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Variations in response to non-steroidal anti-inflammatory drugs

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Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed groups of drugs. Over 20% of all visits to general practitioners in Great Britain are for musculoskeletal complaints (Nuki, 1983) and it has been estimated that nearly 1 in 7 Americans is likely to be treated with a non-steroidal anti-inflammatory drug in any 1 year (Clive & Stoff, 1984). Not only are rheumatic diseases common but they are often chronic and thus the patient can be exposed to pharmacological treatment over a long period of time. The last 30 years has seen a tremendous increase in the number of available non-steroidal anti-inflammatory drugs. Unfortunately the increase in the number of NSAIDs has not been matched by significant advances in therapeutic efficacy, although therapeutic indices have improved substantially when comparing the newer NSAIDs with regular aspirin and phenylbutazone. Recent data indicate a substantial and increasing use of non-aspirin NSAIDs especially amongst elderly females, which is associated with an enhanced risk for serious adverse effects (Collier & Pain, 1985; Walt *et al.*, 1986). Over the past few years, a number of NSAIDs have had to be withdrawn from the market because of a significant incidence of fatal adverse drug reactions (Taggart & Alderdice, 1982; Halsey & Cardoe 1982; Inman & Rawson, 1983; Inman *et al.*, 1986). It has now become apparent that the relative risk for an individual developing a significant gastrointestinal haemorrhage is of the order of 2 in comparison to a general population. This figure has considerable implications to community health, given the large exposure of the population to NSAIDs. This relative risk increases to 3–4 in those over 60 years taking NSAIDs (Somerville *et al.*, 1986). These data have led to a reappraisal of NSAIDs and their place in the management of rheumatic diseases and a questioning of the need to have such a large number of these drugs available. This has produced conflict between the pharmaceutical industry with its attempts to develop and introduce new NSAIDs and drug regulatory authorities, who may be not convinced of the need for additional drugs of this class.

The practising physician and rheumatologist, however, appreciate that there is considerable intersubject variability in response to NSAIDs (Bellamy, 1985). At present there is no clear method of choosing an appropriate NSAID for a particular patient and, currently, this is achieved by trial and error. Despite the number of NSAIDs and the enormous data bank from clinical trials of these agents, there are a surprisingly small number of studies which have genuinely attempted to rank the efficacy or utility of a number of available NSAIDs (Day, 1985). This is because the majority of clinical trials involving NSAIDs are motivated by licensing and market forces and compare two or, at most, three agents. It is therefore difficult to construct any rank order of efficacy of NSAIDs from these studies. An additional problem is the significant number of design problems which these studies demonstrate (Vallance, 1982). The first demonstration of individual variability in response to NSAIDs in patients with rheumatoid arthritis (RA) was made by Huskisson *et al.* (1976) in a comparison of four NSAIDs in 105 patients. In this study, only minor differences in mean parameters of disease activity between drugs were demonstrated, but there was marked variation in the individual patient responses and preferences for these four NSAIDs. In a similar comparative study of aspirin, fenoprofen, ibuprofen, naproxen and tolmetin, Gall *et al.* (1982) again found difficulty in distinguishing among NSAIDs when group data were compared. These workers also included dose titration in their double-blind, randomized, cross-over study and showed that patient preference correlated with physician preferences. Again, marked individual differences in response to the NSAIDs were noted. In a study comparing a number of NSAIDs, Scott *et al.* (1982) were also unable to show significant differences among NSAIDs on the

basis of mean responses. In this study, analysis of variance revealed that a significant proportion of the study variance could be attributed to individual patients and that, often, patients had particular preferences as indicated by significant drug by patient interactions. Great individual variability in response to NSAIDs was shown by Wasner *et al.* (1982) in their comparison of a range of NSAIDs in rheumatoid arthritis and ankylosing spondylitis, respectively. Again, patient preference was noted to correlate with physician preference whilst other disease activity parameters were not discriminatory. Once a particular NSAID had been chosen as most efficacious by a patient, this preference tended to be sustained for at least 12 months after the study was completed supporting similar findings of Huskisson *et al.* (1976).

