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NONSTEROIDAL ANTI-INFLAMMATORY DRUGS—ANOTHER LOOK

Practising rheumatologists have learned to treat with good humour the baleful anecdotes of their gastroenterology and nephrology colleagues about the shortcomings of nonsteroidal anti-inflammatory drugs (NSAIDs). The adverse effects are well recognized and are surely a justifiable price for the benefits these agents confer. After all, it is estimated that worldwide, more than 30 million people take NSAIDs each day and with such popularity how can one argue that they are more harmful than good? One fine autumn morning my equanimity was sufficiently disturbed to make me spill my breakfast coffee over a headline which ran ‘Arthritis drugs cripple not cure’ [1]. As it turned out, the article was journalistic hyperbole on the familiar theme of NSAID toxicity. The rheumatologist whose sentiments were misrepresented had merely stated that NSAIDs were better suited to the treatment of inflammatory diseases and yet were prescribed mainly for osteoarthritis. Consequently they were given largely to an elderly female population, the very group most at risk of side-effects. Curiously enough I had recently seen something similar in more than one professional journal [2]. Perhaps, I mused, there was material here for an editorial.

More than 50 NSAIDs have been developed over the last two decades and it is no secret that these have displayed more in common than they have differences. Whether there are too many or too few is moot. It is certainly a disappointment that despite the enormous pharmaceutical investment in the development of many drugs with similar pharmacological profiles, none has emerged with really outstanding credentials. It is also regrettable that apart from the universal inhibitory effect of these drugs on the cyclooxygenase pathway their complete mode of action on pain perception and inflammation...
remains a matter of opinion. What is not disputed is the high incidence of gastrointestinal mucosal damage wrought by NSAIDs [3], the deleterious effect on renal function [4] and a wide range of less common side-effects [6]. More contentious is the possible harmful effect on cartilage, especially on that already compromised by disease [7].

It is the regularity with which NSAIDs cause gastric inflammation and ulceration which has attracted most adverse comment. In the last two years, the subject has generated a plethora of publications, not least in this journal [8-10]. In one recent study, 53% of 47 rheumatoid patients receiving NSAIDs had peptic ulcers, the presence of which was often not suspected symptomatically nor by tests for occult bleeding [11]. In another study, positive faecal blood findings seemed to occur in roughly half those taking NSAIDs whether or not they had demonstrable upper gastrointestinal pathology [10]. In this issue, two papers confirm the high prevalence of upper gastrointestinal pathology amongst such patients. In the first, 85% of 52 subjects, the majority examined at random, had histological evidence of gastritis [12]. Symptoms were more likely in the presence of *Campylobacter pyloris* (pyloridis). The association of this organism with gastritis and gastric ulceration has been well documented [13]. In the second study of a small population, ulceration was more frequent amongst patients with gastrointestinal symptoms but macroscopic and histological gastritis also occurred in half of 12 asymptomatic subjects [14]. In the latter survey, there was no clear relationship between dyspepsia or gastritis and the presence of *Campylobacter pyloris*. These investigations imply a high and perhaps invariable risk of gastrointestinal damage when NSAIDs are prescribed [3]. Much of this represents an arguably tolerable cost–benefit ratio but what of the more serious gastrointestinal sequelae?

In a survey of hospital admissions for bleeding peptic ulcer, not only were NSAIDs implicated in a major fashion but some agents were held more responsible than others [15]. A Committee for Safety of Medicines commentary noted that 25% of all adverse drug notifications incriminated NSAIDs and that over a period of 20 years these were associated with 3500 reports of gastrointestinal haemorrhage or perforation sometimes fatal [16]. These occurred predominantly in elderly females. Both the methods of data collection and the conclusions of these reports were roundly criticized in a letter to this journal [17]. Armstrong and Blower [18] observed that of 235 consecutive patients with life-threatening complications of peptic ulcer, 140 were taking NSAIDs. These authors emphasized that the patients on NSAIDs tended to be elderly, that in 58% the first evidence of gastrointestinal disease was its complication and that death was twice as likely when bleeding or perforation occurred in patients receiving NSAIDs. However, a more recent case-control study tended to refute the view that fatal peptic ulcer complications were more likely in patients receiving NSAIDs [19]. A survey of 203 patients aged more than 60 with gastrointestinal bleeding concluded that this problem was more frequent in those on NSAIDs compared with age-matched community controls (relative risk 2.7) and that not all the patients in this category appeared to have a compelling need for the drugs [20]. The vulnerability of the elderly, especially females, was also noted in an earlier retrospective study of NSAID-associated peptic ulcer perforation [21].

