INVITED ARTICLE

CHOICE OF NSAID: SAFETY PROFILE

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SYNOPSIS

All NSAIDS are weak acids with pKa values in the 3.5 – 5 range. Therefore they are hydrophilic in the ionised state and lipophilic in the non-ionised state. The mechanisms of action of NSAIDS are related to the effects, on prostaglandin synthesis, cellular activity, effect on superoxide production and many other inflammatory mediators. Since all possess many of these activities it is not unreasonable to observe that choice is not based on efficacy but on the safety aspects.

In certain circumstances some NSAIDS are more toxic than others and hence less desirable. For example, the potential albeit uncommon, for phenylbutazone to cause bone marrow suppression has to be considered; the diarrhoea secondary to the fenamates may limit their appeal and the central nervous side-effects of indomethacin may be unacceptable in the elderly or even some young patients.

There is little evidence to suggest that any one NSAID has less gastro-intestinal side effects over another. The same amount of gastro-intestinal bleeding may occur from suppositories as from oral medication, but it is usually best to bypass the stomach by either rectal suppository or enteric coated tablets in patients who are clinicaliy at risk of a G/I problem.

It is uncommon for NSAIDS to have any serious effect on liver function other than to elevate the transaminase levels in patients with low albumin, but delay in metabolism of drugs which undergo oxidative metabolism may occur in patients with hepatic insufficiency. Although debatable, we do however agree with the practice of *not* giving aspirin to children with viral disease because of the risk of Reye's syndrome.

Kidney disease secondary to NSAID is not common but interstitial nephritis, renal insufficiency, and electrolyte imbalance are more likely to occur in patients with already compromised kidneys. That is, kidneys which are salt depleted, water depleted, or kidneys that are also attempting to clear diuretics, amino-glycosides or β-blockers. Dosage of NSAID in such patients should be reduced to comply with half-life and clearance rate relative to glomerular filtration rates and other routes of clearance.

Although the biological half-life of a NSAID is not necessarily related to the plasma elimination half-life, it appears that drugs with longer half-lives are more likely to accumulate, produce higher plasma levels and have an increase in the frequency of serious toxicity. Whether these three factors of accumulation, plasma level and toxicity are related remains to be proven scientifically.

In summary, choice of NSAID is not made on grounds of effectiveness but on the safety profile of the drug.

INTRODUCTION

'The salicylates are useless'

Sir William Osler (1)

No disease is associated with more persistent pain, prolonged illness, and soul-destroying functional incapacity than rheumatoid arthritis. The chronicity of the disease makes the duration of drug therapy almost unique in modern medicine. Non-compliance with medication does not appear to be a major problem, since increase in pain acts as a quick reminder of drug omission (2). That such chronic drug therapy is not without its side effects, including death, is evident by the fact that nearly half the deaths attributed to medicaments reported to the Committee of Safety of Medicines in the United Kingdom result from anti-rheumatic agents (3). In studies of the causes of death in rheumatoid arthritis between 13 and 28 per cent were due to the drugs prescribed (4,5). There is also growing evidence that serious toxic effects and deaths from NSAIDs are more common in the elderly (6,7). For these reasons all antirheumatic drugs are currently under close review. Five NSAIDs (alclofenac, benoxaprofen, fenclozic acid, ibufenac and indoprofen) and the analgesic zomepirac have now been withdraw, as well as a novel delivery form of indomethacin (Osmosin); and phenylbutazone and oxyphenbutazone have been restricted to the treatment of ankylosing spondylitis in the United Kingdom (8). It is no exaggeration to say that the NSAIDs now confront the practising physician and government drug regulatory authorities with one of their major problems in modern-day therapeutics.

Before discussing some of the recent advances in knowledge regarding the mode of action of NSAIDs, and the therapeutic problems being encountered with their use, it might be fitting to briefly outline the history of their introduction.

