and sex as the bleeding patient in a consecutive record card examination. Each control was approached initially by letter, asking him to participate in a health survey, but without specifying the interest of the investigation. If no reply was received we visited his home, if necessary up to three times, in an effort to make contact. Approximately 90% of the controls originally selected agreed to take part in the study. Of the remainder, a small number, mostly old ladies, refused interview, and the rest could not be contacted despite our efforts. For these 10% alternative controls were chosen by a similar process.

The interviews were conducted by one of two trained research assistants using a standard questionnaire (in almost all instances the patient and his control were interviewed by the same person). Patients were seen in hospital within three days of admission, and were asked about past and present dyspeptic symptoms, and their exposure to drugs,

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especially analgesics, before admission. Where analgesics had been taken, brand names were requested. Controls were visited at home and asked the same questions. The significance of associations between drugs and bleeding was assessed by the McNemar test. Point and interval estimates of relative risk were calculated using the method for individual matched pairs described by Miettinen.[2]

Results

A total of 346 matched pairs took part in the study (238 male and 108 female). Their ages ranged from 17 to 91 years (median 61 years). Despite our method of selection, there were slightly more individuals of social classes I and II among the control group (Table 1), but as analgesic consumption did not correlate with social class it was not necessary to allow for this difference in our analysis. Patients and controls were similar in their smoking and drinking habits, except that there was an excess of heavy drinkers (more than 20 pints of beer or one bottle of spirits per week) in the haematemesis group ($\chi^2=6{\cdot}2$, $P<0{\cdot}02$). Although indigestion was a common symptom in bleeding patients, less than one-third had previously been investigated in hospital for dyspepsia, while 15% of controls had also attended hospital because of dyspepsia at some time in the past.

Table 1 *Comparison of patients and controls: social class, smoking, alcohol and dyspeptic history*

	Patients		*Controls*	
	No.	*%*	*No.*	*%*
Social classes I and II*	54	22	72	29
Smokers	175	51	162	47
Alcohol at least once a week	212	61	210	61
Indigestion in past week (other than haematemesis)	229	66	116	34
Previous hospital investigation for dyspepsia	113	33	52	15

* In 95 patients and 101 controls social class was not determined. Most of these were housewives.

The numbers of patients and controls taking corticosteroids were identical, but twice as many patients as controls were using non-steroidal anti-inflammatory drugs (NSAI) (Table 2).

Table 2 *Prescribed drugs taken by patients with bleeding and by controls*

Drug	*Patients with bleeding (no.)*	*Controls (no.)*
Corticosteroids	8	8
Non-steroidal anti-inflammatory	40	18
Warfarin	3	1

All pairs in which either the patient or his control were taking steroids, NSAI, or warfarin were excluded from further analysis, leaving a total of 277 matched pairs in which we compared exposure to aspirin and paracetamol. Aspirin consumption was independent of paracetamol intake in both cases and controls, allowing us to examine the relationship of each drug to bleeding independently. Both drugs were used more often by the haematemesis group than by controls (Table 3), but the association of paracetamol with bleeding disappeared when only long-term use of the drug was considered (Table 4). While the association between aspirin and bleeding

Table 3 *Analgesic exposure in past week*

Drug	*Taken by:*		*P (McNemar's test)*
	Patient, not by control (number of pairs)	*Control, not by patient (number of pairs)*	
Aspirin	71	19	<0·001
Paracetamol	50	26	<0·01

Table 4a *Associations between analgesic exposure and upper gastrointestinal haemorrhage, expressed in terms of relative risk (with 95% confidence limits)*

Analgesics taken	*Aspirin*	*Paracetamol*
At some time in past two days	4·8*** (2·4–10·7)	2·1* (1·1–4·1)
At some time in past week	3·7*** (2·2–6·4)	1·9** (1·2–3·3)
At some time in each of last two weeks	3·6* (1·3–12·4)	1·5 (0·7–3·0)
Regularly† for at least three months	2·2 (0·7–8·1)	1·0 (0·4–2·5)

*$P<0{\cdot}02$ **$P<0{\cdot}01$ ***$P<0{\cdot}001$ (by McNemar's test).
† Defined as intake of at least one tablet every week.

