Plasma viscosity—a new appraisal of its use as an index of disease activity in rheumatoid arthritis

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SUMMARY The suitability of the plasma viscosity (PV) test has been examined in relation to the more commonly used erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) estimations as a diagnostic aid in 120 outpatients with rheumatoid arthritis (RA) and as an index of improvement during subsequent specific antirheumatic drug treatment (60 outpatients). Correlation data based on 7 clinical variables suggest that PV estimations are at least as reliable as ESR and CRP in terms of diagnosis and as indices of improvement. The methodological advantages offered by the PV test lend support to its application in RA.

In 1976 the Lancet¹ reported 'the ESR has successfully resisted other challengers in the past, though after 50 years pathologists would not be sorry to see it go.' This comment prompted us to look at the alternatives, in particular plasma viscosity (PV). The measurement of PV to detect nonspecific changes in one or more plasma protein fractions has been reviewed by Harkness.² It was first advocated as an index of activity in the rheumatic diseases by Whittington.³ Subsequent evidence of its superiority over the erythrocyte sedimentation rate (ESR) has been described,⁴ but to date this view has not been rigorously quantified.

This paper compares PV with the more commonly used ESR and C-reactive protein (CRP) in rheumatoid arthritis (RA) firstly as a diagnostic aid and secondly as an index of improvement during specific antirheumatic drug therapy. The specific effect of individual drugs used in the treatment of rheumatoid arthritis on PV, ESR, and CRP is also investigated.

Patients and methods

The use of PV as a diagnostic aid was investigated in a selection of 120 patients with classical or definite RA (American Rheumatism Association criteria). None had received specific antirheumatic therapy (e.g., gold, penicillamine, hydroxychloroquine) and all showed evidence of at least moderate disease

activity as defined by Dixon *et al.*⁵ For each patient EDTA PV was measured with a capillary viscometer (Coulter Electronics Ltd.), ESR by the Westergren method,⁶ and CRP by the method of Mancini.⁷

Sixty of the 120 patients originally investigated went on to be treated for 6 months with D-penicillamine (125 mg/day increasing to 500 mg/day), or hydroxychloroquine (200 mg b.d.), or sodium aurothiomalate (50 mg weekly until 1g had been given, then 50 mg monthly intramuscularly), or alclofenac (1 g t.d.s.). This was preceded by a 2-week period during which the 15 patients in each 'drug group' were asked to take 3.9 g Nuseal aspirin per day to establish 'baseline' conditions. Nuseal aspirin was also prescribed as required as supplementary treatment during the 6-month dosage period.

Patients were assessed both clinically and biochemically at weeks 0, 2, 4, 8, 12, 16, 20, and 24 (week 0 = date of starting specific antirheumatic therapy).

In addition to PV, CRP, and ESR determinations 7 clinical parameters (articular index, summated change score, grip strength, joint size, functional grade, pain score, and early morning stiffness) were assessed at each visit by methods previously described.⁵

Results

91% of the 120 patients studied had a raised ESR, while 94% had raised PV and 97% raised CRP (Table 1).

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Table 1 The prevalence of raised ESR, CRP, and PV in patients with RA

Parameter	n	Normal range	% Above normal
ESR	120	4–20 mm. h ⁻¹ male 10–25 mm. h ⁻¹ female	90.8
PV	120	1.5–1.72 centipoise	94.2
CRP	120	0.007–0.058 mg/100 ml	97.0

The patients' improvement during antirheumatic therapy is illustrated by a reduction in ESR, CRP, PV, and articular index for D-penicillamine, hydroxychloroquine, and gold (Fig. 1). Articular index is highlighted as the most objective of the clinical parameters measured for disease activity at a large number of joints.⁸ With the exception of ESR

during hydroxychloroquine treatment the reductions were statistically significant when compared with week 0 data (Wilcoxon rank sum test for paired data). The poor improvement in ESR with hydroxychloroquine treatment is illustrated in terms of a low percentage improvement over 24 weeks (Table 2). The failure of alclofenac to improve disease status⁹ is exemplified by the lack of improvement in biochemistry and articular index over the 24-week period (Fig. 1 and Table 2). At the end of the 6-month period it was observed that, of the 60 patients treated, 8 had normal ESRs but still had raised PV and CRP. Only 1 patient showed evidence of a raised ESR but normal PV.

The correlation of PV, CRP, and ESR with disease activity at a given time is illustrated in Tables 3 and 4.

Fig. 1 Mean data ($\pm$ SE) for ESR, PV, CRP, and AI for groups of RA patients treated for 6 months with gold, D-penicillamine, hydroxychloroquine, or alclofenac. Changes in individual parameters reaching statistical significance (Wilcoxon rank sum test) when compared with data at week 0 are indicated by hatched ($P < 0.05$) and closed ($P < 0.01$) data points.

