Gastrointestinal Intolerance and Bleeding with Non-Narcotic Analgesics

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**Summary**

Aspirin and paracetamol (acetaminophen) are the most commonly used minor analgesics, but their effects on the gastrointestinal tract differ widely. The effects of other non-steroidal anti-inflammatory drugs (NSAIDs), including phenylbutazone, are intermediate. Aspirin is significantly associated with major upper gastrointestinal haemorrhage, whereas paracetamol is not. Short term use of aspirin produces erythema, erosions and occasionally ulcers; paracetamol does not, while other NSAIDs do so to varying degrees. Chronic gastric ulcer is linked to aspirin intake in patients with rheumatic disease, and epidemiologically in all heavy aspirin users. In only one epidemiological study was a paradoxical significant association reported between paracetamol intake and chronic gastric ulcer. Faecal occult blood loss is increased in most regular aspirin users but not in those taking paracetamol. Although formal studies in children have apparently not been made, in isolated small clinical series it has been reported that gastrointestinal bleeding and anaemia do occur in the paediatric age group after the use of aspirin. Pathophysiological, aspirin alters the gastric mucosal barrier to hydrogen ions and lowers gastric potential difference; paracetamol has no effect on these parameters. Such changes correlate ultrastructurally with damage in surface epithelial cells and microerosions after the use of aspirin, but not after the use of paracetamol. Aspirin and other NSAIDs cause a dramatic reduction in the ability of gastric mucosa to generate protective prostaglandins; however, paracetamol also reduces prostaglandins. Other postulated mechanisms of aspirin damage include reduction in gastric mucosal secretion, reduction in bicarbonate output, and alteration of cell turnover. Because damage to gastric mucosa by aspirin and NSAIDs is often 'silent', the clinician needs a high level of suspicion and awareness regarding this problem. In patients prone to gastric damage, or in those with a past history of aspirin-induced gastric damage, paracetamol is the drug of choice when a minor, non-inflammatory problem requires an analgesic.

Millions of doses of minor analgesics are ingested daily. In the United States alone, between 20 and 30 billion aspirin tablets are consumed each year (Moyersolm et al., 1977). The use of paracetamol (N-acetyl-p-aminophenol) is becoming increasingly popular in the United States and in other countries. Either alone or in combination with other drugs, it is present in over 200 formulations for the symptomatic relief of pain, cough, colds and fever (Ameer and Greenblatt, 1977). This review concentrates on the gastrointestinal side effects of the two most commonly used analgesics, aspirin and paracetamol, as well as those of other non-steroidal anti-inflammatory agents including indomethacin and the pyrazolidine derivative phenylbutazone.
Such a review is timely, since the intake pattern of the two major selling drugs in the United States has undergone a remarkable alteration in the past decade and a half. In the Boston area in 1966 to 1967, 20% of patients took plain aspirin compared with 5% who took paracetamol. In 1970 to 1971, the ratio reversed, with 10% taking aspirin and 15% taking paracetamol; in 1974 to 1975, the last year for which figures are available, 7% took plain aspirin and 36% used paracetamol (Jick, 1981). This reversal has occurred largely because of the reported gastrointestinal side effects of aspirin.

Mucosal susceptibility to gastric irritants appears to be increased under certain clinical circumstances: pre-existing gastric disease, hepatic cirrhosis and portal hypertension, severe stress, central nervous system lesions, congestive heart failure, sustained emotional tension, and certain acute infectious diseases (e.g. influenza). Mucosal irritants may provoke mild or severe changes (congestion, mucus secretion, inflammatory reaction, petechial bleeding, erosions or ulcerations). Acute lesions may heal completely in a matter of hours, but recently accumulating evidence indicates that prolonged or repeated abuse of certain drugs will give rise to chronic lesions.

1. Definitions of Gastritis

Endoscopically verified and histological gastritis are not synonymous and will be referred to separately (Weinstein, 1981). One does not necessarily coincide with the other.

1.1 Endoscopic Gastritis

Endoscopic gastritis refers to macroscopic changes visible to the naked eye through the endoscope and includes: (1) erythema (increased redness), which may be diffuse or patchy; patchy erythema may be linear or macular; (2) erosions – loss of mucosal surface with a white, yellowish or haemorrhage base with surrounding marginal erythema; erosions have a limited depth and range in diameter from 1 to 2mm to several centimetres; and (3) ulcers, which are lesions of greater depth with a punched-out white base and are usually greater than 0.5cm in diameter but range from 2 to 3mm to many centimetres.

1.2 Histological Gastritis

Histological gastritis is divided into acute gastritis and chronic gastritis (Whitehead, 1979). Acute gastritis, common after acute drug damage, is characterised by damage to or loss of surface epithelial cells, haemorrhage, congestion and oedema, often focal in nature, with normal mucosa between the focal lesions. Chronic histological gastritis, on the other hand, is diffuse and characterised by infiltration of inflammatory cells. It is subdivided into chronic superficial gastritis, chronic atrophic gastritis and gastric atrophy.

2. Gastrointestinal Toxicity of Aspirin and Salicylates

Since 1877, salicylates have been recognised as gastrointestinal irritants. Muir, cited by Roth (1963), reported dyspepsia after aspirin in 1 in 15 of a random group of 3000 patients, 1 in 10 of 70 arthritic patients and 1 in 3 of 300 patients with peptic ulcer. Roth et al. (1963) demonstrated a topical effect of aspirin by placing it in the stomach of cats to achieve direct mucosal contact. Localised mucosal damage (desquamation of surface epithelium, focal mucosal necrosis or superficial erosion) was observed in 84% of the animals within 1 to 4 hours. More recent sophisticated and controlled studies have demonstrated that gastric mucosal damage results in exfoliation of epithelial cells, erosion and ulceration of the stomach and duodenum, and bleeding, either occult or overt. Endoscopic studies in healthy volunteers by O'Laughlin et al. (1981a) showed that a single dose of 2 aspirin tablets produces petechial haemorrhages in the stomachs of all healthy volunteers within an hour of ingestion. Continued intake of aspirin for 24 hours in recommended doses (2 tablets every 6 hours) results in gastric erosions, especially in the antrum, in all subjects and duodenal erosions in about 50% of subjects. Continuous intake for 2 weeks results