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Quantitation of dose and concentration–effect relationships for fenclofenac in rheumatoid arthritis

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1 Response to non-steroidal anti-inflammatory drugs (NSAIDs) is not usually assessed on the basis of concentration measurements: identification of a concentration–effect relationship has proved difficult to achieve.

2 Dose and concentration–effect relationships of fenclofenac have been determined in a group of 18 patients with rheumatoid arthritis at three dose levels (600, 1200 and 1800 mg day^{-1}). The study was double-blind and treatments were randomised according to a Latin square design.

3 A multiple linear regression technique (GLIM) was used in the analysis. The best model to describe the change in effect in terms of dose and concentration incorporated an average slope and an individual subject intercept for each effect measurement.

4 On average, an improvement in grip strength of 20 mm Hg could be obtained with an increase in fenclofenac (trough) concentration of 100 $\mu g\ ml^{-1}$.

Keywords NSAIDs rheumatoid arthritis concentration–effect relationship fenclofenac

Introduction

Dose or concentration–effect studies of non-steroidal anti-inflammatory drugs (NSAIDs) in rheumatoid arthritis are few and have rarely shown that significant clinical improvement can be detected with an increment in dose or in concentration (Brooks *et al.*, 1975; Orme *et al.*, 1976; Day *et al.*, 1982; Grennan *et al.*, 1983). Response to an increase in dose or in concentration has proved difficult to detect due to variability in the disease, differences between individuals and difficulties in the measurement of clinical effect. Any advantage in accurate measurement of drug concentrations is apparently offset by the relative crudeness of the techniques used to assess clinical effect. Despite attempts to improve the assessment of clinical effect (i.e., same observer, same time of day) these studies typically generate very 'noisy' data. Comparative studies of NSAIDs indicate that patient response to different drugs is variable and unpredictable (Huskisson *et al.*, 1976; Scott *et al.*, 1982). Some studies have tried to explain this variability in pharmacokinetic terms, but have failed to do so (Capell *et al.*, 1977; Orme *et al.*, 1981). To date, only one study has shown a significant concentration–effect relationship (Day *et al.*, 1982). Using a ranking method to obtain a 'summed efficacy score', and defining patients as responders or non-responders for each of three doses, these authors showed that the proportion of responders increased at higher naproxen trough concentrations. We have looked further at this and have used a multiple linear regression approach (GLIM, Baker & Nelder, 1978) to explore the response to increasing doses and concentrations of fenclofenac in a group of patients with rheumatoid arthritis. Fenclofenac, an acetic acid derivative, is a relatively new NSAID. The efficacy of a standard 1200 mg daily dose was shown to compare favourably with 150 mg daily of indomethacin (Aylward *et al.*, 1980) and was found to be more effective than 750 mg daily

dose of naproxen (Tiselius, 1980). In long term trials of fenclofenac the frequency of gastrointestinal side effects compared favourably with other NSAIDs (Smith, 1977). However, fenclofenac was withdrawn from clinical use shortly after the completion of this study due to the unacceptably high incidence of skin rashes.

Methods

Patients

Eighteen outpatients with 'definite' or 'classical' rheumatoid arthritis (diagnostic criteria of the American Rheumatism Association) took part in the study. Each patient had been diagnosed as having had the disease for at least 4 months (range 4 months–20 years, median 3.5 years). Twelve patients were female, six were male. Their ages ranged from 22–74 years (median 56 years) (Table 1). None of the patients was receiving corticosteroids or any other second line anti-rheumatic drug. All patients gave their informed consent to take part in the study and Ethics Committee approval was obtained.

Study design

The study was designed as a double-blind Latin Square three-way crossover comparison of three doses of fenclofenac (600, 1200 and 1800 mg day^{-1}) given for 12 days at a time. On each dose patients took two tablets three times a day; in the morning (09.00 h), afternoon (15.00 h) and in the evening (21.00 h). Thus the 600 mg and 1200 mg doses were given in two divided doses every 12 h, while the 1800 mg dose was given in three divided doses. Trough blood samples were taken and clinical assessments were carried out in the morning 12 h after the previous evening dose. Fenclofenac (300 mg) and placebo were formulated in identically appearing tablets. A washout period of 2–3 days was included between treatments in order to bring patients back to baseline. A symptomatic 'flare' was observed in all patients after an initial washout period of at least 3 days. Clinical assessments were carried out after the initial washout (baseline measurements) and at the end of each treatment period and corresponding blood samples were taken for the measurement of total and free fenclofenac concentrations. In addition, blood samples for full blood count, biochemical screen and ESR were taken. The pharmacokinetics of a single 600 mg dose of fenclofenac were determined in each patient at the beginning of the study by multiple blood sampling over 48 h. All blood samples were collected into heparinised tubes, the plasma fraction was separated and stored at −20° C until subsequent analysis. Patients were given paracetamol to relieve pain during washout periods only. No other NSAID or second line anti-rheumatic drugs were taken. Other drugs needed to treat any coexisting disease were continued throughout the study.

