from clinically indicated knee arthrocentesis, on a patient with osteoarthritis (OA), and two with rheumatoid arthritis (RA), who had not received intra-articular injections for at least 3 months. With all specimens, exposure to air was minimized by appropriate sample collection and storage, and synovial fluid pH was within the published range for these diseases [3]. pH was measured by a Jencons PHM1 with automatic temperature compensation.

All the corticosteroid preparations had a pH near neutrality, as the pH is adjusted during manufacture. Titration curves resulted in pH values that were within the physiological range for all volume ratios. Inspection of the titration curves of the nine lignocaine-containing solutions suggested minimal buffering from the corticosteroid solutions so that the molar amount of lignocaine alone determined the pH. Thus the figures in Table I, given for the most alkaline synovial fluid obtained (OA), titrated against 2% lignocaine solution, could be extrapolated by simple proportion to other lignocaine dilutions. Titration curves obtained with the RA synovial fluid were similar, allowing for the higher hydrogen-ion concentration, but not all curves could be done in these cases because of an insufficient quantity of synovial fluid.

One ml of 1% lignocaine solution, added to 4 ml of synovial fluid, resulted in a pH of 7.16, lower than that recorded in OA (range 7.54–7.25) [3]. The lower range of pH in RA (range 7.41–6.85) [3] was exceeded at quite modest volume ratios of 2% lignocaine to OA synovial fluid, and was reached even sooner with the more acidic synovial fluid obtained from the RA patients.

These results suggest that lignocaine-containing solutions should be used with circumspection in intra-articular procedures. Intra-articular synovial fluid may be an inadequate buffer for lignocaine solutions, particularly in small joints, where common clinical practice is to use lignocaine corticosteroid mixtures [1], although some manufacturers do not recommend this practice for other reasons (Upjohn, Depo-Medrone product information). Since an isotonic buffer at pH 4.0 induces irreversible cartilage damage in rabbits, the action on cartilage of hypotonic lignocaine solutions with typical pH 4.4 may not be trivial. While there is no present evidence that articular cartilage is adversely affected by lignocaine solutions, this question should be addressed further, given the common use of such solutions.

M. L. Jenkinson

Rheumatology Unit, Guy's Hospital, London SE1 9RT, UK
Received 20 August 1987


Macrocytosis and Sulphasalazine Treatment of Rheumatoid Arthritis

SIR—Macrocytic anaemia is a recognized complication of sulphasalazine treatment in patients with rheumatoid arthritis (RA) [1, 2]. Although the mechanisms of macrocytosis are unclear, a recent report has suggested that patients who develop macrocytosis while taking sulphasalazine usually have evidence of pre-existing but subclinical, folic acid deficiency [2].

We have recently conducted a survey of the prevalence and mechanisms of macrocytosis in a consecutive series of 57 sulphasalazine-treated patients with classical or definite RA (A.R.A. criteria). The patients’ ages ranged between 21 and 87 years (mean 58.6). The mean daily dose of sulphasalazine (as the enteric-coated preparation) was 2.16 g (range 1.0–3.0) and the mean duration of treatment was 12.1 months (range 3–36).

Significant macrocytosis (MCV > 97 fl) was noted during treatment in seven cases, although one of these patients also had a macrocytic blood film before treatment (Table II). In the study group as a whole, the only significant difference between those with and those without macrocytosis was the red cell folate level during treatment. The mean (range) of the macrocytic patients was 655 (40–301) µg/l and of the remainder 247 (112–511) µg/l (p < 0.01). There was no significant correlation between the post-treatment MCV and red cell folate levels overall nor with the dose or duration of sulphasalazine treatment. The MCV fell significantly (i.e. more than 2 fl) after folic acid supplementation in four patients (patients 1, 5, 6, 7), but was not substantially changed in the remainder.