Table 4b *Data for Table 4a*

Analgesic taken	*Taken by patient, not taken by control (number of pairs)*	*Taken by control, not taken by patient (number of pairs)*
Aspirin		
At some time in past two days	48	10
At some time in past week	71	19
At some time in each of past two weeks	18	5
Regularly for at least three months	11	5
Paracetamol		
At some time in past two days	36	17
At some time in past week	50	26
At some time in each of past two weeks	22	15
Regularly for at least three months	11	11

also decreased for longer periods of exposure, it remained discernible, and, for each of the periods of exposure which we considered, the association of aspirin with bleeding (in terms of relative risk) was approximately twice that of paracetamol.

Examination of relative risks in heavy and light users of analgesics showed that the highest risk ratio (16·0) obtained in heavy aspirin users (more than 20 tablets in the past week): by contrast in heavy paracetamol users the risk ratio was 2·4, little more than the overall ratio.

Table 5 gives the indications for which subjects took analgesics. More patients than controls took paracetamol for indigestion, but not for headache or upper respiratory tract infections, and for arthritis the difference was small. In contrast, aspirin was used more often by patients than controls for all indications, although again the difference was most marked among those taking the drug for dyspepsia.

Table 5 *Indications for which analgesics were taken*

	Aspirin		*Paracetamol*	
	Patients	*Controls*	*Patients*	*Controls*
Headache	24	8	14	14
Indigestion	18	1	7	1
Colds and 'flu	15	11	6	6
Arthritis	11	5	19	12
Other	19	9	22	10

Figures total more than the numbers of patients because dual indications were often given.

Table 6a *Association of gastrointestinal haemorrhage with analgesics taken in past week (in terms of risk ratio) according to underlying lesion*

Lesion	*No. of patients*	*Aspirin*	*Paracetamol*
D.U.	83	9·3***	2·3
G.U.	49	3·3	0·9
Erosion or no lesion found	53	1·6	1·0
Miscellaneous	92	4·3**	5·0**

Each subgroup of patients was compared with the corresponding subgroup of controls.
**P<0·01 ***P<0·001 (by McNemar's test).

Table 6b *Data for Table 6a*

Lesion	*Total no. of pairs*	*Drug*	*Taken by patient, not taken by control (number of pairs)*	*Taken by control, not taken by patient (number of pairs)*
Duodenal ulcer	83	Aspirin	28	3
Duodenal ulcer	83	Paracetamol	16	7
Gastric ulcer	49	Aspirin	13	4
Gastric ulcer	49	Paracetamol	7	8
Erosion or no lesion found	53	Aspirin	13	8
	53	Paracetamol	7	7
Miscellaneous	92	Aspirin	17	4
	92	Paracetamol	20	4

Table 6 shows the risk ratios for aspirin and paracetamol consumption in bleeding patients relative to their controls, subdivided according to the lesions found in the bleeding patients. The risk ratios were high in all comparisons for aspirin; they were also raised for paracetamol consumption in individuals with duodenal ulcer and in the miscellaneous group that was left when all those with chronic or acute ulcers or who had unequivocally normal findings were removed. By comparing the risk ratios for aspirin and paracetamol in each diagnostic group it was possible to estimate the degree of extra association present for aspirin. This was greatest for duodenal ulcer, followed by gastric ulcer, and then erosions, or no lesion found, with no excess of risk ratio for the miscellaneous group.

The excess of heavy alcohol drinkers noted in the patients was small, 56/346 (16%) in the cases and 33/346 (10%) in the controls. Examination by the matched pairs technique showed that in neither patients nor controls was there any association between heavy drinking and aspirin consumption (Table 7).