History of Aspirin and other NSAIDs

There is evidence that the use of salicylates in the form of extracts of willow bark and other herbs in the treatment of pain is of great antiquity, Hippocrates himself having recommended their use (9-11). However, it was not until 1763 when the Reverend Edward Stone of Chipping Norton, England, wrote his historic letter to the Royal Society's Philosophical Transactions (12) on the therapeutic value of an extract of the common white willow, *salix alba*, that the story of modern salicylate therapy began. The Reverend Stone made his discovery from this study of the Humanities of the so-called 'Doctrines of Signatures', which implied that Nature was constantly giving signs to the observant of inner healing properties of herbs and trees, and the best place to look for a cure was in the same location as the cause. Since rheumatism and fever were worse in damp conditions, was it not likely, therefore, that their cure would be found in the willows which grew so profusely in the marshes?

The chemical isolation of salicin and salicylic acid, and the preparation of sodium salicylate and acetylsalicylic acid or aspirin involved a number of different chemists working in different European countries during the last century (9,10,11). Felix Hoffmann, a chemist working with the Bayer Company in Germany, is credited with first producing acetylsalicylic acid or aspirin. His father suffered from severe arthritis, probably rheumatoid arthritis, and had dyspepsia from both sodium salicylate and salicylic acid. Hoffman searched through the stores of synthetic salicylate preparations in the company's laboratories, and decided (for reasons that have not been recorded, if indeed there were reasons!) to try acetylsalicylic acid, which had been prepared some years previously in 1853 by a French chemist with a somewhat Germanic name, Charles Frederick von Gerhardt (13). The Bayer Company introduced acetylsalicylic acid in 1899, the name aspirin being coined from 'a'; for acetyle, 'spir' from the *spirea* plant family, and 'in' for good measure. It should be noted that salicylaldehyde and salicylic acid had initially been extracted from the flowers of *spires ulmaria*, otherwise known as the green-of-the-meadow or meadowsweet, and not willow bark (9-11). Aspirin was the drug which began the pharmaceutical industry, and remains the only proprietary name to become generic, except in Canada.

It is of interest and not without a little amusement that we look back on the clinical and animal studies carried out prior to the introduction of salicylic acid and aspirin. Several open studies were performed (11) but it was Maclagan's papers in the Lancet of 1876 (14) which established salicin in the treatment of acute rheumatism among the English speaking profession. Before prescribing the remedy to a patient Maclagan first took 5, then 10, and finally 30 gr himself "without experiencing the least inconvenience or discomfort". Thus satisfied with "the safety of its administration" Maclagan prescribed for the patient 12 gr every three hours. The result, he recorded, "exceeded my most sanguine expectations" with rapid improvement in fever, tachycardia and arthritis. Maclagan, being a canny Scot, was "quite aware that cases of acute rheumatism do sometimes unexpectedly improve without treatment", and he "had no surety that this was not a case in point". Maclagan then described the effects of salicin in other patients, noting that the more acute the case the more effective the therapy appeared to be, a fact that we know today to be true in rheumatoid arthritis (15). Maclagan was also aware that "it is very possible that less might suffice; for I have not tried to find the minimum dose".

According to Rainsford (11), Buss in 1875 was the first to perform experiments on the anti-pyretic effects of salicylates in animals, and recognised the gastric irritation of salicylic acid in rabbits. Apart from these observations no other experimental studies in animals appear to have been performed.

The first clinical trials of aspirin were reported in 1899 (11), and again these were conducted on small numbers of patients. Some patients were even prescribed aspirin in a alcoholic solution without experiencing any abdominal discomfort (11)! Dresner (11) in the same year reported the irritant action of aspirin on the tails of goldfish, but did not extend his researches on the stomachs of laboratory animals.

It is, indeed, a sobering fact that most of our really effective medications in use today originated not from

intellectualism of the discoverer planning his research with a certain objective in view, nor on the basis of extensive experiments on innumerable animals, and without any clinico-pharmacological studies or randomised controlled clinical therapeutic trials. Indeed, like the salicylates, many of our best drugs were discovered on mistaken beliefs, culled from the hedge rows, so to speak, and even derived from folklore remedies.