In patients 5–7, sulphasalazine therapy was con-
MEAN CORPUSCULAR VOLUME (MCV) IN SEVEN PATIENTS IN WHOM SIGNIFICANT MACROCYTOSIS WAS NOTED DURING SULPHASALAZINE TREATMENT FOR RA

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>76</td>
<td>55</td>
<td>48</td>
<td>79</td>
<td>60</td>
<td>75</td>
<td>51</td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Hb (g/dl) Before treatment</td>
<td>8.6</td>
<td>16.8</td>
<td>15.6</td>
<td>13.2</td>
<td>11.0</td>
<td>11.2</td>
<td>12.6</td>
</tr>
<tr>
<td>During treatment</td>
<td>10.7</td>
<td>16.9</td>
<td>15.6</td>
<td>12.3</td>
<td>12.6</td>
<td>10.5</td>
<td>12.4</td>
</tr>
<tr>
<td>MCV (fl) Before treatment</td>
<td>78</td>
<td>93</td>
<td>104</td>
<td>96</td>
<td>95</td>
<td>78</td>
<td>90</td>
</tr>
<tr>
<td>During treatment</td>
<td>97</td>
<td>96</td>
<td>100</td>
<td>102</td>
<td>94</td>
<td>93</td>
<td>97</td>
</tr>
<tr>
<td>Reticulocyte count (x 10^6)</td>
<td>140</td>
<td>&lt;100</td>
<td>&lt;100</td>
<td>&lt;100</td>
<td>&lt;100</td>
<td>&lt;100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Red cell folate (µg/l)</td>
<td>&lt;40</td>
<td>298</td>
<td>301</td>
<td>123</td>
<td>104</td>
<td>112</td>
<td>167</td>
</tr>
<tr>
<td>Serum B₁₂ (ng/l)</td>
<td>163</td>
<td>660</td>
<td>292</td>
<td>189</td>
<td>140</td>
<td>168</td>
<td>303</td>
</tr>
<tr>
<td>Contributory factors to macrocytosis</td>
<td>Haemolysis +ve</td>
<td>Heinz bodies</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Poor diet</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
</tr>
</tbody>
</table>

Reference ranges: Hb 11.5–16.5 (female), 13.0–18.0 (male) g/dl; MCV 78–96 fl; reticulocyte count <100 x 10⁶/l; red cell folate 120–700 µg/l; serum B₁₂ 160–960 ng/l.

continued, along with folic acid supplements and the MCV was maintained within normal limits. In three further cases (patients 2–4), the drug was continued despite the raised MCV with no obvious adverse effects. In one patient who had a combination of haemolysis and folic acid deficiency, the sulphasalazine eventually had to be withdrawn because of progressive anaemia (patient 1).

These findings confirm that macrocytosis is a common feature of sulphasalazine treatment in RA [1,2]. In this study, 6/57 (10.5%) patients developed macrocytosis while taking sulphasalazine compared with previously reported incidences of 6.7% to 14% [1,2]. In contrast with the findings of Prouse et al. [2] who found evidence of folic acid deficiency in all cases of macrocytosis associated with sulphasalazine treatment, folate deficiency could be clearly incriminated as an aetiological factor in only four of our patients; those in whom a substantial rise in MCV occurred during treatment (i.e. >5 fl) which was reversed by a course of oral folic acid. Moreover, in one of these, a contributory factor was drug-induced haemolysis. In three further cases, the macrocytosis responded poorly to folic acid therapy, and did not appear to be due to haemolysis, suggesting that the drug may have a direct effect on red cell morphology in some cases.

Our findings confirm that folic acid deficiency is a common and easily treatable cause of macrocytosis in patients taking sulphasalazine therapy for RA. Failure of macrocytosis to respond to folic acid suggests the presence of an underlying haemolytic state, or a nonfolate-dependent effect of sulphasalazine on red cell morphology.

The authors wish to thank Drs. I. R. McNeill and J. W. Whitelaw of the Haematology Department for their helpful comments.

S. H. RALSTON*
LORNA J. WILLOCKS
R. W. SHAW
D. A. PITKEATHLY

Rheumatology Unit,
Medical Unit A,
Southern General Hospital,
Glasgow, UK
* Present address: Centre for Rheumatic Diseases,
Glasgow Royal Infirmary, Glasgow G4 0SF, UK.
Received 27 August 1987


Adenocarcinoma of the Lung Presenting with Raynaud’s Phenomenon, Digital Gangrene and Multiple Infarctions in the Internal Organs

SIR—Digital ischaemia and gangrene have been described in association with a number of systemic disorders including arteriosclerosis, diabetes mellitus and the collagen vascular disorders, systemic lupus erythematosus, polyarteritis nodosa and scleroderma. It has also been noted to occur in disseminated intravascular coagulation, cold agglutinaemia and with the thoracic outlet syndrome [1].