Br. J. clin. Pharmac. (1983), **15**, 311–316

DOSE-RESPONSE STUDY WITH IBUPROFEN IN RHEUMATOID ARTHRITIS: CLINICAL AND PHARMACOKINETIC FINDINGS

DAVID M. GRENNAN, LEON AARONS[1], MASOOMA SIDDIQUI, MARGARET RICHARDS, ROBERT THOMPSON & CAROL HIGHAM

University of Manchester Rheumatic Diseases Centre, Hope Hospital and [1]Department of Pharmacy, University of Manchester, Manchester

1 Clinical response and plasma pharmacokinetics were studied in 20 rheumatoid patients receiving three dosages of ibuprofen.

2 There was a significant response to 1600 mg daily of ibuprofen by all three clinical measurements but increasing the daily dosage to 2400 mg produced no overall increase in response.

3 The AUC increased with increasing daily drug dosages from 800 to 2400 mg daily and the dose normalised AUC fell by 15% over the same dosage range.

4 The fraction of ibuprofen not bound to plasma proteins increased with increasing dosage and may contribute to the fall in the dose normalised AUC.

5 There was a considerable inter-individual variation in the AUC. There was no significant correlation between AUC and clinical response as measured by articular index and there was a weakly significant correlation between AUC and clinical response as measured by a visual analogue pain index.

6 Pharmacokinetic variables probably account for only a small part of the inter-individual variation in response of rheumatoid patients treated with increasing dosages of the non-steroidal, anti-inflammatory drug ibuprofen.

Introduction

The group of non-steroidal anti-inflammatory drugs (NSAID) provide the first choice in drug therapy in patients with active rheumatoid arthritis. There is a considerable inter-individual variation in patients' response to such drugs. The aim of the present study was to examine the contribution of pharmacokinetic factors to this inter-individual variation. In the study we have looked at the relationship between oral dosage, plasma pharmacokinetics and response in a group of rheumatoid patients treated with the short plasma half-life NSAID ibuprofen, given in a range of dosages. The clinical and laboratory methods which we have utilised in this study have been defined in a pilot study in which we have shown that the plasma pharmacokinetics of ibuprofen are not time dependent and that maximum response to a single dose of the drug can be demonstrated in less than 1 week of therapy (Aarons *et al.*, 1983).

Methods

Patients

Twenty out-patients with classical or definite rheumatoid arthritis (Ropes *et al.*, 1959) and aged between 20 and 65 years were studied. None was receiving corticosteroids or other anti-rheumatic drugs. All patients gave their full and informed consent to take part in the study and Ethical Committee approval was obtained.

Assessments

Clinical assessments of articular index (Ritchie *et al.*, 1968; Deodhar *et al.*, 1973), pain index using a visual analogue scale (Huskisson, 1974) and pain score graded on a 1–4 scale (Lee *et al.*, 1973) were used. A thermographic index was measured as an objective index of disease activity (Collins *et al.*, 1975; Rajapakse *et al.*, 1981). Clinical and thermographic

0306–5251/83/0300–0311 $02.00

assessments were carried out by a single observer throughout the study who was unaware of the treatment sequences which the patients were receiving.

Laboratory measurements

On the last day of each dosage period a series of blood samples was taken at 30 min, 1 h, 2 h, 3 h, 4 h and 5 h after ingestion of the drug for measurement of total and unbound plasma levels of ibuprofen. Plasma ibuprofen concentrations were measured after extraction by a reverse phase h.p.l.c. method (Aarons *et al.*, 1983). Ibuprofen plasma protein binding was measured by an ultracentrifugation method (Aarons *et al.*, 1983). Blood samples for full blood count, urea and electrolyte measurements and serum albumin estimations were also taken at each assessment and did not change significantly throughout the study.

Capsules

Ibuprofen capsules or dummy ibuprofen capsules of identical appearance were taken on a 4 times daily regime. Capsules were taken at 07.00 h, 12.00 h, 17.00 h and 22.00 h before food. Compliance was checked by a capsule count at the end of each treatment period.

