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# Analgesic ingestion and other factors preceding relapse in ulcerative colitis

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SUMMARY To investigate factors which predispose to relapse in patients with ulcerative colitis, we conducted a survey to compare the events occurring in the four weeks preceding the clinic attendance of 62 outpatients in remission with those taking place in the same period before the onset of relapse in 21 patients attending with active disease. The only event which occurred significantly more often in patients who subsequently relapsed was ingestion of paracetamol and other inhibitors of prostaglandin synthesis (76% (16/21) relapse *vs* 39% (24/62) remission, $p<0{\cdot}01$). Recent upper respiratory tract infection (38% *vs* 26%) was not significantly more common in patients in relapse than in remission, and emotional stress, atopic events, antibiotic treatment, dietary indiscretions, foreign travel, and gastroenteritis were relatively rare in both groups. The surprisingly high prevalence of analgesic ingestion before relapse itself requires confirmation but does lend indirect support to the theory that colonic mucosal prostaglandin deficiency induces relapse in some patients with ulcerative colitis.

The factors inducing relapse in patients with ulcerative colitis are unknown. Although respiratory tract infection, emotional disturbance, gastroenteritis, and foreign travel are commonly believed to predispose to recrudescence of disease activity,[1] the only quantitative study of possible risk factors is that of Mee and Jewell[2] who found recent upper respiratory tract infections in a higher proportion of patients attending hospital with active disease (60%) than of those presenting in remission (27%). We have conducted a similar survey to evaluate some of the factors which may initiate relapse in ulcerative colitis.

Drugs which inhibit prostaglandin synthesis cause inflammation, ulceration, and haemorrhage in the upper gastrointestinal tract,[3] but information about their effect on the large bowel is limited. Thus, indomethacin suppositories have been reported to cause proctitis in one patient,[4] oral indomethacin to provoke perforation of colonic diverticula in two,[5] and various agents of this group to precipitate relapse of previously quiescent ulcerative colitis in four more.[6] To assess the frequency with which the latter event occurs, and so shed light on the possibility that transient colonic mucosal prostaglandin deficiency might initiate recrudescence of colitis, we also asked our patients specifically about recent analgesic consumption.

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## Methods

Over a 14 month period, 69 adults with ulcerative proctocolitis established by conventional clinical, radiological, and histological criteria (Table 1) were asked, by means of a standardised questionnaire, about the events occurring in the four weeks (1) before clinic attendance of the 62 patients presenting in remission, or (2) preceding the onset of relapse in the 21 patients attending with active disease.[2] Remission was defined by the passage of a formed stool up to three times daily without rectal bleeding, abdominal pain, or systemic ill-health; in the 14 patients in remission in whom sigmoidoscopy was performed, the rectal mucosa was normal or oedematous only.[7] Relapse was indicated by more frequent passage of loose stools with rectal bleeding and often mucopus, abdominal pain, and malaise; in every case it was confirmed by the presence of mucosal inflammation with contact or spontaneous bleeding at sigmoidoscopy.[7]

Table 1 *Clinical details of patients studied*

| | *Relapse (21 patients)* | *Remission (62 patients)* |
|---|---|---|
| Age (median (range)) (yr) | 42 (22–79) | 43 (19–80) |
| Sex (male:female) | 9:12 | 26:36 |
| Extent of disease | | |
| Proctitis | 7 | 25 |
| Left-sided colitis | 7 | 24 |
| Subtotal/total colitis | 7 | 13 |
| Treatment* | | |
| Sulphasalazine (oral) | 11 | 38 |
| Cromoglycate (oral) | 2 | 3 |
| Azathioprine (oral) | 0 | 1 |
| Corticosteroids (oral) | 3 | 10 |
| Corticosteroids (rectal) | 5 | 8 |
| No treatment | 5 | 12 |

* Some patients on combination therapy.

The questionnaire was not addressed to patients (1) in whom the onset of relapse could not be precisely dated; (2) in whom the clinical state could not be clearly defined; (3) in remission for less than six weeks; or (4) attending the clinic in the same clinical state as on a previous occasion: thus 14 patients were questioned twice, once when in remission and once when in relapse, while the remaining 55 answered on only one occasion.

The results were analysed by the $\chi^2$ test with Yates's correction, Wilcoxon's sum of rank test, and Wilcoxon's signed rank test (each two-tailed), as appropriate.

## Results

Analgesics were taken in the preceding four weeks by nearly twice as high a proportion of patients attending with active (76%) as with inactive ulcerative colitis (39%) ($p<0.01$), and of these drugs, paracetamol, when considered alone, was significantly related to relapse (48% (10/21) *vs* 21% (13/62), $\chi^2$ 4·33, $p<0.05$) (Tables 2 and 3). The drugs were taken for symptoms which were similar in both groups of patients and not clearly gastrointestinal (Table 3). The dose of paracetamol ingested by patients who subsequently relapsed (4 g) was significantly greater than that consumed by those who remained in remission (1 g) ($p=0.02$, Wilcoxon's sum of rank test) (Table 3), and there was a tendency for the dose of paracetamol to have been larger in the four weeks before disease recrudescence in the individuals questioned in both relapse and remission ($p=0.1$, Wilcoxon's signed rank test). The only two patients who had taken more than 30 analgesic tablets in the preceding month (paracetamol 30 g and phenylbutazone 10 g) presented with active disease (Table 3). Forty per cent (16/40) of the patients using analgesics attended in relapse, whereas only 12% (5/43) of those not taking painkillers developed a recrudescence of disease activity within a month.

