Multicentre trial of naproxen and phenylbutazone in acute gout

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SUMMARY   Naproxen 750 mg as a single dose followed by 250 mg three times daily has been compared with phenylbutazone 200 mg four times daily for 48 hours followed by 200 mg three times daily for the treatment of acute gout in an open study on 41 patients. The drugs were equally effective with few and relatively mild side effects. Naproxen is a useful alternative agent for the treatment of acute gout.

There are three drugs in general use in the treatment of acute gout. Colchicine has been in intermittent use since Byzantine times but it requires frequent administration, and gastrointestinal side effects too often terminate the treatment before the attack. Phenylbutazone is as effective as colchicine (Freyberg, 1962; Gutman, 1965) and untoward reactions occurring during the treatment of acute gout are rare (Smyth and Percy, 1973), although gastrointestinal intolerance and fluid retention are predominant among the side effects that occasionally limit its usefulness. Indomethacin in adequate dosage has been shown to be as effective as phenylbutazone (Smyth and Percy, 1973) but unpleasant side effects are not infrequent (Boardman and Hart, 1965). There is therefore need for further exploration of safe and rapid therapy in acute gout, particularly as the sufferers are often relatively young and active members of the community.

Naproxen is an anti-inflammatory and analgesic agent which is widely used in rheumatoid arthritis with fewer reported side effects, particularly those of gastrointestinal intolerance, than aspirin or indomethacin (Kogstad, 1973; Hill *et al.*, 1974). It has been suggested that naproxen is effective in the treatment of acute gout (Cuq, 1973; Willkens *et al.*, 1975) and it was accordingly decided to compare the efficacy of this agent with that of phenylbutazone.

Methods

41 patients with acute gout were seen at one of four centres: King's College Hospital (5 patients), The London Hospital (4 patients), the Royal National Hospital for Rheumatic Diseases, Bath (6 patients), and Charing Cross Hospital (Kennedy Institute of Rheumatology) (26 patients). The diagnosis was made by the investigating physician on generally acceptable clinical grounds, and all but 2 patients, who had recently started allopurinol, were hyperuricaemic.

The trial was of open design and the patients were assigned to either naproxen 750 mg as a single dose followed by 250 mg three times daily (22 patients), or to phenylbutazone 200 mg four times daily for 48 hours followed by 200 mg three times daily (23 patients), 4 patients receiving both drugs in different attacks. Treatment was continued until the affected joint was pain-free. For each individual the age, sex, and duration of attack before starting treatment was recorded. At follow-up the patient was asked to assess the length of time the attack had taken to settle down in terms of absence of pain, swelling, and tenderness and ability to walk in shoes without a limp. He was also asked if the treatment had upset him in any way.

Results were analysed for statistical significance by the Mann-Whitney and Spearman's rank correlation tests.

Results

Comparability of the two treatment groups is shown in Tables 1 and 2. The phenylbutazone-treated

Table 1

Drug	No. of patients		Mean age (yr) (range)
	Male	Female	
Naproxen	20	2	58·8 (34–84)
Phenylbutazone	23	0	50·4 (30–73)

Table 2 *Time in days from onset of attack to start of treatment*

Drug	1 or less	2	3	4	5	6	7 or more
Naproxen	9	1	3	2	1	1	5
Phenylbutazone	15	1	5	0	0	0	2

patients were found to be younger than the naproxen group (P=0·03) and duration of attack before starting treatment was significantly shorter (P=0·03) in the phenylbutazone group (mean < 1 day) than in the naproxen group (mean 2 days).

There was, however, no significant difference in the duration of the attack after starting treatment between the phenylbutazone-treated patients (mean 3·4 days) and the naproxen-treated patients (mean 2·9 days) (Table 3). In both groups there were positive but not statistically significant correlations between age and duration of attack after starting treatment and between delay in starting treatment and duration of attack after treatment (Table 4).