The basis for preferences of patients for particular NSAIDs is poorly understood. A great deal of work still has to be done to ascertain the extent and duration of these preferences and their relationships to more objective measures of disease activity. Similarly, the reasons for interindividual variability in relatively objective responses in rheumatoid arthritis to a range of NSAID requires more study. However, recent evidence indicates two possible but not mutually exclusive causes for the observed variability in response. First, it appears that significant differences exist between these agents in respect to pharmacodynamic actions. Second, some variability in response to NSAIDs may be a function of intersubject variability in pharmacokinetic parameters for particular NSAIDs.

A number of NSAIDs have been shown to have varying effects on arachidonic acid metabolism in addition to cyclooxygenase inhibition. Thus, diclofenac alters the release of arachidonate from precursor lipids in monocytes and therefore limits the supply of prostaglandins and leukotrienes (Ku *et al.*, 1985) and indomethacin may promote the formation of the arachidonate metabolite leukotriene B4 while simultaneously inhibiting prostaglandin production (Higgs *et al.*, 1980). The release of other inflammatory mediators from polymorphonuclear leucocytes (PMN), such as reactive oxygen species or lysosomal enzymes may also be differentially inhibited by various NSAIDs, these effects varying with the agent selected to activate the PMN. These effects have been demonstrated on PMN removed from patients treated chronically with usual doses of various NSAIDs (Abramson *et al.*, 1983).

A small number of studies have examined the pharmacokinetics of NSAIDs in 'responder' and 'non-responder' groups of subjects. It has become apparent that NSAIDs have considerable actions on the immune response and some of these actions may not be due to the inhibition of prostaglandin synthesis (Cueppens *et al.*, 1986). However comparison between NSAIDs in immunomodulatory effects have not been reported as yet.

No difference in the pharmacokinetics of indomethacin was observed between 'responders' and 'non-responders' (Baber *et al.*, 1979). Furthermore recent data show significant within subject, dose and concentration-response relationships for NSAIDs in rheumatoid arthritis (Day *et al.*, 1982; McGill, 1985; Dunagan *et al.*, 1986). However, in these dose-response studies, some patients do not respond, despite much higher than usual NSAID doses. It may be that significant dose and plasma concentration-response relationships will be observed in 'responders', but that 'non-responders' will not demonstrate these relationships since their lack of response is on the basis of a pharmacodynamic mechanism. In the pursuit of relationships between NSAID concentrations and effect, it is becoming apparent that measurements of the active component of the drug is most likely to provide these correlations. For the propionic acid derivatives such as ibuprofen, fenoprofen, ketoprofen and flubiprofen, the active S-enantiomer of the racemic R–S mixture administered would be expected to relate more precisely to response than the concentrations of racemate. This is because inversion of the inactive R- to the active S-enantiomer, may vary considerably between individuals (Lee *et al.*, 1985). Concentration-response relationships may also be improved by measuring unbound concentration of NSAID in the plasma or synovial fluid, but improved predictions of response, using unbound NSAID concentrations, have yet to be demonstrated. One NSAID, tolmetin, has been shown to suppress the production of prostaglandin synthesis in joint fluid for a considerable period of time after the drug is undetectable in the synovial compartment (Dromgoole *et al.*, 1982) raising doubts about the usefulness of synovial fluid NSAID concentration measurements.

There is also considerable intersubject variation in the incidence and intensity of the common side effects of NSAIDs such as dyspepsia (Lanza *et al.*, 1979). Whether this represents true variation in response in a pharmacodynamic sense, or is related to variation in concentration of drug at the site of the adverse drug reaction, is not known.

At present, it would seem that interpatient variability in response to an NSAID has to be accepted as a reality on the basis of wide concordance with this view of practising physicians and the consensus of the small number of studies

that have addressed this question. Both pharmacokinetic and pharmacodynamic mechanisms appear to be contributing to this effect. This is important as it pertains to a number of other important issues: is there a variable balance of pathophysiological mechanisms in rheumatic diseases such as rheumatoid arthritis; what prostaglandin-independent mechanisms are important in NSAID action in rheumatic diseases; can responders to particular NSAID be efficiently identified; what number of and which NSAID are optimal for effective treatment of rheumatic diseases? Further investigation of response variability with carefully designed clinical trials which take cognizance of the critical issues of patient selection, trial design, disease measurements, sample size and data analysis techniques is vital to a proper understanding of this phenomenon.

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