Schedule

The study was a controlled, double-blind, cross-over study starting with a 2 day washout period. Each patient took each of the three different drug dosages for 1 week. An initial pilot study on six patients showed that maximal clinical response with ibuprofen could be demonstrated within 1 week of starting treatment with a 1600 mg daily dosage. The active daily dosages of ibuprofen chosen for the present study were 800 mg, 1600 mg and 2400 mg. The study began with a 2 day washout period when the patients took three placebo capsules 4 times daily. The sequence of drug combinations was determined by a Latin sequence design where period A = one 200 mg ibuprofen capsule plus 2 placebo capsules 4 times daily, period B = two 200 mg ibuprofen capsules plus one placebo capsule 4 times daily, and period C = three 200 mg ibuprofen capsules 4 times daily. Additional analgesics were not allowed. Patients were brought up to hospital on the last day of each treatment period and plasma samples for drug estimations taken in relation to the midday dose. A standard lunch was taken between the 1 and 2 h samples.

Provision was made for any patient who developed either side effects or intolerable worsening of joint pain during the study to contact the trial co-ordinator before the next assessment day.

Pharmacokinetic calculations and statistics

Area under the curve (AUC) was determined by trapezoid rule. Time to peak ibuprofen concentration (t_{max}) and peak ibuprofen concentration (C_{max}) were calculated. Elimination rate constant (k_{el}) was determined by log linear regression of the post-peak ibuprofen concentrations. The results of the clinical assessments were compared by the Wilcoxon matched pairs signed rank test. Two-way analysis of variance was used to analyse the pharmacokinetic changes against dose and time. The relationship between clinical measurements and AUC was analysed by the correlation coefficient. Two of 20 patients were excluded from the study because of non-compliance (noted anomalies in count of unused capsules at end of each treatment period plus admitted taking of additional non-trial analgesics in one patient). Four of the other 18 subjects completing this study were excluded from analyses involving AUC because erratic concentration-time curves were obtained.

Results

AUC increased with dosage (Table 1). This increase was not linear and AUC/dose fell by 15% with increasing dose as shown in Figure 1. Analysis of variance of AUC/dose showed that this decrease was statistically significant (Table 2). AUC/dose also varied significantly between subjects (Table 2). There was a tendency for C_{max}/dose to decrease with dosage (Table 1) although this was not statistically significant probably due to the greater variability in the determination of C_{max}. t_{max} and k_{el} did not change significantly with dose although both varied significantly between subjects (Tables 1 and 2).

The fraction of ibuprofen not bound to plasma protein (f_u) increased by 20% with increasing plasma

Table 1 Relationship between ibuprofen pharmacokinetics and dosage (mean ± s.d.)

Dose (mg four times daily)	*200*	*400*	*600*
AUC (mg l^{-1} min)	3042 ± 966	5564 ± 1152	7962 ± 1653
C_{max} (mg l^{-1})	19.4 ± 6.8	18.2 ± 4.0	17.5 ± 3.9
t_{max} (min)	61.4 ± 18.1	56.9 ± 12.4	58.3 ± 13.9
k_{el} (min^{-1})	0.00676 ± 0.00178	0.00705 ± 0.00208	0.00773 ± 0.0024

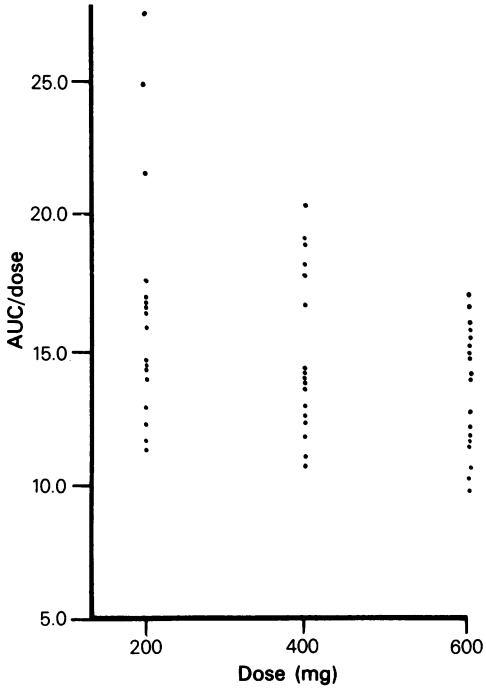

Figure 1 Dose normalised AUC at different dosages of ibuprofen given 4 times daily.