Table 1 Patient characteristics

Patient	*Sex*	*Age (years)*	*Weight (kg)*	*R.A. duration (years)*	*ESR ($mm\ h^{-1}$)*	*Albumin ($g\ l^{-1}$)*
1	M	67	64.9	10	72	38
2	F	22	59.5	1.5	7	42
3	F	64	48.5	1	114	30
4	M	65	78.0	20	3	39
5	M	40	90.7	3	10	46
6	F	53	76.2	1	31	40
7	F	57	73.0	4	73	44
8	F	63	61.7	1	54	41
9	M	62	59.9	3	12	45
10	F	54	90.3	5	85	43
11	M	59	85.7	0.33	65	39
12	F	41	45.9	2	17	40
13	F	23	50.8	0.5	24	40
14	F	45	68.0	4	30	42
15	F	51	63.5	4	40	42
16	F	52	90.3	20	25	42
17	M	62	96.6	4.5	57	35
18	F	74	82.0	19	26	43

Clinical assessments

Subjective and semi-objective assessments of the patients' pain and mobility were carried out by the same observer (clinical metrologist) and at the same time of day for the duration of the study. Only numerical assessments were used in the dose and concentration effect analysis. The semi-objective assessments were: the Ritchie Articular Index (Ritchie *et al.*, 1968), a measure of joint tenderness and mean grip strength, mean of two measurements of each hand using a small bag inflated to 30 mm Hg. The subjective assessments were: the duration of morning stiffness stated by the patient and recorded in minutes and the patient's assessment of pain using a horizontal 10 cm visual analogue scale.

Measurement of total and free fenclofenac

Total fenclofenac plasma concentrations were measured by a modification of an h.p.l.c. method previously described (Nielsen-Kudsk, 1980). The mobile phase was a mixture of 50% acetonitrile and 50% distilled water acidified to pH 3 with orthophosphoric acid. This gave a good separation of fenclofenac from the internal standard, [2-(2,3,5,6-tetrachlorophenoxy) phenyl] acetic acid, when pumped through a 12.5 cm Hypersil column at 2.5 ml min^{-1}. The retention times were 4.6 and 6.7 min, respectively. The UV absorbance of the eluent was monitored at 215 nm. The extraction procedure was both simple and rapid. Acetonitrile (0.5 ml) containing the internal standard was added to 0.1 ml of plasma giving a protein precipitate. After brief centrifugation, aliquots (10–50 μl) of the supernatant were injected directly onto the h.p.l.c. Plasma standards over the concentration range 1–200 μg ml^{-1} and quality controls were run for each assay. Patient samples were analysed in duplicate. Quantitation was achieved by the Peak Height ratio (PHR) method. Plots of fenclofenac concentration against PHR were linear over the concentration range of interest (1–200 μg ml^{-1}). The inter-assay coefficient of variation was less than 4%.

Fenclofenac plasma protein binding was investigated using equilibrium dialysis (DIANORM dialyser). Duplicate 1 ml plasma samples were dialysed against phosphate buffered saline (0.02 M) containing a trace amount of ^{14}C-labelled fenclofenac (t.l.c. 98% pure) at pH 7.4 for 3 h at 37° C.

The coefficient of variation in the determination of the free fraction was < 4.5% over the concentration range 24–200 μg ml^{-1}. The volume shift during the 3 h dialysis was less than 10%; any change in protein concentration during dialysis was not brought into the calculation of free drug concentrations.