Table 3 *Time in days from start of treatment to end of attack*

Drug	1 or less	1–2	2–3	3–4	4–5	5–6	7 or more
Naproxen	5	2	5	3	3	1	3
Phenylbutazone	2	3	5	6	3	1	3

Table 4 *Duration of attack after starting treatment correlated with age and duration before starting treatment*

Patient group	Age	Duration before starting treatment
Naproxen	+0·410	+0·296
Phenylbutazone	+0·112	+0·365
Combined patients	+0·220	+0·281

An attack persisting for more than 7 days after therapy was started might be taken as indication of treatment failure. 3 patients in the naproxen group, 2 of whom started treatment late in the attack, fulfilled this criterion, as did 3 patients in the phenylbutazone group, 1 of whom started treatment late in the attack.

One elderly patient receiving naproxen for 7 days developed ankle oedema which resolved on completion of therapy. One patient on phenylbutazone developed mild diarrhoea, and one complained of 'wind and palpitations'.

Discussion

There are indications that the worldwide prevalence of gout is increasing (Talbott, 1976), an impression which is in accord with the postulate that gout is related to the 'associates of plenty' (Acheson and Chan, 1969). However, there is also an impression among rheumatologists in this country that gout is becoming less common in hospital practice, presumably because of the ease and effectiveness of contemporary methods of therapy applicable in general practice. Hence a multicentre trial was planned and to simplify the procedure the open method was used comparing the trial drug with an agent known to be effective in acute gout. A placebo comparison was not used as it was thought unlikely that patients suffering from gout would consent to this type of investigation. Assessment was entirely subjective, but it has been shown that patients' assessment of pain relief and drug preference correlate well with changes in more complicated clinical and investigative indices of joint inflammation, at least in rheumatoid arthritis (Deodhar *et al.*, 1973), and the aim of treatment in acute gout is largely to obtain symptomatic relief.

The ages of the patients and the delay in starting treatment were significantly greater in the naproxen group than in the phenylbutazone group. Both these variables tended to be positively correlated with duration of attack after starting treatment and may therefore have introduced a bias against naproxen. Nevertheless, the present study shows that naproxen is equally as effective as phenylbutazone in the treatment of acute gout, the success rate (87% phenylbutazone, 83% naproxen) being similar to that previously reported for phenylbutazone (Boardman and Hart, 1965; Wilson *et al.*, 1956).

Side effects were mild and infrequent, occurring in only 3 of the 41 patients in the trial. The single side effect recorded with naproxen was ankle oedema in one patient. Fluid retention has been an infrequently reported side effect of this drug but was probably the explanation for weight gain of 4 kg in a patient with known cardiovascular disease receiving this drug for acute gout in a similar dose regimen to that used in our study (Willkens *et al.*, 1975), and has been noted in a patient with rheumatic heart disease by one of us (E.B.D.H.).

This study shows that naproxen is a safe and effective addition to the small group of drugs in current use for the treatment of acute gout. A

previous study has suggested that the present dose regimen is close to optimal, lower doses being less effective and higher doses providing no increased benefit (Cuq, 1973). The long plasma half-life of the drug (14 hours) suggests that more frequent administration is unnecessary.

There is now identified a group of drugs—naproxen, phenylbutazone, indomethacin, and possibly other anti-inflammatory agents—whose often dramatic efficacy in acute gout is in striking contrast to the variable and relatively mediocre response which they produce in more chronic forms of inflammatory arthritis, such as rheumatoid disease. Is it justifiable to conclude from this that a single inflammatory pathway is predictably interrupted by these drugs in gouty arthritis whereas in rheumatoid arthritis a number of alternative mechanisms may be operating, varying from patient to patient? The mechanism of the intensely painful but eventually self-limiting inflammation of the acute gouty joint is unknown. Activation of Hageman factor, complement, and the kinin system have been implicated in the past, but their importance doubted in subsequent work (Phelps *et al.*, 1966; Phelps and McCarty, 1969; Spilberg, 1974), and even the role of the polymorphonuclear leucocyte has been thrown in doubt (Ortel and Newcombe, 1974). The drugs in question are all potent inhibitors of prostaglandin synthetase (Tacheguchi and Sih, 1972; Flower *et al.*, 1973), suggesting that prostaglandins play a major part in the inflammation of acute gout. Animal studies support this hypothesis (Denko, 1974). It is conceded that colchicine does not inhibit prostaglandin synthesis, but this drug is not an anti-inflammatory agent in the usual sense of the term, and presumably acts by a mechanism different from that of the other drugs.

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