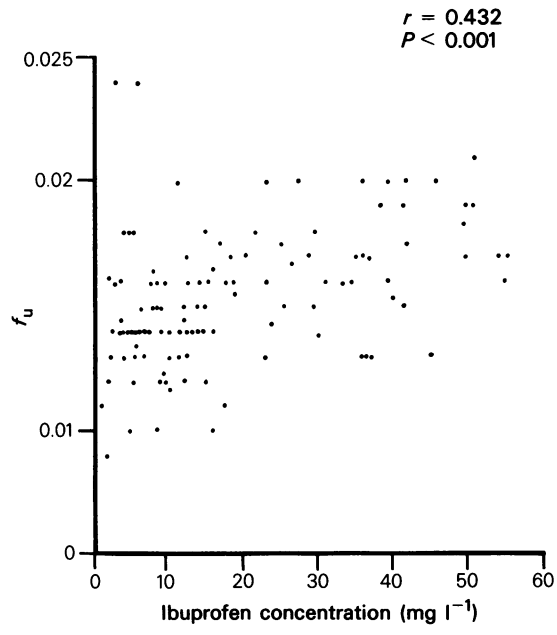

Figure 2 Fraction of ibuprofen unbound (f_u) plotted against total plasma ibuprofen concentration.

concentration of ibuprofen over the dosage range tested as shown in Figure 2. This increase was statistically significant ($r = 0.432$, $P < 0.001$, $n = 101$).

The clinical responses as measured by articular index, visual analogue pain index and pain score are shown in Figures 3, 4 and 5 and the results of the statistical analysis are shown in Table 3. Maximum response by all three assessments occurred with the 1600 mg and 2400 mg daily drug dosages. There were no significant differences seen between the 2400 mg and 1600 mg daily dosages. There was no significant correlation between AUC and change in articular index (Figure 6) but there was a relationship between AUC and change in visual analogue pain index ($r = 0.365$, $P < 0.01$). (Figure 7). There were no significant changes seen in the overall thermographic indices throughout the study (Table 4).

Discussion

In this study we have examined the clinical response and plasma drug pharmacokinetics in 20 rheumatoid patients treated with a range of dosages of ibuprofen. Clinical response was measured by well documented assessment methods of pain and tenderness and by a standard technique of infra-red thermography (Deodhar *et al.*, 1973; Rajapakse *et al.*, 1981). Dosage periods of 1 week were used after a pilot study had shown maximum response to ibuprofen could be demonstrated in less than this time. In the present study the articular index of tenderness and visual analogue pain index showed clear-cut differences between placebo and active drug treatment periods. Infra-red thermography like other objective assessment techniques is considerably less sensitive and in the present study showed no significant differences between active and inactive treatment periods. This in no way invalidates the study as the main objective

Table 2 Analysis of variance of area under curve/dose *vs* dose and subject

	SS	*Df*	*MS*	*F*	*Significance*
Residual	3530477	21	168118		
Dose	1332271	2	666136	3.9623	0.03467
Subject	1344528	13	1034348	6.1525	0.00013

SS sum of squares, MS mean squares, Df degrees of freedom

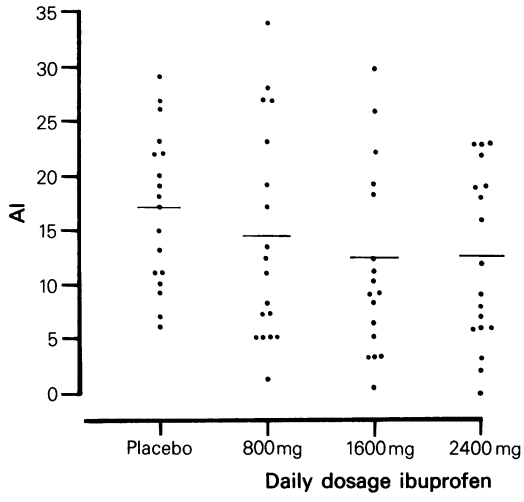

Figure 3 Articular index (AI) at different daily dosages of ibuprofen.