Pharmacokinetic analysis

A two compartment model with zero order absorption and a time lag was fitted to individual single dose concentration–time data using non-linear least squares regression analysis (Figure 1). Parameter values obtained from individual fits were used to predict trough drug concentrations at steady state on each of the three dosage schedules taking into account unequal dosing intervals on the 1800 mg dose. Linear kinetics should result in a proportional increase in trough drug concentrations from 600 to 1200 mg day^{-1}. The unequal dosing schedule on 1800 mg per day should give slightly lower troughs than the proportional increase expected if this dose had also been given 12 hourly. In each subject and at each dose a prediction error was calculated. Linear kinetics were thus tested for by Friedman two way analysis of variance on the basis that prediction errors should show no trend from dose to dose.

Dose and concentration–effect analysis

Corresponding dose or 12 h trough fenclofenac concentrations (total and free) and clinical effect data (articular index, mean grip strength, duration of morning stiffness and pain score) were analysed using the multiple linear regression pro-

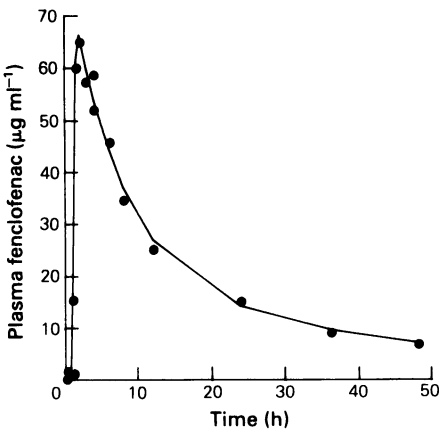

Figure 1 Fenclofenac plasma concentration–time profile for a representative subject given a single oral dose of 600 mg. A two compartment model with zero order absorption incorporating a time lag was fitted to the data.

gram, GLIM (Baker & Nelder, 1978). Dose, total or free concentration–effect data for each rheumatological measurement were analysed simultaneously. A number of linear models were investigated to explain the clinical effect in a given individual ($Effect_i$) in terms of dose or concentration $[C]_i$. The full model

$$Effect_i = a_i + b_i [C]_i$$

had an individual intercept (a_i) and individual slope (b_i). In addition three reduced forms of the above model were tested:

(1) $Effect_i = A + b_i [C]_i$
where the intercept (A) was constant for all individuals.

(2) $Effect_i = a_i + B[C]_i$
where the slope (B) was constant for all individuals.

(3) $Effect_i = a_i$
where the slope is zero.

The most appropriate model to describe the data was chosen on the basis of a series of F ratio tests. Two-way analysis of variance was used to test for time or treatment order effects. Biochemical and haematological data were analysed in terms of dose using Freidman two-way analysis of variance.

Results

The derived parameter values obtained by fitting a two compartment model with zero order absorption to individual drug concentration–time data are given in Table 2 together the coefficient of determination. Mean 12 h trough concentrations at steady state are shown in Figure 2.

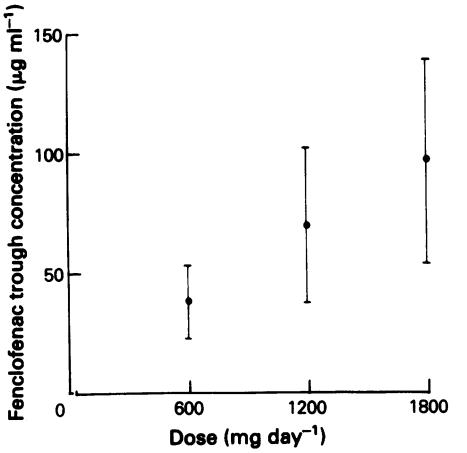

Figure 2 Mean fenclofenac trough concentration (± s.d.) at steady state for 18 patients given 600, 1200 and 1800 mg daily.

Table 2 The derived pharmacokinetic parameters for a single 600 mg dose of fenclofenac

Patient	V_c *(l)*	t_{max} *(h)*	$t_{½,\alpha}$ *(h)*	$t_{½,\beta}$ *(h)*	*CL* *(l h⁻¹)*	*CDET*
1	12.4	1.11	0.40	21.0	0.688	0.967
2	5.7	0.69	0.44	12.2	0.568	0.986
3	14.4	0.80	3.65	14.1	1.230	0.941
4	9.2	1.75	2.13	26.6	0.455	0.991
5	13.1	0.49	3.38	11.2	1.488	0.994
6	6.4	1.80	0.42	17.3	0.436	0.955
7	11.1	1.25	4.33	25.7	0.656	0.987
8	10.2	0.74	6.36	34.5	0.698	0.959
9	10.4	1.75	2.62	18.2	0.539	0.996
10	12.0	0.80	6.19	27.7	0.600	0.994
11	13.5	1.03	0.80	16.5	0.687	0.966
12	6.3	3.02	0.94	11.6	0.625	0.899
13	12.2	3.60	3.46	16.1	1.365	0.988
14	10.4	2.00	4.33	20.4	0.759	0.965
15	8.6	0.76	4.75	30.1	0.492	0.998
16	14.0	1.85	0.99	20.4	0.395	0.980
17	9.4	4.10	1.58	25.7	0.378	0.916
18	9.1	1.80	2.77	30.1	0.336	0.999
Mean	10.5	1.63	2.75	21.1	0.698	
s.d.	2.6	1.03	1.94	7.0	0.335	