Using retrospective data from many thousands of patients exposed to NSAIDs, Carson et al. [22] concluded that the risk of NSAID-induced haemorrhage was real but relatively small when judged in the context of the enormous numbers taking the drugs (relative risk 2.5 in the first 30 days). In another study which attempted to define gastrointestinal complications in relation to the population at risk, hospital admission for peptic ulceration did not seem to be measurably influenced by NSAID [23]. The varying magnitude with which these serious gastrointestinal problems are viewed can thus be seen as one of perspective. To the surgeon and gastroenterologist, NSAIDs may appear iniquitous but to the rheumatologist who weekly sees hundreds of patients in pain they are drugs which provide tangible benefits and only a remote risk of serious complications.

It is difficult but possible to make some judgement on these conflicting and often emotive publications. First, all NSAIDs have the potential to cause gastritis and ulceration and probably do so at some time in the great majority of patients for whom they are regularly prescribed. Second, the risk of frank gastrointestinal bleeding and peptic ulcer perforation is increased by NSAIDs but not to such an extent that they should be considered a public health menace or even proscribed. Third, the elderly and possibly females in particular are more susceptible to those gastro-
intestinal complications which may be life-threatening. What should be done?

The pharmaceutical industry has tried by various formulations to reduce the impact of NSAIDs on the gut but, as Collins et al. [24] illustrate in this issue, to little avail. There is another interesting consideration. Patients with rheumatoid arthritis demand from rheumatologists pain relief above all else [25] and in essence that is what NSAIDs provide. The pure anti-inflammatory effect of these drugs is small and although there are no substitutes for the treatment of crystal-induced arthritis and ankylosing spondylitis, it is worth noting that, in rheumatoid arthritis, a simple analgesic may reduce not only pain and stiffness but increase grip strength, some of the very indices employed to affirm the anti-inflammatory potential of NSAIDs [26]. Apart from pain relief, it has been difficult to demonstrate any dose-related effects which clearly imply suppression of inflammation by NSAIDs in rheumatoid arthritis [27-29]. Indeed, a paper in the current issue of this journal purports to show that doses of indomethacin which exceed 50 mg daily exert increased benefits by an accentuated analgesic effect [30]. Extrapolation from this study requires caution, but if it were generally true that high doses of NSAIDs were useful in rheumatoid arthritis by virtue of their modifying pain perception, would there not be justification for resorting more often to relatively safe, simple analgesics? Might not this philosophy be even more pertinent to osteoarthritis? Would this not lessen the risks of gastrointestinal patholoy especially when applied to the elderly? In General Practice, the most frequent recipients of NSAIDs are unquestionably patients aged more than 60 and the most frequent reason for their prescription is soft-tissue rheumatism [31, 32]. There is a case for prescribing NSAIDs with only the greatest circumspection in the elderly and not at all where the need is for pain relief of disorders with little or no inflammatory component. A similar editorial plea was made to a general readership two years ago but without obvious impact [33]. It is rheumatologists who must set the standards in these things.

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**EDITORIAL NOTE**

This issue contains a ‘Brief Report’. The attention of contributors is drawn to the willingness of the Editorial Board to give priority to short reports of completed work or brief preliminary work. The scientific content of such submissions will be exposed to peer review in the normal way and, if satisfactory, publication will be expedited.

Short or preliminary reports should comprise no more than 1000 words and contain a maximum of two tables or figures.
NEW

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