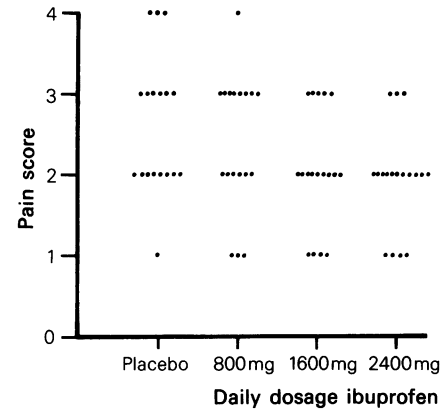

Figure 5 Pain score at different daily dosages of ibuprofen.

of non-steroidal, anti-inflammatory drugs like ibuprofen is to provide symptomatic relief of pain and such drugs are not considered to reverse the underlying inflammatory disease process (Hart *et al.*, 1978). Using the articular index and both pain indices we have demonstrated a significant response to ibuprofen given in dosage of 1600 mg and 2400 mg daily. No overall increase in response was noted on increasing the dosage from 1600 mg to 2400 mg daily of ibuprofen. This is of interest in that ibuprofen is used in clinical practice in such high dosages. In one previous study a daily dosage of 2400 mg daily of ibuprofen was found to be more effective than 1200 mg daily of the drug but an intermediate drug dosage was not studied (Godfrey & DelaCruz, 1975). Although a minority of patients might respond preferentially to dosages as high as 2400 mg daily, the majority studied at least in the short term with documentation of pain and tenderness, do not. A similar situation may occur with other anti-inflammatory drugs so that the onus is on the physician who uses such high dosages to demonstrate their greater efficacy *vs* lower and less potentially toxic regimes in the individual patient. In the present study although the articular index showed a trend for a dose response over the range 0 to 1600 mg daily, the differences between the placebo and 800 mg dosage period were not statistically significant.

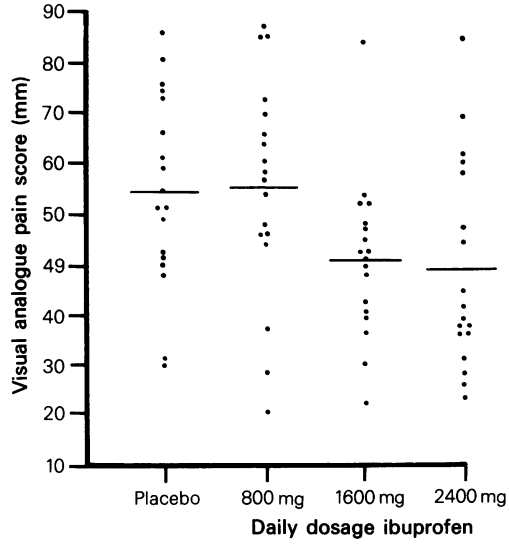

Figure 4 Visual analogue pain score at different daily dosages of ibuprofen

Plasma pharmacokinetics of ibuprofen were studied at the end of each weekly treatment period. Although the pharmacokinetics of ibuprofen (and other anti-inflammatory drugs) have been well documented in single dose studies in normal individuals (Boots Co. Brufen Technical Bulletin) there is much less information on drug pharmacokinetics in rheumatoid patients receiving multiple doses prescribed in clinical practice. In a pilot study we have excluded any time dependency for kinetics of this drug (Aarons *et al.*, 1983). In the present study plasma concentrations as measured by AUC increased with increasing drug dosage but the dose normalised AUC fell by 15% over dosage range of 800 to 2400 mg daily. This decrease in itself is unlikely to be clinically significant. However, as AUC/dose = F/CL were F = bioavailabiity and CL = clearance, then a fall in AUC/dose might theoretically be caused by either fall in bioavailability or an increase in clearance (CL = $k_{el} \times V$ where V is

Table 3 Statistical analysis of clinical response measurements

	Placebo vs *800 mg*	*Placebo* vs *1600 mg*	*Placebo* vs *2400 mg*	*800 mg* vs *1600 mg*	*800 mg* vs *2400 mg*	*1600 mg* vs *2400 mg*
Articular index	NS	< 0.005	< 0.005	< 0.25	< 0.025	NS
Pain index (Visual analogue)	NS	< 0.01	< 0.005	< 0.01	< 0.01	NS
Pain score (1–4)	NS	< 0.05	< 0.02	NS	NS	NS

NS non significant

distribution volume). Without measurement of urinary metabolites or intravenous dosing, bioavailability is not directly measurable. Ibuprofen however has been estimated as 95–100% bioavailable by measurement of urinary metabolites (Marchant, personal communication). Distribution volume (V) although not directly measured is influenced by the proportion of drugs unbound. In the present *in vivo* binding studies in rheumatoid patients the fraction of drug unbound increased by about 20% with drug concentrations ranging from 2 to 50 mg l^{-1}. This binding change could produce an increase in clearance and hence could contribute to the fall in dose normalised AUC with increasing dosage. As both CL and V have increased, this explanation is in keeping with the constant k_{el} observed at different dosages.