Phenylbutazone was the first nonsteroidal anti-inflammatory analgesic to be introduced as an alternative to salicylates. Its anti-inflammatory effects were discovered quite serendipitously (16), and early clinical trials employed alarmingly large doses (17). Indeed, it is only recently that dose-response studies have been reported (18). The fenemates-mefenamic acid (19), flufenamic acid (20) and meclofenamic acid (21) were introduced by Parke Davis Co. Ltd. in the early 60's, to be followed soon after by indomethacin by Merck, Sharpe and Dohme (22). Ibufenac, a propionic acid derivative, was marketed in the UK by Boots Pure Drug Company in 1966, but proved hepatotoxic (23) and was removed two years later. The drug is still used in Japan, where it does not cause liver damage, perhaps because of the increased rate of metabolism among Japanese (24). The company, however, persisted with their research on similar compounds and in 1969 marketed ibuprofen (25). This was quickly followed by Syntex's naproxen in the early 70's (26), and since then some thirty or more NSAIDs have produced *un embarrassement en fait de nombres*. It is quite evident in reviewing the literature on the introduction of these compounds that the quality of clinical, pharmacologic and therapeutic assessment has gradually improved, when one, for instance, compares the quality of clinical trials on indomethacin (27) and those of naproxen (28). Indeed, it is difficult to see how any improvements could have been made in the clinical and laboratory evaluation of the ill-fated benoxaprofen.

Choice of Nonsteroidal Anti-inflammatory Analgesic

Table 1 lists the currently marketed nonsteroidal anti-inflammatory analgesics grouped according to their chemical class. All are weak acids with a pKa values of 3.5 to 5 and thus demonstrate either hydrophilic (in ionised state) or lipophilic properties (non-ionised state) dependant on the pH of the surrounding milieu. At therapeutic concentrations all are highly bound to plasma proteins, especially albumin (29), and their analgesic and anti-inflammatory activity directly correlates with the degree of albumin binding(30). This is somewhat difficult to understand since it is pharmacologic dogma that free drug is active whereas bound drug is not. In terms of clinical efficacy there appears to be no major difference among the various NSAIDs (31-33), and the differences between patients is greater than the differences between the drugs (34-39). The striking individual responses of the nonsteroidal anti-inflammatory analgesics cannot be attributed to either plasma concentration (40,42,43) or pharmacokinetic behaviour (40-44). Indeed, nonsteroidal anti-inflammatory analgesics with short plasma t½ disappearance rates can be given less frequency than their pharmacokinetic behaviour would dictate without apparent loss of clinical effect (45-48). An example is a dose of indomethacin taken before retiring providing maximum pain relief in the morning when the plasma concentration is virtually zero (49). Why the duration of action of nonsteroidal anti-inflammatory analgesics exceeds the plasma half-life is not known, but may be due to accumulation of the drugs in synovial fluid and tissues where they persist long after blood concentrations have declined (50-55). In addition, all the nonsteroidal anti-inflammatory analgesics are less protein-bound in synovial fluid than in blood (56), and Dromgoole et al (57) have demonstrated that their biological effect of suppression of prostaglandin formation is more prolonged than the plasma t½ disappearance rate. It is also possible that the plasma t½ disappearance rates of active metabolites may be more prolonged than the parent drug, as has been shown for the S(+) isomer of ibuprofen (58,59). Finally, there is evidence that circadian rhythms may be important in determining clinical efficacy of nonsteroidal anti-inflammatory analgesics (60,62,63), and a drug with a short pharmacological half-life may have its biological action prolonged if administered when synovitis is most active (61).

