GASTROINTESTINAL TOXICITY OF MINOR ANALGESICS

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- 1 The evidence for the risk of gastric erosions from aspirin is fragmentary.
- 2 Occult gastric bleeding following aspirin is poorly studied and the skewed distribution is unexplained; platelet factors may be relevant.
- 3 Overt gastric bleeding may follow aspirin; the risk is probably about one episode per two million doses.
- 4 There is epidemiological, clinical, experimental and histopathological evidence for an association between chronic aspirin use and chronic gastric ulcer.
- 5 An alternative to the Davenport hypothesis is proposed to explain the gastric action of aspirin and the non-steroidal anti-inflammatory agents.
- 6 Paracetamol is probably bland in its gastric actions.

Introduction

THE history of the gastrointestinal toxicity of the mild analgesics goes back to 1893 when Hoffmann, in his search for an analgesic with better gastric tolerance than sodium salicylate, developed aspirin. In the past 40 years especially, a vast literature on the gastric side-effects of aspirin has appeared. In this review, I propose to concentrate on aspirin and paracetamol (acetaminophen), the major impact of which is on the stomach and liver. The effects may be acute or chronic (Table 1).

Table 1 Gastric toxicity of minor analgesics

(1) <i>Acute</i>	
(a) Gastric erosions	
(b) Haemorrhage	
Occult	
Overt	
(2) <i>Chronic</i>	
Chronic gastric ulcer	

The gastric erosions produced by aspirin have been known since 1938 and a large number of observations have been documented (Salter, 1968; Lanza, Royer & Nelson, 1975). These erosions usually heal completely in several days. The effects of varying rates of tablet dissolution require further study; many of the early observations showing dramatic gastroscopic changes seem to have used poorly soluble preparations. Adequate studies using modern fibreoptic gastroscopes and modern tablet formula-

tions are needed. Muir & Cossar (1959) have described histological lesions in 2 out of 20 stomachs excised after aspirin 600 mg, but Wolf & Woolfe have found that the application of aspirin produced no change in Tom's stomach (Wolf, 1965).

The question of gastric haemorrhage following aspirin is a vexed one. It is clear that, following therapeutic doses of aspirin, about 70% of normal subjects have an increased loss of blood into the gut, from about 3 ml to about 5–15 ml, with much greater loss in a few others. The pathogenesis of the inter-subject variation is unknown; in particular the reason why about 30% of subjects do not bleed at all is obscure. The presence of a chronic peptic ulcer is irrelevant to gastric micro-bleeding. Continued gastric bleeding is a significant cause of hypochromic anaemia in subjects chronically taking aspirin, forming part of the 'analgesic syndrome' (Duggan, 1974).

Ever since the observation of Muir & Cossar (1955) that 46% of patients admitted with haematemesis and melaena had taken aspirin within the previous 24 h compared with 5% in controls, it has been widely held that aspirin may cause overt gastric haemorrhage (Salter, 1968), a view opposed by Langman (1974). Quantification of this risk is important, particularly as the Boston Collaborative Drug Surveillance Program (Jick & Porter, 1978) has recently shown that, in hospital patients, aspirin taken in a 7-d period is followed by gastric bleeding sufficient to warrant blood transfusion in 0.3% of patients and by bleeding of a lesser degree in 1.6%. It is possible to

attempt an assessment of the risk, based on data on 290,000 persons from this region. Two estimates of the annual consumption of aspirin are available, 16 and 67 million doses, say 50 million doses. Similarly, there are two estimates for the annual incidence of aspirin-related bleeding requiring hospital admission, a figure of 5 based on the Boston Collaborative Drug Surveillance Program (Levy, 1974) and 50 if every bleeding erosion were due to aspirin. Based on this data, the maximum risk of bleeding is 50 episodes per 16 million doses, whereas the minimum estimate is 5 episodes per 50 million doses. Thus, the risk lies somewhere between 3 and 0.1 episodes per million doses. A realistic estimate may be 1 episode per 2 million doses, a risk many would find acceptable.

This brings us back to the frequency of aspirin intake before bleeding.

In a personal series of 333 patients admitted with bleeding gastric or duodenal ulcer or acute erosions, there was no difference between the three groups in the frequency (11%) with which aspirin had been taken as an isolated event in the 48 h before admission. Another 32% of the total were regular aspirin takers (unpublished observations). This is the fallacy in the aspirin bleeding controversy; in patients admitted with acute gastrointestinal haemorrhage, 43% had taken aspirin before bleeding but in 32%, this was part of a regular habit.

A largely neglected feature in any discussion of aspirin and gastric bleeding is the role of platelets. The platelet membrane is irreversibly affected by aspirin, impairing haemostasis, and there is evidence suggesting that some individuals may have platelets that are intrinsically more sensitive to aspirin (Mills, Borda, Philt & Eldridge, 1974).

The role of paracetamol in gastric bleeding requires further epidemiological study. Laboratory studies (Ivey, Silvosio & Krause, 1978) have suggested that it is benign but Langman, Edmond & Hardy (1979) have shown an increased prevalence of paracetamol intake before an episode of overt gastrointestinal bleeding.

