Variability in response to nonsteroidal anti-inflammatory analgesics: evidence from controlled clinical therapeutic trial of flurbiprofen in rheumatoid arthritis

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- 1 A clinical trial was conducted with flurbiprofen 100 mg three times a day by mouth in rheumatoid arthritis to determine variability in response.
- 2 Forty patients entered the study, but only 32 completed it. Patients were treated with flurbiprofen on two occasions at a month's interval, each being preceded by a 3 day wash out period. Pain relief and a Ritchie articular index of joint tenderness was assessed at the beginning and end of each treatment period.
- 3 Flurbiprofen produced significant improvement in both pain relief and articular tenderness. No significant differences were observed between the two trial periods in the mean of these outcome measures.
- 4 No evidence was found to support the concept of responders and non-responders.

Keywords nonsteroidal anti-inflammatory analgesics responders and non-responders flurbiprofen

'Proof, in science, never establishes certainty without counterproof.'

Claude Bernard, 1865

Introduction

Clinical rheumatologists have long considered that there is a considerable variability in pain relief obtained by non steroidal anti-inflammatory analgesic therapy in inflammatory joint diseases, such as rheumatoid arthritis (Bellamy, 1985; Day 1985; Day & Brooks, 1987). Evidence for such variability was first supported by a study of Huskisson *et al.* (1976), where the response to four different nonsteroidal anti-inflammatory analgesics was compared in 105 patients with rheumatoid arthritis. Despite only minor differences in the mean of outcome measures with the four different drugs, marked individual patient responses and preferences were noted. Further observations by other workers (Scott *et al.*, 1982;

Gall *et al.*, 1982; Wasner *et al.*, 1982) tended to support these findings. Significant within-patient variation was also noted by other workers in dose-response studies of nonsteroidal anti-inflammatory analgesics in rheumatoid arthritis (Day *et al.*, 1982; McGill, 1985; Dunagan *et al.*, 1986). No pharmacokinetic differences were observed with ibuprofen (Capell *et al.*, 1977), indomethacin (Barber *et al.*, 1977) and flurbiprofen (Orme *et al.*, 1981) in so-called responders and non-responders to these drugs in this disease.

In a careful and critical review of the evidence for such variability in response to nonsteroidal anti-inflammatory analgesics in rheumatoid arthritis, both Bellamy (1985) and Day & Brooks

Figure 1 Design of the trial: The dose of flurbiprofen was 100 mg three times a day. During the interval period, treatment with the patient's previously administered non-steroidal anti-inflammatory drug was recommenced.

(1987) concluded with the Scottish legal verdict of 'not proven'. The present study was undertaken therefore to test whether a variability in such response to nonsteroidal anti-inflammatory analgesics does exist, and, if so, to determine what its magnitude might be.

Methods

Patients and assessment

Forty patients with definite or classical rheumatoid arthritis, as defined by the diagnostic criteria of the American Rheumatism Association (Ropes *et al.*, 1959), agreed to freely participate in the study after its nature had been explained. The patients were, however, not told that the two drug treatments were with the same drug (although after completion of the study, this was explained to them). They did, however, fully understand that there would be an initial 3 day washout period prior to a 1 week trial with the active drug. The drug chosen for the study was flurbiprofen, 100 mg by mouth three times daily. The tablets were identical, without any identifiable markings. This was considered important since differences in colour or formulation may have influenced the results. The patients were assessed by the same observer at the end of the 3 day washout period and after 1 week of treatment. All assessments were made at the same time of day. The study was repeated after an interval of approximately 4 weeks. Figure 1 represents the design of the study.

All the patients were sero-positive for rheumatoid factor and all had articular erosions. Their mean age was 55.4 years (range 37 to 72 years) and 28 were female. None of the patients had previously received flurbiprofen. No patient suffered any co-existing illness such as hepatic or renal disease, which might have exposed them to unacceptable side-effects.