V_c is the volume of the central compartment; t_{max} is the time to peak concentration; $t_{½,\alpha}$ is the half-life of the distribution phase; $t_{½,\beta}$ is the half-life of the elimination phase; CL is the systemic clearance of fenclofenac (assuming complete absorption) and CDET is the coefficent of determination for the fit to the two compartment model.

Trough concentrations predicted using parameter values from individual single dose profiles were compared with those observed. Friedman two way analysis of variance indicated that there was no significant trend in the prediction errors over the dose range indicating that fenclofenac kinetics are consistent with linearity.

Figure 3 shows a plot of total fenclofenac concentration against free drug concentration determined in 12 h trough samples at the end of each treatment period. In general there was a proportional increase in free drug concentration with increasing total concentration up to 100 μg ml^{-1} (the free fraction remained constant). Above this concentration the free fraction increased dramatically with increasing total concentration. One patient with an albumin concentration of 30 g l^{-1} showed an increase in the free fraction of fenclofenac at lower total plasma concentrations.

Four patients showed little, if any, improvement in symptoms at any dose. Corresponding trough concentrations were 52, 82, 79 and 101 μg ml^{-1} on the highest dose. All other patients showed an improvement in at least three of the effect measurements when receiving 1800 mg day^{-1}. All patients with trough concentrations greater than 101 μg ml^{-1} on 1200 or 1800 mg day^{-1} showed an improvement in all effect measurements compared to baseline. Analysis of variance showed that there was no treatment order or time effects. An example of the typically noisy clinical effect data is shown in Figure 4. This plot of total fenclofenac (trough) concentration against mean grip strength illustrates the intersubject and intrasubject variability in the rheumatological measurements. To quantitate the clinical response associated with dose or concentration increments a number of linear models were proposed. The most appropriate model was chosen on the basis of a series of F ratio tests. Table 3 gives the results of the comparison of the full model with the two reduced models for mean grip strength–concentration data. The full model was rejected in favour of a simpler, reduced model.

$$\text{Effect}_i = a_i + \text{B}\,[C]_i$$

This was the most appropriate model used to describe the data, both in terms of dose, total and free concentrations. The effect in a given individual (Effect_i) was related to the severity of disease before treatment (a_i) plus the product of a constant slope (B) for all individuals and the dose or trough concentrations of fenclofenac in that individual ($[C]_i$). This reduced model was in turn tested against the simplest model where the slope (B) is equal to zero (Table 3) and in all cases was found to be significantly better in describing the data. Table 4 gives the results of the GLIM analysis. The slope of the regression line (B) for each effect measurement indicates an improvement in symptoms in all cases. The average intercept shows the range of severity of disease within this group of patients before treatment and the coefficient of determination (CDET) expresses the adequacy with which the model describes the data (CDET is the ratio of explained to total variation). The CDET values

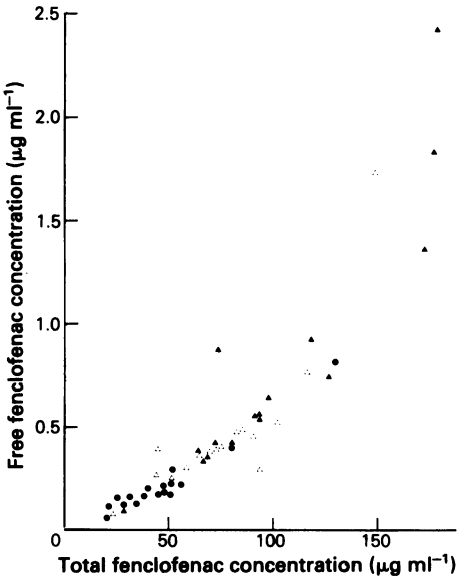

Figure 3 The non-linear relationship between total and free fenclofenac concentrations determined in 12 h trough samples at steady state on 600 mg (●), 1200 mg (△) and 1800 mg (▲) daily.