The association of aspirin and chronic gastric ulcer is controversial (Langman, 1974; Spiro, 1974). The case for an association follows four threads, epidemiological, clinical, experimental and histopathological; the case against rests on the circumstantial and indirect nature of some of this evidence.

The epidemiological story begins with a series of papers by Billington, who has shown that in north-eastern Australia an epidemic of gastric ulcer in young women began in the 1940s, apparently due to an unknown environmental influence (Billington, 1965).

Subsequently, several papers from different parts of Australia have all shown an imposing association between chronic gastric ulcer in women and the chronic use or abuse of aspirin, principally in the form of a proprietary preparation of aspirin,

phenacetin and caffeine (Duggan, 1976). The Boston Collaborative Drug Surveillance Program has also shown a significant association of regular aspirin intake and gastric ulcer (Levy, 1974).

Clinical studies on patients with ulcer, whether uncomplicated, bleeding, perforated (Duggan, 1972; Jorgensen, 1977) or associated with hour-glass contracture (Floate & Duggan, 1976), have all shown the same association. The findings have been substantiated by reports from the US (Cameron, 1975; Dagradi, Falkner & Lee, 1974).

The histopathological evidence is strong. Examination of gastric ulcers excised from patients whose aspirin-taking history is known reveals two groups: a large group in which the ulcer is situated in abnormal gastric mucosa and a smaller group in which the ulcer is situated in normal or near normal mucosa. The latter group took large quantities of aspirin-containing analgesics, the former did not (McDonald, 1973).

Experimentally, if aspirin is given orally to rats for 6 months, sufficient to produce a therapeutic blood level, 50% develop a chronic gastric ulcer (St John, Yeomans & de Boer, 1973). In cats given aspirin intravenously for 1 week, again sufficient to produce a therapeutic blood level, 20% develop a chronic gastric ulcer (Bugat, Thompson, Aures & Grossman, 1976).

Although most work has been done on oral aspirin, gastric lesions are produced by aspirin given subcutaneously (Barbour & Dickerson, 1938), intravenously (Bugat *et al.*, 1976), into the small gut (Lynch, Shaw & Milton, 1964) and in Heidenhain pouches (Cooper, Meade & Ellison, 1966) and Pavlov pouches (Schnedorf, Bradley & Ivy, 1936) after oral administration. The conventional view of the pathogenesis of aspirin-related gastric lesions (Davenport, 1967), fails to explain a large number of observations, for example, the production of gastric lesions by aspirin given by other routes, the common side-effects it shares with the other acidic non-steroidal anti-inflammatory drugs, and the cytoprotective effect of prostaglandin E₂ analogues.

Alternatives to the Davenport hypothesis have been proposed. The pharmacokinetic theory of Brune, Graff & Rainsford (1977) proposes that acidic anti-inflammatory drugs depend for their action on being protein bound and present in highest concentration in tissues of lower pH such as inflamed tissues and gastric mucosa.

This theory, however, ignores the common effect of acidic anti-inflammatory drugs on cyclooxygenase (prostaglandin synthetase) (Vane, 1971).

Bennett, Stamford & Unger (1973) have proposed that inhibition of prostaglandin synthesis might play a role in the production of the gastric mucosal lesion by producing vasoconstriction, ischaemia, and tissue necrosis. Certainly there is now evidence of gastric mucosal vasoconstriction with aspirin (O'Brien &

Figure 1 Scheme for production of gastric mucosal injury by non-steroidal anti-inflammatory drugs (NSAID).

Silen, 1973) and cytoprotection by prostaglandin E_2 analogues (Robert, 1976).

The situation is complicated in Australia, where the association of aspirin and ulcer is best recognized, by the presence in analgesics of caffeine, a stimulant of gastric secretion. A possible mechanism incorporating these concepts (Figure 1) envisages the gastric mucosal lesion beginning in an actively secreting parietal cell in the presence of ischaemia

produced by prostaglandin E_2 deficiency produced by acidic anti-inflammatory drugs, leading to death of the cell and leakage of hydrogen ions back into the mucosa.

There is good evidence that acidic anti-inflammatory drugs may cause small bowel ulceration and this can be prevented by prostaglandin administration (Robert, 1976); in man, the problem does not seem to arise clinically with aspirin.

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Discussion

DR G. LEVY said that some years ago Professor Jack Leonards and he published a study in the *New England Journal of Medicine* concerning occult blood loss in a group of individuals who received aspirin 4 or 5 g daily for 1 month. They noticed that there were some individuals who consistently bled in fairly large quantities, 15 or 20 ml daily and others who consistently showed very minor blood loss — 1 or 2 ml daily throughout the period. He thought that there were interindividual differences which were fairly consistent. With regard to the relative

effects of intravenous and oral aspirin on occult bleeding, he emphasized that it concerned occult bleeding rather than ulcers. The effect seemed to be local, inasmuch as the doses necessary to produce bleeding after intravenous aspirin in man were very much larger than with oral administration. With equivalent doses there was more blood loss from oral administration. This was related to the concentration of aspirin at the epithelial cell. Obviously local administration produces higher concentrations.