There was no overall correlation between either total or non-protein bound plasma drug concentration and clinical response as measured by articular index although there was a weakly significant correlation between plasma drug concentration and clinical response as measured by visual analogue pain index. Both of these findings may be related to the inability of plasma measurements to reflect drug concentrations at inflammatory sites in the tissues. It has been shown previously that synovial fluid ibuprofen levels lag behind plasma concentrations and stay elevated for longer (Glass & Swannell, 1978) although the unbound drug concentration in synovial fluid has recently been shown to be about equal to plasma unbound concentrations (Whitlam *et al.*, 1981).

Current pharmacological thinking suggests that the amount of drug which reaches its site of action and hence its drug efficacy are influenced more by unbound than by total plasma concentrations (Koch-Weser & Sellers, 1976). There is no evidence from the present or from previous studies that this is true for

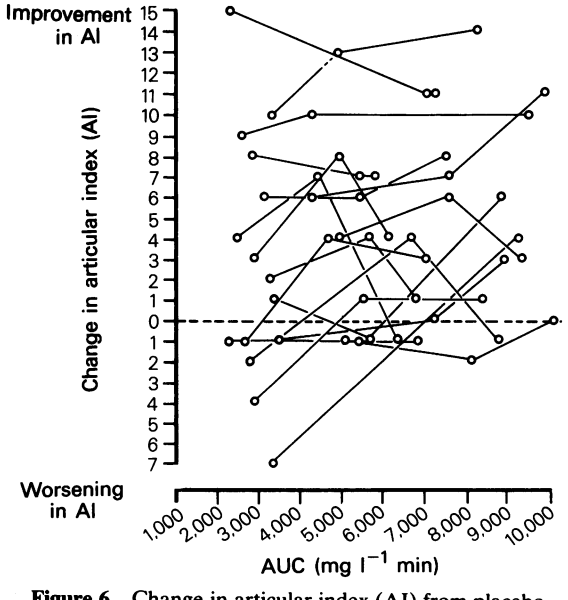

Figure 6 Change in articular index (AI) from placebo period plotted against AUC.

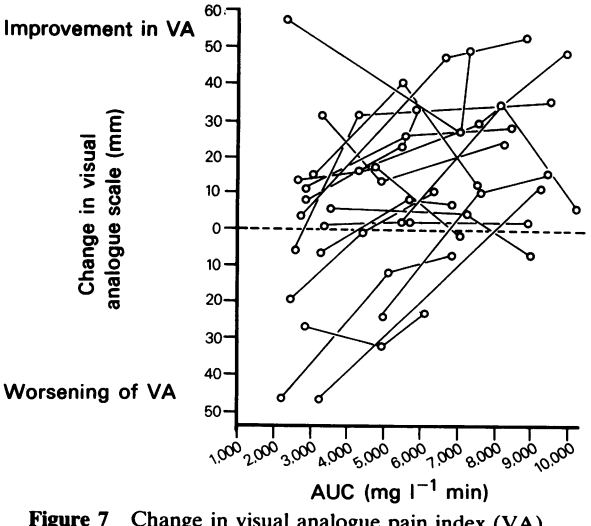

Figure 7 Change in visual analogue pain index (VA) plotted against AUC.

Table 4 Total thermographic index (mean ± s.d.) at different daily ibuprofen dosages

	Daily ibuprofen dosage (mg)			
	Placebo	*800*	*1600*	*2400*
Total thermographic index	445.4 ±188.5	429 ±220.2	443.6 ±204.6	462 ±203.9

anti-inflammatory drugs other than via the effect which protein binding has on drug pharmacokinetics. On the other hand as all non-steroidal anti-inflammatory drugs are acidic and highly protein bound, albumin binding may be fundamental to their mechanism of action. Graf and co-workers (1975) have previously demonstrated that pKa and protein-binding influence concentration of these drugs in inflammatory sites. The efficacy of anti-inflammatory drugs has been related to their *in vitro* protein binding (McArthur *et al.*, 1971). Plasma albumin binding might mimic binding of anti-inflammatory drugs to their site of action or receptor sites (Gund & Shen, 1977) in the tissues. If this were so then the failure of drug dosages above 1600 mg daily to increase response might be partially explainable by saturation of the tissue receptors.