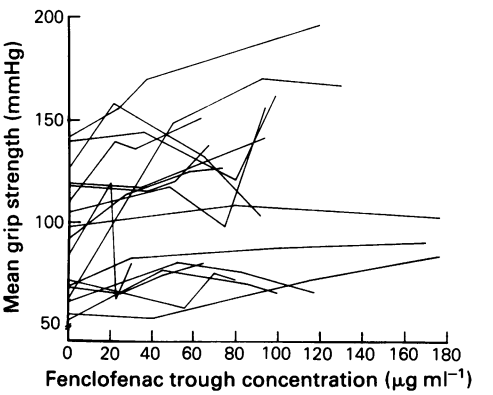

Figure 4 Mean grip strength plotted against total fenclofenac concentration.

Table 3 Total concentration and mean grip strength data fitted to four linear models. The most appropriate model is determined using the *F*-ratio test

Linear model	*Residual sum of squares*	df_1, df_2	F *value*	P *value*
Full model:				
1. $Effect_i = a_i + b_i [C]_i$	1.13×10^4			
Reduced models:				
2. $Effect_i = A + b_i [C]_i$	4.60×10^4	17,36	6.50[1]	< 0.01
3. $Effect_i = a_i + B [C]_i$	1.87×10^4	17,36	1.39[1]	NS
4. $Effect_i = a_i$	2.34×10^4	1,53	13.3[2]	< 0.01

[1] comparison with model 1.
[2] comparison with model 3.

were slightly higher for all effect measurements when analysed in terms of total concentration. However, the difference in CDET for dose, total and free concentration was small for individual effect measurements. Thus, clinical effect data were explained equally well by dose, total or free drug concentrations.

Side effects are given in Table 5. These were minor in nature and consisted of gastrointestinal, central nervous system and dermatological complaints. None were so serious as to require discontinuation of treatment or withdrawal from the study. There did not appear to be any consistent relationship between side effects and dose or total fenclofenac concentration. In addition, patients with very high free drug concentrations (due to non-linear binding over 100 $\mu g\ ml^{-1}$) reported no adverse effects.

Analysis of biochemical and haematological indices revealed a significant reduction in the white blood cell count on 1200 and 1800 mg day^{-1} ($P < 0.05$) when compared with baseline. However, all values remained within the normal range. Alkaline phosphatase was significantly reduced from baseline on 1800 mg day^{-1}. The reduction was most noticeable in patients with a high initial value.

Discussion

Non-steroidal anti-inflammatory drugs are widely used in the treatment of rheumatoid arthritis. Dosage of these drugs is usually established on a trial and error basis, the upper limit being determined by clinical response rather than by adverse effects.

Few clinical studies of newer NSAIDs include measurement of plasma concentration. No 'therapeutic range' has been established. If higher doses (or concentrations) can be shown to produce clinical improvement without a significant increase in side effects, then NSAIDs should be exploited in preference to more toxic drugs such as gold and penicillamine. However, satisfactory demonstration of a dose or concentration–effect relationship has proved remarkably elusive, even in studies designed to minimise a number of sources of variability, e.g. rheumatological measurements, patient response and disease progress. No relationship between dose or plasma concentration could be shown for indomethacin (Ekstrand *et al.*, 1980) or phenylbutazone (Orme *et al.*, 1976). Grennan *et al.* (1983) investigated three doses of ibuprofen. There was a trend for a dose response relationship with one effect measurement which reached a maximum on the second dose. On the other hand, Day *et al.* (1982) were able to demonstrate progressive improvement in symptoms with incremental doses of naproxen up to 1500 mg day^{-1}. By using a non-parametric ranking of clinical effect measurements for each patient on three doses, and a summation of all indices, they were able to show an increase in the percentage of responders with increasing trough concentrations. In the present study we have used a general linear modelling approach (GLIM, Baker & Nelder, 1978) in an effort to explain concentration–effect data. A number of models was tested. The full model described the data in terms of an individual slope and intercept for each patient. However, this model had to be rejected statistically in favour of a reduced (simpler) model (constant slope for all patients but individual intercepts) to explain the concentration–effect data. The usual E_{max} response model might have been more realistic, but in view of the variability in clinical effect measurements the simpler linear model was considered adequate. Thus clinical response was quantitated in terms of an average (linear) improvement in symptoms associated with an increment in concentration (Table 4). With all effects, the slope of the regression line indicated