Pain was assessed on a five point Likert scale, where 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain and 4 = very severe pain. The articular index of joint tenderness was assessed by the method of Ritchie and her colleagues (Ritchie *et al.*, 1967). The patients' assessment of drug efficacy was recorded likewise on a five point Likert scale, where 0 = no benefit, 1 = slight benefit, 2 = moderate benefit, 3 = considerable benefit, and 4 = excellent.

Statistical methods

A variety of different methods was used to analyse the data. These included: Student's *t*-test for paired samples, Pearson's correlation, Spearman's rank correlation, and Cohens' kappa (Fleiss, 1981).

Results

The results of the two 7 day trials are summarised in Table 1. Only 32 patients were able to complete both sections of the trial; the remaining eight patients withdrew due to dyspepsia. Three of these patients withdrew in the first section and were not included in the second part of the study. It can be seen from Table 1 that both pain and the articular index of joint tenderness were significantly reduced by treatment.

An analysis was made of the patients' response to treatment with regard to pain on the two occasions: 13 patients improved in terms of pain on both occasions, 14 responded on one occasion only but remained the same on the other, three patients responded on one occasion, but worsened on the other, and two were the same on both occasions.

Statistical analysis using a Student's *t*-test for paired samples showed no significant difference in the pain at the commencement of flurbiprofen therapy in the two trials. There was no significant

Table 1 Pain scores and articular index of joint tenderness in 32 patients with rheumatoid arthritis treated with flurbiprofen (mean $\pm$ s.d.)

Clinical outcomes	First trial 0 $\leftarrow$ Days $\rightarrow$ 7		Significance	Second trial 0 $\leftarrow$ Days $\rightarrow$ 7		Significance
Pain	2.81 $\pm$ 0.69	1.97 $\pm$ 0.86	$P < 0.001$	2.66 $\pm$ 0.60	1.88 $\pm$ 0.88	$P < 0.001$
Articular index of joint tenderness	23.88 $\pm$ 9.32	19.25 $\pm$ 8.74	$P < 0.001$	21.91 $\pm$ 7.76	17.88 $\pm$ 6.68	$P = 0.01$

Statistical analysis by Student's *t*-test for paired data.

difference in the mean analgesic response between the two treatment periods.

There was a significant correlation ($P = 0.04$) between degree of pain relief and pain level at day 0 during the second trial period as tested by Spearman's rank correlation. However, this was just short of statistical significance ($P = 0.08$) during the first trial. These findings are consistent with the findings of Lee *et al.* (1973), who showed that the most important variable in determining pain relief from a nonsteroidal anti-inflammatory analgesic in rheumatoid arthritis was the degree of pain at commencement of therapy.

The patients' assessment of drug efficacy did not correlate with the pain at commencement of treatment in either period of the trial, but did correlate significantly with pain relief ($P < 0.001$) in both trial periods. The patient's rating of drug efficacy at the end of both sections of the study are summarised in Table 2. Cohen's kappa statistic was used to analyse the concordance of the two ratings of efficacy. There was no evidence of concordance other than that due to chance.

Discussion

The present study was designed to test the hypothesis that there might be significant variation in an individuals' response to nonsteroidal anti-

inflammatory analgesics in rheumatoid arthritis. A number of carefully conducted studies in large numbers of patients have shown that there are no differences in the mean responses of groups of patients with rheumatoid arthritis treated with different nonsteroidal anti-inflammatory drugs (Deodhar *et al.*, 1973; Huskisson *et al.*, 1976; Lee *et al.*, 1976; The Australasian trial group, 1980; Gall *et al.*, 1982; Scott *et al.*, 1982; Wasner *et al.*, 1982; Rosenbloom *et al.*, 1985).

In the present study of patients treated with flurbiprofen 100 mg three times daily by mouth in two separate trials, each of 1 week duration, each preceded by a 3 day washout period, no significant difference in the mean responses in either pain relief or articular index of joint tenderness was found (Table 1). There was evidence that response to flurbiprofen correlated with the degree of pain at the commencement of the two trial periods, confirming the previous observations of Lee *et al.* (1973).