Choice of a nonsteroidal anti-inflammatory analgesic cannot be made on mode of action and only to a limited extent on potential toxicity. The nonsteroidal anti-inflammatory analgesics share the same analgesic and anti-inflammatory actions, inhibiting

TABLE 1: NONSTEROIDAL ANTI-INFLAMMATORY ANALGESICS

ACETIC ACID DERIVATIVES
- Diclofenac
- Fenclofenac

FENEMATES
- Clofenamic Acid
- Flufenamic Acid
- Meclofenemate Sodium
- Mefenamic Acid
- Tolfenamic Acid

INDENE DERIVATIVES
- Idomethacin
- Sulindac
- Tolmetin

OXICAMS
- Isoxicam
- Piroxicam
- Sudoxicam

PROPIONIC ACID DERIVATIVES
- Carprofen
- Fenbufen
- Fenoprofen
- Flurbiprofen
- Ibuprofen
- Indoprofen
- Ketoprofen
- Naproxen
- Oxaprozin
- Pirprofen
- Suprofen

PYRAZOLES
- Azapropazone
- Feprazone
- Oxyphenbutazone
- Phenylbutazone

SALICYLATES
- Aspirin
- Benorylate
- Choline Magnesium Trisalicylate
- Diflunisal
- Sodium Salicylate

OTHERS
- Proquazone

prostaglandin synthesis (63-67), in addition to many other biochemical (68-71) and immunological functions (72-74). Many of the side effects of nonsteroidal anti-inflammatory analgesics can be explained on the basis of prostaglandin inhibition e.g. asthma, gastric disturbance and renal effects (75-77), but also by virtue of being weakly acidic compounds (78-82). Also some of the drugs are only weak inhibitors of prostaglandins e.g. isoxicam (83) whereas others are potent inhibitors e.g. indomethacin (84), but are equipotent in their analgesic and anti-inflammtory effect (85). Nonsteroidal anti-inflammatory analgesics appear to be effective in animals which cannot synthesise prostaglandins as a result of feeding with diets deficient in essential fatty acids (86). Acetylsalicylic acid acetylates proteins, such as albumin, and cyclooxygenase and is a more a potent anti-inflammatory agent than sodium salicylate in animal models of inflammation, but clinically in man is no more effective (87).

The overall profile of toxicity of nonsteroidal anti-inflammatory analgesics is remarkably similar (36,88). Phenylbutazone and oxyphenbutazone, however, cause bone marrow depression in one in 250,000 prescriptions, and elderly females appear particularly prone to aplastic anaemia (89). The latter may be due to slower metabolism in the elderly (90), leading to excessive accumulation of the drug, which has been shown to predispose to this complication (91). It is, of course, for this reason that these drugs have had their use restricted in the United Kingdom (8). The fenemates cause diarrhoea in a significant proportion of cases, and may be serious in elderly and debilitated patients (92).

Dyspepsia is the most frequent and troublesome side effect of the NSAIDs, resulting in cessation of treatment in at least a third of patients (33). The cause of dyspepsia has been attributed to inhibition of prostaglandin synthesis (93), but could also be due to their acidic nature since other acidic drugs which do not inhibit prostaglandins such as probenecid, valproic acid, and furosemide also cause dyspepsia, whereas acetaminophen which is neutral does not. Dyspepsia also shows individual variation (94,95), and when caused by aspirin has been shown not to correlate with either gastric erosions or increased faecal blood loss (96).

All of the NSAIDs, but especially aspirin, have been shown to cause acute gastric erosions. This rarely leads to sufficient intestinal blood loss to cause anaemia (97,98), and the ^{51}Cr erythrocyte method probably overestimates the amount with aspirin therapy, since aspirin increases the rate of flow of bile by approximately 50 per cent (99). Acute gastric erosions and chronic intestinal blood loss with aspirin and other NSAIDs can be minimised with enteric-coated and sustained release preparations (100,101). However, rectal administration of indomethacin has been shown to cause the same extent of gastric erosions as when administered orally (102), and the prodrug sulindac causes dyspepsia due to its circulating metabolite (103). Apart from studies in Australia (87) there is no evidence that chronic ingestion of aspirin or other NSAIDs cause peptic ulceration, and the risk of acute gastro-intestinal haemorrhage is of the order of one per two million doses (104), if indeed it occurs at all (105). Aspirin therapy does not slow the rate of healing of peptic ulcers (106). There is some evidence that NSAIDs may cause exacerbation of inflammatory bowel disease, presumably due to inhibition of prostaglandin synthesis (107). Aspirin and other NSAIDs have been reported as causing a mild elevation of serum transaminases, especially in patients with hypoalbuminaemia (108), but since this does not lead to significant histological changes and returns to normal on discontinuing therapy (108), it is of little importance in choosing an NSAID. The evidence that aspirin causes Reye's syndrome in children is debatable (109), but does constitute a dilemma in the use of the drug in either rheumatic fever or juvenile rheumatoid arthritis, especially as the use of other NSAIDs with the exception of tolmetin have not been fully evaluated in childhood.