Table 7 *Heavy drinking and aspirin consumption*

	Aspirin intake in past week				
	Patients			*Controls*	
Heavy drinking	*No*	*Yes*	*Heavy drinking*	*No*	*Yes*
No	224	66	No	285	28
Yes	41	15	Yes	28	5
	$\chi^2=0·23$.			$\chi^2=0·71$.	

P>0·3 in each case.

Discussion

Our study differs in two important respects from earlier investigations. We chose a community-based control group as being more directly comparable with the patients with haematemesis and melaena. This may initially appear perverse, but we found, in fact, that two-thirds of our patients with bleeding had never attended hospital with dyspepsia. For these a community control was plainly appropriate. The remaining third had attended, but so had one-sixth of the control group, so that in the event there was overall equivalence for five out of six of the patients and controls, much closer than if a hospital control had been used. Furthermore, the use of hospital controls has been found to introduce significant biases in case-control studies.[3]

Secondly, our choice of paracetamol as a reference drug for comparison has allowed us to measure the extent to which analgesic intake may be consequential upon the presence of a bleeding lesion and the extent to which it may be the cause of bleeding, the key assumptions being that paracetamol does not induce bleeding itself and is used for parallel indications to aspirin.

That patients were interrogated in hospital while controls were questioned at home was a potential source of error; but any bias which might have arisen because the interviews were not 'blind' or because of differences between the recall of individuals in the two different situations should have applied equally to aspirin and paracetamol, and should not have affected comparisons between the two.

The excess use of NSAI by haematemesis patients may simply reflect a reluctance to prescribe these drugs on the part of doctors in the two practices from which our controls were drawn. It seems more likely, however, that it represents a genuine association between NSAI and upper gastrointestinal haemorrhage. Such an association has often been suggested but is supported, outside this study, only by anecdotal evidence, and it deserves further investigation. By contrast, the equivalence of corticosteroid intake in our cases and controls suggests that little, if any, risk attaches to the use of corticosteroid drugs in ordinary small clinical doses.

The correlation which we have demonstrated between paracetamol and bleeding has not been described before and was probably not causal. It applied to recent intake but not to long-term exposure, and such a pattern is to be expected if patients took paracetamol for symptoms associated with bleeding or with the presence of a lesion which was already destined to bleed. This suggestion is supported by consideration of the indications for which patients took paracetamol; thus, seven patients but only one control took paracetamol to control indigestion and these were short-term takers of paracetamol. In addition one other patient took paracetamol for chest pain which was probably indigestion associated with a hiatal hernia, and two in the latter part of the survey, when a specific question was asked which had not before been included, said the indications were feelings of dizziness and malaise. By contrast, patients and controls matched exactly in numbers when the indications were headache and colds or influenza. There was a modest excess of paracetamol intake in patients with arthritis compared with controls, but it seemed likely that several of these had been previous takers of NSAI.

For each of the time periods of analgesic exposure which we examined the association of aspirin intake with bleeding was stronger than that for paracetamol. The association was demonstrable for long-term as well as short-term use, and there was an excess of patients compared with controls for all indications, including those such as headache which were unlikely to be associated with the presence of a bleeding lesion. Also, a dose-related response relationship was found between aspirin and haemorrhage but not for paracetamol.

On the basis of these findings we believe that there is a non-specific correlation between analgesics and gastrointestinal haemorrhage resulting from the use of such drugs to relieve indigestion and other symptoms associated with the onset of bleeding, but that there is an additional association with aspirin which cannot be explained in this way and which may indicate a causative role for salicylates in haematemesis and melaena.

The variety of aspirin preparations used made it difficult to test for the strength of any association between bleeding and the use of an individual product. This difficulty was increased by the need to take account of the indications for which products were used. Thus, if any aspirin preparation were used exclusively for headache, a tripling of intake relative to controls would be likely to be important, as headache is not a symptom to be confused with one associated with the presence of a bleeding lesion.