Table 2 Percentage improvement* in individual parameters after 24 weeks' antirheumatic drug treatment

Parameter	Drug			
	Penicillamine	Hydroxy-chloroquine	Gold	Alclofenac
Articular index	54	38	57	14
CRP	42	41	75	-28
ESR	64	20	107	-30
PV	44	50	75	10

$$* (\text{wk } \bar{0} - \text{wk } \bar{24}) \times 100$$

$$\text{wk } \bar{0} - \text{normal}$$

Table 3 Pearson correlation coefficients (r) on individual patient data

Drug	n	r			
		ESR v. AI	PV v. AI	CRP v. AI	ESR v. PV
D-penicillamine	68	0.658***	0.600***	0.644***	0.807***
Hydroxy-chloroquine	101	0.400***	0.420***	0.370***	0.640***
Gold	101	0.390***	0.290**	0.310**	0.750***

** = P<0.01. *** = P<0.001.

Alclofenac data omitted—insufficient data due to patient withdrawal.
AI = articular index.

Table 4 Multiple correlation coefficients (R) against a set of 7 clinical parameters

Drug	n	R		
		ESR	PV	CRP
D-penicillamine	68	0.78***	0.65***	0.78***
Hydroxychloroquine	101	0.69***	0.63***	0.66***
Gold	101	0.65***	0.70***	0.55***

*** = P<0.001.

Alclofenac data omitted—insufficient data due to patient withdrawal.

In terms of correlation with articular index alone (Table 3) little difference was observed between parameters. Slightly stronger correlations were observed for ESR with the exception of the hydroxy-chloroquine-treated group, where PV correlated more strongly. Correlation coefficients listed in Table 4 are based on multiple correlations with the set of 7 clinical parameters¹⁰ and suggest again that there is little to choose between parameters in terms of strength of correlation. Correlations listed in Tables 3 and 4 are based on individual patient data.

The relative merits of ESR, CRP, and PV as indices of disease improvement are illustrated in terms of correlation coefficients calculated on a longitudinal basis between mean data at successive clinic visits (n=8) (Table 5). In general, PV and CRP showed slightly stronger correlations with disease

Table 5 Pearson correlation coefficients (r) on mean sequential data (n = 8)

Drug	r			
	ESR v. AI	PV v. AI	CRP v. AI	ESR v. PV
D-penicillamine	0.896**	0.959***	0.931***	0.843**
Hydroxychloroquine	0.850**	0.891**	0.913**	0.697NS
Gold	0.856**	0.906**	0.954***	0.974***
Alclofenac	0.525NS	0.511NS	-0.261NS	0.480NS

** = P<0.01. *** = P<0.001. NS = Not significant (P>0.05).

improvement (measured as improvement in articular index) than did ESR. Correlations with articular index were significant for all parameters measured with the exception of the alclofenac-treated group, where correlations were poor owing to patient withdrawal, lack of response, and consequent 'baseline variability' in all parameters.

Discussion

In comparison with the ESR the PV has been shown previously to have a number of distinct advantages.² For example, its range for normal subjects is independent of age and sex and is well defined, its sensitivity is greater, becoming abnormal earlier in the disease (a small change only in the order of 0.03–0.05 centipoise has clinical significance) and the incidence of false positives and negatives is lower. In addition, reproducibility studies have indicated a very small experimental error of about 0.5%,² a figure confirmed in our own studies. Each test takes only 1 minute to perform, and interlaboratory variation is negligible. Blood specimens can be tested up to 1 week after collection in contrast to a 4-hour limit on ESR (24 hour limit for EDTA plasma).

Harkness² has also argued that PV can be used to detect 'quiescent' activity, that is, even in the absence of clinical symptoms and with a normal ESR a high PV may indicate persistent abnormalities in plasma proteins and the possibility of relapse on drug withdrawal. Our week 24 data, showing a greater incidence of patients with normal ESR and raised PV rather than vice versa, would argue in favour of this hypothesis.

The ESR has also been compared unfavourably with CRP levels,¹¹ serum CRP correlating more closely than ESR with radiographic lesions in RA.¹²

In terms of correlation with clinical status the present results show minimal differences overall between ESR, CRP, and PV (Tables 3, 4, and 5). While a slight preference could be argued for ESR or CRP for D-penicillamine-treated patients,⁵ the use of ESR is perhaps questionable only during hydroxy-chloroquine therapy owing to the lack of significant

change observed (Fig. 1 and Table 2). The failure of ESR to return towards normal despite clinical improvement has also been reported for 34 RA patients treated for 16 weeks with chloroquine.¹³ It is possible that chloroquine and hydroxychloroquine may have a specific action on erythrocytes which affects rouleaux formation and hence the ESR.

Our data indicate that PV estimations are at least as reliable as ESR and CRP in terms of diagnosis and as indices of disease activity and improvement during specific antirheumatoid drug therapy. However, in terms of both methodology and the detection of 'quiescent' disease activity PV estimations may have distinct advantages over other more traditional indices.

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