Annals of the Rheumatic Diseases, 1989; **48**, 368–371

Influence of non-steroidal anti-inflammatory drugs and disease activity on serum alkaline phosphatase concentrations in rheumatoid arthritis, osteoarthritis, and polymyalgia rheumatica

A DOUBE,[1] J DAVIES,[1] M DAVIS,[2] AND P J MADDISON[1]

From the [1]Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath and the [2]Gastroenterology Unit, Royal United Hospital, Bath

SUMMARY The influence of non-steroidal anti-inflammatory drugs (NSAIDs) and of disease activity on the serum alkaline phosphatase concentration was examined in patients with rheumatoid arthritis, osteoarthritis, and polymyalgia rheumatica. Concentrations of serum alkaline phosphatase were similar both in patients with rheumatoid arthritis taking NSAIDs and in those not taking NSAIDs. In patients with osteoarthritis NSAID use was not associated with a significant increase in serum alkaline phosphatase. In rheumatoid arthritis no correlation was found between clinical indices of disease activity and serum alkaline phosphatase concentrations. There was significant correlation with plasma viscosity in rheumatoid arthritis, both in those taking and not taking NSAIDs, and in polymyalgia rheumatica. Serum alkaline phosphatase concentrations are not influenced by NSAIDs. Concentrations correlate with laboratory parameters, but not clinical indices of disease activity.

Increase of serum alkaline phosphatase is a common finding in rheumatoid arthritis, being noted in up to 35% of patients.[1] Concomitant rises in serum 5-nucleotidase,[2] γ-glutamyltransferase,[3] and isoenzyme analysis[1 4] indicate that this alkaline phosphatase is hepatic in origin. Hepatic histological changes, though common in rheumatoid arthritis, are non-specific and include Kupffer cell hyperplasia, fatty infiltration, and mononuclear cell infiltration of the portal tracts.[1 5] Non-steroidal anti-inflammatory drugs (NSAIDs) are recognised to be hepatotoxic and are capable of causing increases in serum alkaline phosphatase.[6] Studies to date have not directly examined the effect of NSAIDs on the concentration of serum alkaline phosphatase in patients with rheumatoid arthritis.

Previous studies attempting to relate the concentration of serum alkaline phosphatase to disease activity have been conflicting. Fernandes *et al* were unable to correlate alkaline phosphatase concentrations with disease severity, as assessed by articular index, grip strength, and duration of morning stiffness,[1] whereas Akesson *et al* found a weak correlation with laboratory indices such as erythrocyte sedimentation rate and serum orosomucoid.[7]

This present study examines the direct effect of NSAIDs on serum alkaline phosphatase concentrations in rheumatoid arthritis and osteoarthritis. In addition, the correlation of alkaline phosphatase concentration with clinical and laboratory indices of disease activity is assessed in rheumatoid arthritis and polymyalgia rheumatica.

Patients and methods

Prospective data were collected for 17 patients with rheumatoid arthritis who had not taken NSAIDs for at least four weeks before examination. These were compared with data collected prospectively from 57 patients with rheumatoid arthritis taking NSAIDs at entry to a study evaluating their response to an initial second line agent (auranofin). These two groups were similar in age (mean ages 65 and 57 years respectively) and sex distribution (14 of 17 female and 40 of 57 female respectively) but were disparate in duration of disease. Those not taking

Accepted for publication 2 October 1988.
Correspondence to Dr A Doube, Waikato Hospital, Private Bag, Hamilton, New Zealand.

Table 1 *Comparison of disease activity in patients with rheumatoid arthritis taking and not taking non-steroidal anti-inflammatory drugs (NSAIDs). All values are medians (SD)*

	No NSAID	*Taking NSAID*	*p Value**
Early morning stiffness (min)	60 (97)	30 (40)	0·38
Visual analogue scale for pain (0–100 mm)	54 (28)	40 (24)	0·22
Ritchie index	13 (11)	12 (10)	0·67
Platelet count ($\times 10^9$/l)	321 (172)	348 (98)	0·9
Plasma viscosity (cP)	1·795 (0·24)	1·82 (0·30)	0·9

*No p value reached significance (Mann-Whitney U test).