On the other hand, where the complaint for which the patient chose treatment was indigestion, the situation becomes more complex. There is no clinical or experimental evidence to suggest that paracetamol causes gastrointestinal bleeding, and yet seven of our bleeding patients took paracetamol for indigestion, as compared with only one control. This difference probably occurred because indigestion is common in patients with lesions which have the potential to bleed, and is therefore a frequent indication for analgesia. For this reason, if an analgesic preparation is favoured particularly by individuals with dyspepsia, its use by the haematemesis group will be relatively more frequent. As an example, on the basis of anecdotal evidence it has been claimed that highly buffered aspirin solutions cause haematemesis and melaena.[4] Five of our bleeding patients took highly buffered aspirin, all for indigestion, as compared with only one control, a difference which at first sight appears large. However, in relation to the use of paracetamol for indigestion (seven users in the patients and one control), which is the most appropriate comparison, this excess becomes insignificant. Our evidence therefore suggests that highly buffered aspirin preparations are no more dangerous than paracetamol, a conclusion which is in harmony with experimental evidence.

In contrast, the association between bleeding and non-buffered aspirin taken for indigestion (13 takers

in the patients and none in the controls) was stronger than for paracetamol and therefore argues for a causal association with bleeding.

It has been proposed that the risk of bleeding due to aspirin is particularly high in patients with upper respiratory tract infections[5] or when the drug is taken with alcohol,[6] but we found no evidence to support either of these suggestions. Others have, in general, found the association between aspirin intake and bleeding to be strongest in patients who had non-chronic ulcer bleeding. By using the results for paracetamol in Table 6 to make allowance for analgesic intake associated with, rather than causal of, the bleeding lesion, the strongest association in our data is for chronic duodenal ulcer followed by gastric ulcer and then the acute lesion and no lesion group. It would be unwise, however, to place reliance upon precise calculations using the individual pairs of risk ratios. The results suggest an association for all three diagnostic groups; they are not strong enough to say that particular patients are at special risk of aspirin damage.

The final proof that aspirin can cause haematemesis and melaena can only come from randomised controlled trials, such as current investigations into the use of aspirin in the prevention of strokes and heart attacks. In the meantime, our results allow us to predict the risk of bleeding which is likely to be associated with aspirin once allowance has been made for any excess of aspirin intake by patients with haematemesis and melaena that is a consequence of their bleeding lesion and is not a cause of it.

We suggest that, of the overall aspirin consumption by a group of patients with haematemesis and melaena, about one-third can be accounted for by the amount ordinarily consumed in a control population, and another third can be attributed, by reference to the paracetamol excess, to intake which is consequential upon the presence of the bleeding lesion, but is not causal of bleeding. The remaining third is unaccounted for and could be causal of bleeding.

The actual chances of bleeding in an individual taking aspirin cannot be calculated directly from a retrospective controlled study such as ours, because the cases analysed have not been drawn from a defined population, and because there is at least one other hospital serving the local population to which cases might be taken. Assuming, however, that the analgesic habits of our controls are representative of the general population, the risk ratios in Table 4 can be used to obtain an estimate of the relative risk involved in aspirin intake. The use of these ratios has a particular advantage in that the paracetamol figures allow us to take account of drug intake which is consequential upon the presence of a lesion that is already destined to bleed. As the ratios for all time periods are about twice as high for aspirin as for paracetamol, they suggest a doubling of risk for aspirin intake. There are some 300 admissions with acute upper gastrointestinal bleeding in Nottingham each year and these are drawn from a population of 700 000 people, so that the overall chances of bleeding irrespective of the nature of any causative factors are between 40 and 50 per 100 000 population per year. Again, assuming that the analgesic consumption of our controls is typical of the general population, this would imply for a regular user of aspirin an attributable risk of 35 to 45 hospital admissions per 100 000 regular users per year. Given the uncertainties involved in such calculations, this figure is compatible with Levy's estimate[7] of 15 per 100 000 regular users per year.

Our results differ from those of Levy, however, because they suggest that some risk attaches to short-term use. If this is still a doubling, then for the occasional user this would be of the order of one episode for every quarter million courses of treatment.

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