Table 4 Dose and concentration-effect fitted to the linear model. $Effect_i = a_i + B\,[C]_i$ using GLIM (Baker & Nelder, 1978)

Clinial effect measurement	*Dose relationship*			*Total concentration relationship*			*Free concentration relationship*		
	Slope (B) (*units mg^{-1} day^{-1} × 10^{-3}*)	*Mean intercept* (a_i) ± *s.d.*	r^2	*Slope (B)* (*units μg^{-1} ml^{-1} × 10^{-2}*)	*Mean intercept* (a_i) ± *s.d.*	r^2	*Slope (B)* (*units μg^{-1} ml^{-1}*)	*Mean intercept* (a_i) ± *s.d.*	r^2
Ritchie articular index	−4.9 ± 1.1*	22.0 ± 8.1	0.672	−8.9 ± 2.2*	22.0 ± 8.3	0.689	−7.6 ± 2.3*	20.0 ± 8.0	0.643
Mean grip strength (mm Hg)	11.4 ± 3.6*	102 ± 39	0.852	20.0 ± 5.5*	102 ± 41	0.854	15.9 ± 6.2*	106 ± 41	0.838
Duration of morning stiffness (min)	−65 ± 17*	208 ± 107	0.631	−125 ± 26*	201 ± 103	0.666	−119 ± 30*	184 ± 99	0.633
Pain score (cm)	−1.6 ± 0.3*	6.6 ± 1.5	0.613	−2.7 0.5*	6.5 ± 1.6	0.636	−2.6 ± 0.5*	6.0 ± 1.5	0.590

*S.E. in the estimate of the slope (B)

Table 5 Side effects reported on each dose and associated trough concentrations. Patient number is given in parenthesis

Side effect	*Dose (mg day^{-1})* 600	1200	1800
Indigestion	13 (5)	20 (5)	93 (3)
Vomiting		81 (16)	101 (12)
Drowsiness			52 (5), 108 (6)
Headache	51 (15)		
Dizzy spells	51 (6)		
Haematuria			78 (7)
Hot flushes	41 (14)		
Slight rash		29 (13)	
Mild skin irritation			93 (1)
Blotches on skin		71 (9)	140 (2)

a reduction in disease activity. As an example, a patient with a mean grip strength of 100 mm Hg before treatment could expect, on average, to achieve 120 mm Hg with a trough concentration of fenclofenac of 100 μg ml^{-1} (mean trough concentration on 1800 mg day^{-1}). However, trough concentrations of up to 180 μg ml^{-1} were observed on the highest dose; at this level an average improvement in grip strength of 36 mm Hg would be attained.

Despite the observation that there was an increase in the free fraction of fenclofenac in patients with trough concentrations above 100 μg ml^{-1}, 12 h trough concentrations were consistent with linear kinetics by carrying out a comparison with predicted trough concentrations. There was no evidence that trough concentrations on the 1800 mg dose were lower than expected assuming linear kinetics. The variability in CL/*F* determined from the initial individual single dose studies (Table 2) is reflected in the range of the 12 h trough concentrations at steady state (Figure 2). These observations indicate that there is considerable intersubject variability in the pharmacokinetics of fenclofenac. Despite this, clinical response was explained equally well by dose as by total or free drug concentration using the same linear model (Table 4). This is probably due to the marked intrasubject variability in response.

In terms of toxicity, any changes in biochemical or haematological indices were of no clinical significance in the short term. The decrease in alkaline phosphatase was interesting as this was most dramatic in patients with high initial levels. This effect has been noted in studies with benoxaprofen (Jones, 1982). It is proposed that this may be an effect on the production of alkaline phosphatase by osteoclasts. Table 4 gives a list of the side effects reported, together with dose and

trough concentrations. These data cannot be analysed further, but it appears that there are no trends with dose, total or free drug concentrations.

In the absence of any dose or concentration related toxicity these findings suggest that fenclofenac could have been given in doses of up to 1800 mg day^{-1} with the expectation that on average greater symptomatic relief would have been obtained than was available with the standard 1200 mg dose.

Although fenclofenac has now been withdrawn from clinical use, this study serves to present an alternative approach to the difficult problem of evaluating the response to NSAIDs in rheumatoid arthritis.

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