NSAIDs had a mean disease duration of 16 years and the comparison group all had disease of less than one year's duration. Disease activity was not significantly different between these groups, however (Table 1).

Prospective data were collected for 58 patients with osteoarthritis at entry into a drug tolerance study. These patients had an age and sex distribution similar to those of the rheumatoid arthritis group (mean age 63 years, 32 of 58 female). Serum alkaline phosphatase concentrations were available for all patients and were divided into values for patients not taking NSAIDs (n=25) and those taking NSAIDs (n=33) according to the detailed drug history taken at entry to the drug tolerance study.

Retrospective laboratory data were obtained from the notes of 57 patients with polymyalgia rheumatica, and the first available paired haematology and biochemistry results were noted.

Patients with known or suspected hepatic or bony disease were excluded from all groups. No attempt was made to characterise the alkaline phosphatase as hepatic in origin as previous studies have reported the raised alkaline phosphatase to be almost exclusively hepatic in origin in inflammatory diseases. Alkaline phosphatase was measured using *p*-nitrophenyl phosphate and adenosine phosphate buffer (pH 10·2). The normal laboratory reference range for alkaline phosphatase is 21–92 IU/l with a coefficient of variation of 3% for the method used. Plasma viscosity was measured with a Luckhams viscometer.

The Mann-Whitney U test was used to compare non-parametric data. Comparison of age was made with Student's *t* test. The significance of correlation between variables was assessed by linear aggression analysis.

Results

With one exception all patients had normal concentrations of bilirubin and aspartate transaminase. One patient in the osteoarthritis group had a bilirubin concentration raised to 24 μmol/l (reference range 1–17 μmol/l) without other clinical or biochemical evidence of liver disease. In the patients with rheumatoid arthritis the serum alkaline phosphatase concentration was greater than 92 IU/l in 32 of the 57 patients taking NSAIDs and in 11 of 17 patients not taking NSAIDs. In the patients with osteoarthritis the serum alkaline phosphatase concentration was greater than 92 IU/l in 16 of 33 patients taking NSAIDs and in nine of 25 patients not taking NSAIDs.

The serum alkaline phosphatase concentration of patients with rheumatoid arthritis taking NSAIDs was not significantly raised compared with that of patients with similar disease activity not taking NSAIDs (median 101 IU/l *v* 105 IU/l respectively, $p>0·5$). Similarly, NSAID use was not associated with significantly greater increase in concentrations of serum alkaline phosphatase in patients with osteoarthritis (median 90 IU/l *v* 82·5 IU/l respectively; $p>0·33$).

Concentrations of serum alkaline phosphatase did not correlate with duration of early morning stiffness or severity of joint pain, as assessed by a visual analogue scale, in either patients with rheumatoid arthritis taking NSAIDs or those not taking NSAIDs. A significant correlation existed with degree of stiffness as assessed by visual analogue scale in patients with rheumatoid arthritis not taking NSAIDs, but this parameter was not assessed in the group taking NSAIDs. No correlation was found with Ritchie's index in either group with rheumatoid arthritis.

A significant correlation was found between alkaline phosphatase concentrations and plasma viscosity in all three groups with inflammatory disease ($p<0·05$ for rheumatoid arthritis—no NSAID, rheumatoid arthritis+NSAID, and polymyalgia rheumatica) (Fig. 1; data for polymyalgia rheumatica not shown). Platelet count correlated significantly with alkaline phosphatase concentrations in the rheumatoid arthritis 'no NSAID' group ($p<0·05$) but not in either the rheumatoid arthritis 'NSAID' group or polymyalgia rheumatica group.

