Sulphasalazine in rheumatoid arthritis

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Summary and conclusions
Seventy-four patients with rheumatoid arthritis were treated with sulphasalazine. There was a significant improvement in clinical score, with substantial falls in serum C-reactive protein concentrations and erythrocyte sedimentation rate four weeks after starting the drug. Improvement was maintained in the 38 patients who remained on the drug for one year. The mean Rose-Waaler titre did not change. There was little difference between the results in seropositive and seronegative patients. The commonest adverse effect was dyspepsia, but five patients developed a megaloblastic anaemia and one patient neutropenia; all made a complete recovery.

The results suggest that the drug has a disease-modifying action not attributable to its "salicylate" content. The mode of action might be by an antibacterial effect on gut flora.

Introduction
The finding that dapsone is effective in rheumatoid arthritis (RA) led us to consider related alternatives. We had studied dapsone partly because of its effect in leprosy and dermatitis herpetiformis; its mode of action in those diseases may be through its immunosuppressant properties. Another drug used in dermatitis herpetiformis is sulphapyridine; it did not attract us as a contender but it is a constituent of salicyl-azo-sulphapyridine (sulphasalazine), a compound originally formulated for RA and latterly found to have immunosuppressant properties. The early trials of sulphasalazine in rheumatoid arthritis produced conflicting results; our recent pilot study encouraged us to perform a larger investigation of the effects of sulphasalazine over period up to a year in 74 patients with rheumatoid arthritis.

Patients and methods
We studied 74 patients with definite or classical rheumatoid arthritis (according to the criteria of the American Rheumatism Association). Each patient had clinically active disease with a serum C-reactive protein concentration of over 20 mg/l or an erythrocyte sedimentation rate (ESR) of over 20 mm in the first hour.

Six patients stopped sulphasalazine within 28 days and their data are excluded from the results; they are accounted for under "adverse effects." The remaining 68 patients, 52 women and 16 men, had a mean age of 51.7 years (range 20-77 years) and a mean duration of rheumatoid arthritis of 8.1 years (range 3 months-33 years). Thirty-nine patients were seropositive with Rose-Waaler titres of 1/32 or greater. All patients were taking a non-steroid anti-inflammatory drug, but no other drugs were used. Forty patients had previously been treated with disease modifying drugs. In only six cases was the interval between stopping these drugs and starting sulphasalazine less than six months.

After a preliminary assessment period of six weeks, enteric-coated sulphasalazine was started at an initial dose of 0.5 g daily, increasing by 0.5 g increments at weekly intervals to a usual maintenance dose of 2 g per day.

Subjective clinical state was recorded as clinical score. At the first visit each patient was allotted an arbitrary score of 100. Subsequently, at every visit the patient was asked whether he felt better, worse, or the same compared with last time. The score of 100 was altered by +2 or if better, −2 if worse. These cumulative scores were standardised to 100 at the start of treatment with sulphasalazine. Serum C-reactive protein was measured by radial immunodiffusion and ESR by the Westergren method.

Patients did not attend at exactly regular intervals, and time points (±14 days) with the largest number of results were chosen for data analysis. Student's t test for paired variants was used to assess significance.

Results
During the six-week preliminary period of treatment with a non-steroid anti-inflammatory drug there was slight subjective clinical deterioration and there were minor, but not significant, changes in mean serum C-reactive protein and ESR (see table).

At the start of treatment with sulphasalazine mean serum C-
reactive protein was 64-1 mg/l and mean ESR 58-4 mm in the first hour. Four weeks after starting sulphasalazine there was a significant increase in clinical score and there were significant falls in mean C-reactive protein and ESR (see table). Clinical score continued to rise until 34 weeks and then did not change. Mean serum C-reactive protein changed little after the first four weeks but mean ESR continued to fall.

The data for the seropositive (judged by the Rose-Waaler test) and seronegative patients were analysed separately. In both groups mean clinical score rose and mean serum C-reactive protein and mean ESR fell (see figure); the correspondence between the two groups was close.