Recent upper respiratory tract infections and emotional stress (family bereavement and serious illness, marital separation, unemployment, and moving house) were not significantly more common in the relapsing patients, while gastroenteritis, dietary indiscretions, antibiotic treatment (tetracycline, amoxycillin, metronidazole, penicillin and cotrimoxazole), foreign travel, and atopic events (asthma, hay-fever, and eczema) were relatively rare occurrences in both groups of patients (Table 2).

## Discussion

Although recent upper respiratory tract infection was a relatively common event in both groups of patients, we were not able to confirm the significant association with subsequent relapse that was reported by Mee and Jewell.[2]

The only factor which reached statistical significance in this survey as being more common in the month before presentation with active, as opposed to inactive, colitis was ingestion of paracetamol and other analgesics. Possible explanations for this somewhat surprising finding, which itself needs confirmation, require discussion, bearing in mind that the association between analgesic ingestion and relapse does not necessarily imply a direct causal relationship between them.

It seems unlikely that the prodrome of their subsequent relapse caused patients to take the drugs, as the symptoms for which they were used were not obviously gastrointestinal and were similar

Table 2 *Events occurring in four weeks preceding onset of relapse and in four weeks before clinic attendances of patients in remission*

| | *Relapse (21 patients)* | | *Remission (62 patients)* | | | |
|---|---|---|---|---|---|---|
| *Event* | *(No.)* | *(%)* | *(No.)* | *(%)* | $\chi^2$ | *p* |
| Ingestion of all analgesics | 16 | 76 | 24 | 39 | 7·39 | <0·01 |
| Upper respiratory tract infection | 8 | 38 | 16 | 26 | 0·63 | NS |
| Emotional stress | 4 | 19 | 7 | 11 | 0·29 | NS |
| Gastroenteritis | 2 | 10 | 1 | 2 | 1·01 | NS |
| Dietary indiscretion | 1 | 5 | 5 | 8 | 0·0003 | NS |
| Antibiotic therapy | 3 | 14 | 5 | 8 | 0·17 | NS |
| Foreign travel | 3 | 14 | 8 | 13 | 0·04 | NS |
| Atopy | 3 | 14 | 11 | 18 | 0·001 | NS |

NS = not significant.

Table 3 *Analgesic ingestion in four weeks preceding onset of relapse and in four weeks before clinic attendances of patients in remission*

| | *Relapse* | | | *Remission* | | |
|---|---|---|---|---|---|---|
| *Drug* | *Patients* | *Dose* (g)* | *Indication†* | *Patients* | *Dose* (g)* | *Indication†* |
| Paracetamol | 10 | 4 (1–30) | Headache (7)<br>Joint pains (4)<br>URTI (2)<br>Toothache (1)<br>Dysmenorrhoea (1) | 13 | 1 (0·5–12) | Headache (5)<br>Joint pains (3)<br>URTI (3)<br>Toothache (1)<br>Vomiting (1) |
| Aspirin | 5 | 1·2 (0·3–2·4) | Headache (2)<br>Backache (1)<br>URTI (1)<br>Dysmenorrhoea (1) | 9 | 2·4 (0·6–8) | Headache (5)<br>Joint pains (1)<br>URTI (4) |
| Phenylbutazone | 1 | 10 | Backache (1) | 1 | 2·4 | Backache (1) |
| Mefenamic acid | — | — | — | 1 | 5 | Headache (1) |

URTI = upper respiratory tract infection.
* Median (range).
† The figures in parentheses indicate numbers of patients, some of whom took the analgesic for >1 symptom.

in the subjects who remained in remission (Table 3). An alternative explanation is that these agents are detrimental to patients with inactive colitis,[6] as they may be in those with active disease.[8 9] Such an effect could be mediated by inhibition of mucosal prostaglandin synthesis, and, although paracetamol is generally regarded as a weak cyclo-oxygenase inhibitor, its influence on arachidonic acid metabolism is tissue dependent[10] and does not appear to have been investigated in the normal or colitic human large intestine. Potential consequences of drug-induced prostaglandin deficiency include ulceration due to loss of mucosal cytoprotection,[3] and increased bleeding secondary to defective platelet function; in addition, cyclo-oxygenase inhibition by drugs of this group may enhance synthesis of lipoxygenase products with possibly harmful sequelae.[11]

Finally, the observed association between analgesic consumption and subsequent relapse provides indirect support for the hypothesis that sulphasalazine exerts its prophylactic effect in quiescent disease by inhibiting mucosal prostaglandin degradation,[12] and argues against the suggestion that non-steroidal anti-inflammatory agents might prove beneficial.[13] Indeed, the present results confirm an earlier proposal[6] that analgesics of this kind should be used with care in patients with ulcerative colitis.

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