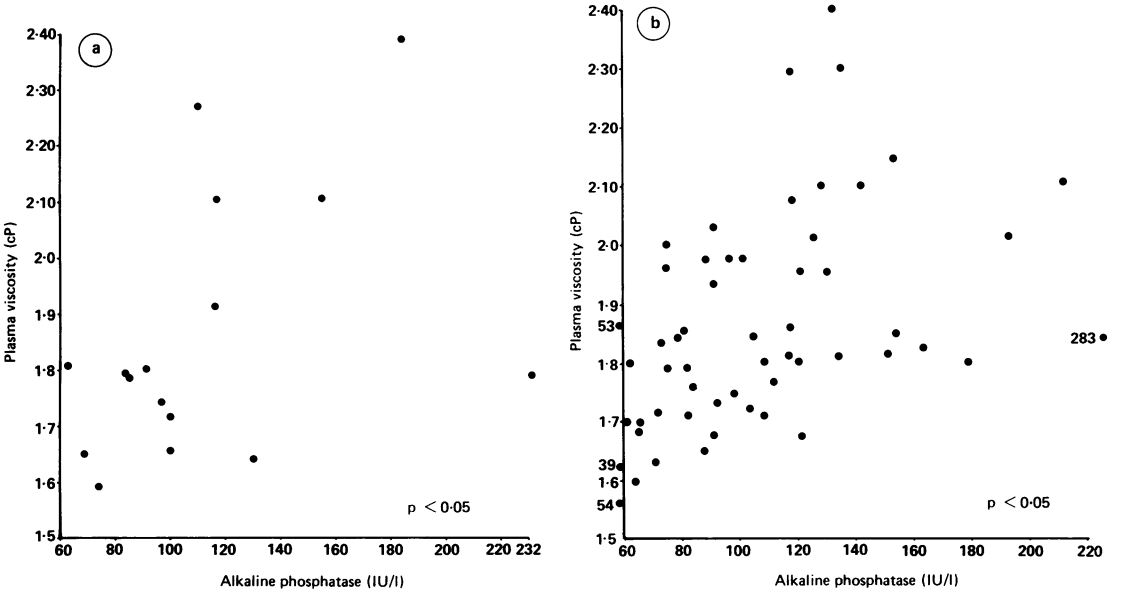

Fig. 1 *Correlation of serum alkaline phosphatase concentrations with plasma viscosity in patients with rheumatoid arthritis (a) not taking non-steroidal anti-inflammatory drugs (NSAIDs) (n=17) and (b) taking NSAIDs (n=56). The correlation is significant at the p<0·05 level in both groups.*

Haemoglobin concentration was inversely correlated with alkaline phosphatase concentration in the polymyalgia rheumatica group, but this parameter, was not examined in the other groups. No correlation was found between alkaline phosphatase concentrations and either platelet count or plasma viscosity in the osteoarthritic patients.

Discussion

Abnormal liver function tests are not confined to patients with rheumatoid arthritis but are also noted in ankylosing spondylitis, psoriatic arthritis, and reactive arthritis.[7] For these other forms of arthritis the pattern of serum enzyme increase is similar to that found in rheumatoid arthritis but differs from that found in other non-rheumatic inflammatory conditions, such as pneumonia.[7] Increased serum alkaline phosphatase of hepatic origin has been documented in 24% to 35% of patients with rheumatoid arthritis.[1 7] The possibility that drugs, particularly NSAIDs, may have an effect on the serum alkaline phosphatase has been raised in earlier studies[1 4] but has not previously been examined directly. The possibility of observing the effect of withdrawal of anti-inflammatory drugs from patients with increased serum alkaline phosphatase concentrations has been considered, but this was felt to be unethical in patients with active arthritis.[8] As NSAIDs are known to be hepatotoxic we attempted to evaluate their effect on serum alkaline phosphatase concentrations by comparing patients of similar disease activity either taking or not taking these drugs. A small consecutive series of 10 patients with rheumatoid arthritis not taking NSAIDs showed no abnormal concentrations of alkaline phosphatase.[9] This suggested that NSAIDs may be a common cause of the raised serum alkaline phosphatase frequently noted in rheumatoid arthritis and prompted our present study. This study shows, however, that concentrations of serum alkaline phosphatase are not more raised in patients with either rheumatoid arthritis or osteoarthritis taking NSAIDs than in patients not taking these drugs. We conclude that NSAIDs do not contribute to the raised alkaline phosphatase in rheumatoid arthritis.