However, the question remains: was there evidence of individual variability in response to flurbiprofen, suggesting discrete groups of responders and non-responders? The answer, on the basis of the present study is that there is no evidence which would allow us to delineate two such groups. On the other hand, Orme *et al.* (1981) found evidence in their study of patients with rheumatoid arthritis who were either respon-

Table 2 Patients' rating of drug efficacy at the end of the two trials (number of patients in each category)

		Second trial					Total number of patients
Efficacy rating		0	1	2	3	4	
First trial	0	1	3	2	1	2	9
	1	1	3	2	0	0	6
	2	5	1	3	0	0	9
	3	2	0	2	3	0	7
	4	1	0	0	0	0	1
Total number of patients		10	7	9	4	2	32

ders or non-responders to flurbiprofen and indomethacin. The design of their study was to identify patients who were responders or non-responders, and then to test this in a controlled double-blind trial. However, to interpret the data with such a design, information as to whether or not the patients' arthritis is capable of responding to any pharmacological intervention must be provided.

It could be argued that the number of patients in this study was too small to detect a consistent individual variation which would have allowed us to categorise patients as either responders or non-responders. In this connection, in the present study, only 13 patients responded positively in terms of pain relief in the two sections of the study, and only three patients were discordant in terms of their pain relief (i.e. responding positively in one section, and negatively in the other). The kappa statistical analysis on the patients' assessment of the efficacy of the two drug treatments showed a value of only 0.097 (which is extremely low, the range being +1 and -1). This is perhaps the strongest argument in our study against the concept of responders and non-responders.

In the present study, a fixed dose of flurbiprofen was used. It could be argued that it would have been preferable to have titrated the dose, since efficacy may be a dose dependent phenomenon. This has been clearly shown, however only with naproxen (Day *et al.*, 1982) and not with other nonsteroidal anti-inflammatory analgesics (Ekstrand *et al.*, 1980; Orme, 1982; Grennan *et al.*, 1983; Verbeek *et al.*, 1983). The dose of flurbiprofen was at the highest recommended level, which probably accounted for the relatively high withdrawal rate due to dyspepsia. Given the high dosage of flurbiprofen used, it would seem unlikely that a lack of clinical response was due to sub-optimal drug dosages.

Pharmacodynamic differences in nonsteroidal anti-inflammatory analgesics are well recognised (Higgs *et al.*, 1980; Abramson *et al.*, 1983; Ku *et al.*, 1985). Orme *et al.* (1981) made the interesting observation of a straight line relationship between indomethacin and flurbiprofen plasma concentrations and inhibition of malonyldialdehyde production by platelets in responders and non-responders.

It is possible that such differences may result in one patient responding to a drug, while

another may not. Variation in side-effects of nonsteroidal anti-inflammatory analgesics e.g. dyspepsia have been reported (Capell *et al.*, 1979; Lanza *et al.*, 1979) which would tend to support such a view.

The use of identical preparations of flurbiprofen was justified in the design of the present study but it could be argued that this does not correspond to everyday clinical practice. Variability in response may be partly, or even largely, due to the patients' expectations of the results of their therapy. The results of the response to flurbiprofen in the two studies does not, however, support this view. It would perhaps have been useful to have included a third period with the formulation noticeably different from that used as colour especially, has been shown to be important in determining the response to both placebos and analgesics (Huskisson, 1974).

It is surprising that despite all that has been written about variability in response to nonsteroidal anti-inflammatory analgesics this, to our knowledge, is the first study to formally address the question of responders and non-responders by testing the same drug on two separate occasions. Only by doing this can one conclude that a patient either does or does not respond to a nonsteroidal anti-inflammatory drug. The reason why such variation may have been thought to exist in patients with rheumatoid arthritis treated with nonsteroidal anti-inflammatory analgesics is the relatively small delta of response. No study has suggested variability in response exists in disorders such as acute rheumatic fever or acute gouty arthritis where the delta of response is large. Nor, to our knowledge, has such variability in response been reported in experimentally-induced inflammation such as adjuvant arthritis in rats. Although our study does not confirm that responders and non-responders to flurbiprofen exist, this does not exclude the possibility. If the frequency of such responders and non-responders is low, then a study of the present size would fail to detect them, and to do so would require further studies with larger numbers of patients.

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