Aspirin and other NSAIDs may cause a decrease in renal function but only when this is already impaired (111-115). Patients receiving diuretic therapy appear to be susceptible to NSAID-induced renal failure, and there appears to be a specific noxious reaction between indomethacin and triamterene in this regard (116,117). Since deterioration in renal function and sodum and chloride retention may occur with any of the NSAIDs a common mechanism of prostaglandin inhibition has been postulated (115). In addition to the unique interaction of indomethacin and triamterene, acute nephrotic syndrome with interstitial nephritis has been reported with fenoprofen, indomethacin, naproxen, phenylbutazone and tolmetin (115). Aspirin and a number of other NSAIDs have been shown to diminish the effects of diuretics (118-120), and indomethacin, in particular, has been noted to attenuate the hypotensive effects of beta blockers and peripheral vasodilators (121). Renal failure significantly prolongs the half-life of drugs which are excreted essentially unchanged e.g. azapropazone (122), or where the metabolite is metabolised back to the parent drug e.g. diflunisal and ketoprofen (123,124). Analgesic nephropathy has been reported in association with a number of NSAIDs taken singly or in combination (115), but there is insufficient evidence to determine choice of an NSAID.

There has been increasing recognition in recent years that NSAIDs may give rise to a variety of rashes (125). Particularly worrisome is the angio-neurotic oedema with aspirin (87) and the toxic epidermal necrolysis reported with piroxicam and tolmetin (125). Fortunately these serious skin toxic effects are rare.

Aspirin has been shown to prolong labour, increase the risk of post partum haemorrhage, and increase perinatal mortality (126,127) but with the exception of a report of phocomelia and agenesia of the penis in an infant born of a mother treated with indomethacin there is no evidence that aspirin or any other NSAID carries an increased teratogenic risk. Acetaminophen, on the other hand, has been implicated in being associated with an increased risk of congenital dislocation of the hip (128). All NSAIDs are excreted into human milk, and this needs to be kept in mind when treating patients who are breast-feeding their infants.

Cost in an important consideratioin in the choice of an NSAID. Aspirin is cheap, whereas the newly introduced NSAIDs are expensive. Other considerations being equal it is probably best to first choose the cheapest drug unless otherwise contra-indicated.

Is plenty enough?

In recent years there has been a querulous cry from Governmental Licensing Agencies and Consumer Groups to limit the number of new NSAIDs allowed to be prescribed. However, in an editorial in the British Medical Journal almost a decade ago the argument was made that in a disease with the chronicity of rheumatoid arthritis and drugs which caused a high rate of dyspepsia and were somewhat weak in the effect "plenty is not enough" (129). In a review of NSAID prescribing in European countries Dukes and Lunde (130) concluded that some 10 to 15 NSAIDs were appropriate to enable a physician to adequately

treat patients with chronic rheumatic disease. We lean towards a laisser-faire system, since any legislation which limits the number of NSAIDs leads inevitably to cessation of research. Elsewhere we have argued for a more enlightened and imaginative approach to the assessment and licensing of new drugs (131). We do, however, agree with the Lancet (132) and with the Greenfield Report in the United Kingdom (133) which advocated greater efforts in the education of doctors in effective prescribing.

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