The findings in this study can be interpreted as suggesting that pharmacokinetic variables account for only a very small fraction of the total inter-individual variation of rheumatoid patients to non-steroidal anti-inflammatory drugs. On a practical level the peaking of the response to ibuprofen at 1600 mg daily is of interest in that ibuprofen is used in higher dosages in clinical practice.

We are grateful to the Boots Co. for providing radiolabelled ibuprofen and for financial support.

References

AARONS, L., GRENNAN, D.M., RAJAPAKSE, C., BRINKLEY, J., SIDIQUI, M., TAYLOR, L. & HIGHAM, C. (1983). Anti-inflammatory (ibuprofen) drug therapy in rheumatoid arthritis—rate of response and lack of time dependency of plasma pharmacokinetics. *Br. J. clin. Pharmac.*, **15**, 387–388.

COLLINS, A.J., RING, E.F.J., COSH, J.A., BACON, P.A. (1975). Quantitation of thermography in arthritis using multi-isothermal analysis. *1.* B. Thermographic index. *Ann. Rheum. Dis.*, **33**, 113–115.

DEODHAR, S.D., DICK, W.C., HODGKINSON, R., BUCHANAN, W.W. (1973). Measurement of clinical response to anti-inflammatory drug therapy in rheumatoid arthritis. *Quart. J. Med.*, **42**, 387–401.

GLASS, R.C. & SWANNELL, A.J. (1978). Concentrations of ibuprofen in serum and synovial fluid from patients with arthritis. *Br. J. clin. Pharmac.*, **6**, 453–454.

GODFREY, R.C. & DELA CRUZ, S. (1975). Effects of ibuprofen dosage on clinical response in rheumatoid arthritis. *Arth. Rheum.*, **18**, 135–137.

GRAF, P., GLATT, M. & BRUNE, M. (1975). Acid non-steroid anti-inflammatory drugs accumulating in inflamed tissue. *Experientia*, **31**, 951–953.

GUND, P. & SHEN, T.Y. (1977). A model for the prostaglandin synthetase cyclo-oxygenation site and its inhibition by anti-inflammatory arylacetic acids. *J. med. Chem.*, **20**, 1146–1152.

HART, F.D., HUSKISSON, F.C. & ANSELL, B.M. (1978). Chapter II. Non-steroidal anti-inflammatory analgesics. In *Drug Treatment of Rheumatic Diseases*, pp. 8–43. New York: Adis Press.

HUSKISSON, E.C. (1974). Measurement of pain. *Lancet*, **ii**, 1127–1131.

KOCH-WESER, J. & SELLERS, E.M. (1976). Binding of drugs to serum albumin. *New Engl. J. Med.*, **294**, 311–316.

LEE, P., WEBB, J., ANDERSON, J. & BUHANAN, W.W. (1973). Method for assessing the therapeutic potential of anti-inflammatory anti-rheumatic drugs in rheumatoid arthritis. *Br. med. J.*, **2**, 685–688.

McARTHUR, J.N., DAWKINS, P.D. & SMITH, M.J.H. (1971). The displacement of L-tryptophan and dipeptides from bovine albumin *in vitro* and from human plasma *in vivo* by anti-rheumatic drugs. *J. Pharm. Pharmac.*, **23**, 393–398.

RAJAPAKSE, C., GRENNAN, D.M., JONES, C., WILKINSON, L. & JAYSON, M.I.V. (1981). Thermography in the assessment of peripheral joint inflammation – a re-evaluation. *Rheumatology and Rehabilitation*, **20**, 81–87.

RITCHIE, D.M., BOYLE, J.A., McINNES, J.M., JASANI, M.R., DALAKOS, T.G., GRIEVESON, P. & BUCHANAN, W.W. (1968). Clinical studies with an articular index with the assessment of joint tenderness in patients with rheumatoid arthritis. *Quart. J. Med.*, **37**, 393–406.

ROPES, N.W., BENNETT, T.A., COBBS, S., JACOX, R. & JESSAR, A. (1959). 1958 Revision of diagnostic criteria for rheumatoid arthritis. *Arthritis & Rheumatism*, **2**, 16–20.

WHITLAM, J.D., BROWN, J.F., CROOKS, M.J. & BROOM, D.F.W. (1981). Trans-synovial distribution of ibuprofen in arthritic patients. *Clin. Pharmac. Ther.*, **29**, 487–492.

(Received October 5, 1982, accepted November 23, 1982)