The relation between serum alkaline phosphatase concentrations and disease activity has not been previously well documented. Kendall *et al* compared 15 patients with rheumatoid arthritis and raised alkaline phosphatase with a similar number of patients with normal alkaline phosphatase and concluded that those with raised alkaline phosphatase concentration had more active disease.[2] It is not clear, however, which clinical parameters of disease activity were determined in their patients. Fernandes *et al* studied 100 patients with rheumatoid

arthritis and were unable to show a statistical association between serum alkaline phosphatase concentration and severity of arthritis as assessed by articular index, grip strength, and duration of morning stiffness.[1] Unfortunately the numerical data and the statistical methods used are not quoted in their paper. A year later Akesson *et al* examined the laboratory data of 182 patients with rheumatoid arthritis.[7] No clinical assessment of disease activity was attempted, but weak correlations were found between serum alkaline phosphatase concentration and erythrocyte sedimentation rate and serum orosomucoid values.

This present study indicates that serum alkaline phosphatase concentrations correlate poorly with clinical indices of disease activity in rheumatoid arthritis. This may be a reflection of the insensitivity of these clinical parameters as there was significant correlation with plasma viscosity in patients with rheumatoid arthritis and polymyalgia rheumatica.

It is of clinical interest to note that most serum alkaline phosphatase values obtained in the rheumatoid arthritis groups and the polymyalgia rheumatica group were below 140 IU/l (Fig. 1). More marked increase in serum alkaline phosphatase concentrations may provide a clue to underlying associated disease, such as hepatic, bone, or even cardiovascular disease. For example, Thould reported five cases of definite constrictive pericarditis associated with rheumatoid arthritis and in each case the alkaline phosphatase concentration was greater than 140 IU/l (maximum 1000 IU/l), falling to normal after pericardectomy.[10]

In summary, serum alkaline phosphatase concentrations are not significantly altered by NSAIDs. Concentrations correlate with plasma viscosity but not with clinical parameters of disease activity. Very high concentrations of serum alkaline phosphatase may indicate an underlying secondary disease.

References

1 Fernandes L, Sullivan S, McFarlane I G, *et al.* Studies on the frequency and pathogenesis of liver involvement in rheumatoid arthritis. *Ann Rheum Dis* 1979; **38:** 501–6.

2 Kendall M J, Cockel R, Becker J, Hawkins C F. Raised serum alkaline phosphatase in rheumatoid arthritis. *Ann Rheum Dis* 1970; **29:** 537–40.

3 Lowe J R, Pickup M E, Dixon J S, *et al.* Gamma glutamyltranspeptidase levels in arthritis. A correlation with clinical and laboratory indices of disease activity. *Ann Rheum Dis* 1978; **37:** 428–31.

4 Webb J, Whaley K, MacSween R N M, Nuki G, Dick W C, Buchanan W W. Liver disease in rheumatoid arthritis and Sjögren's syndrome. *Ann Rheum Dis* 1975; **34:** 70–81.

5 Weinblath M E, Yesser J R P, Gillian J H. The liver in rheumatic diseases. *Semin Arthritis Rheum* 1982; **11:** 399–405.

6 Davis M, Williams R. In: Davies D M, ed. *Textbook of adverse drug reactions*. Oxford: Oxford University Press, 1986: 265.

7 Akesson A, Berglund K, Karlsson M. Liver function in some common rheumatic diseases. *Scand J Rheumatol* 1980; **9:** 81–8.

8 Mills P R, MacSween R N M, Dick W C, More I A, Watkinson G. Liver disease in rheumatoid arthritis. *Scott Med J* 1980; **25:** 18–22.

9 Doube A. Liver function tests and NSAIDs in rheumatoid arthritis. *NZ Med J* 1987; **818:** 120–1.

10 Thould A K. Constrictive pericarditis in rheumatoid arthritis. *Ann Rheum Dis* 1986; **45:** 89–94.