Throughout the study the number of patients fell, though this trend was very small after 34 weeks. Principal reasons were failure to respond (18 patients) and adverse effects (7 patients).

### C-reactive protein and ESR from baseline values after treatment with sulphasalazine. Values are mean differences ± SE

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Clinical score</th>
<th>C-reactive protein (mg/l)</th>
<th>ESR (mm in 1 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
<td>Difference from baseline</td>
<td>No of patients</td>
</tr>
<tr>
<td>0</td>
<td>60</td>
<td>0.5 ± 0.2**</td>
<td>60</td>
</tr>
<tr>
<td>+4</td>
<td>74</td>
<td>100</td>
<td>74</td>
</tr>
<tr>
<td>+10</td>
<td>59</td>
<td>2.3 ± 0.3**</td>
<td>56</td>
</tr>
<tr>
<td>+18</td>
<td>54</td>
<td>3.6 ± 0.4**</td>
<td>53</td>
</tr>
<tr>
<td>+26</td>
<td>45</td>
<td>7.7 ± 0.5**</td>
<td>41</td>
</tr>
<tr>
<td>+34</td>
<td>41</td>
<td>5.0 ± 0.5**</td>
<td>41</td>
</tr>
<tr>
<td>+42</td>
<td>32</td>
<td>5.0 ± 0.7**</td>
<td>32</td>
</tr>
<tr>
<td>+50</td>
<td>31</td>
<td>5.0 ± 0.7**</td>
<td>31</td>
</tr>
</tbody>
</table>

Difference significant at *p* < 0.01 level, **p** < 0.0005 level.

Adverse effects—The six patients who stopped sulphasalazine treatment within 28 days did so because they felt "light headed," had headaches, or felt no improvement in their rheumatoid arthritis. The commonest side effects subsequently were nausea and dyspepsia, but only four patients had the stop the drug because of gastrointestinal symptoms after the first 28 days. Five patients developed megaloblastic anaemia and one other patient had a rising mean corpuscular volume without change in haemoglobin. Three of them had a low serum folate concentration and one a low serum B12. Two had low

values for both measurements. The most serious side effect, neutropenia in one patient, recovered rapidly when sulphasalazine was stopped.

### Discussion

The results showed clinical improvement as well as large falls in serum C-reactive protein and the ESR in the 68 patients who had more than four weeks' treatment with sulphasalazine. The falls in serum C-reactive protein and the ESR are important for they do not occur during treatment with non-steroid anti-inflammatory drugs.9 Such changes suggest that sulphasalazine has an effect qualitatively different from that of the non-steroid anti-inflammatory agents and may have a "disease-modifying" action rather than merely a temporary anti-inflammatory effect. After one year the average results, C-reactive protein 36 mg/l and ESR 30 mm in the first hour, were still higher than desirable. We have not found that other drugs—for example, gold, dapsone, or prednisone—perform significantly better, though the reasons for their limitations are different.

Compared with most other second-line drugs used for rheumatoid arthritis, notably gold and penicillamine, sulphasalazine had few serious adverse effects, and only a few of the patients did not continue the drug. The frequency of dyspepsia in the early stages was reduced by using the enteric-coated preparation and by a gradual increase in dose. The frequency of megaloblastic anaemia was surprising as there is only one other case report10 of sulphasalazine-induced megaloblastic anaemia in ulcerative colitis. The anaemia was usually due to folate deficiency (we shall report the cases in more detail later); possibly the phenomenon reflects the brittle state of folate metabolism in rheumatoid arthritis, though it is hard to see why this should be since sulphasalazine traverses the jejunal unaltered. The occurrence of neutropenia was not surprising since a metabolite of sulphasalazine is sulphapyridine.

Recent work has suggested that 5-aminosalicylic acid is the active moiety of sulphasalazine in the treatment of ulcerative colitis, inhibiting prostaglandin synthesis in the bowel wall. This is unlikely to explain its effect in rheumatoid arthritis for two reasons: firstly, 5-aminosalicylic acid is poorly absorbed from the gut lumen11 and, secondly, salicylates do not lower acute-phase protein levels. Sulphasalazine is "immuno-suppressant," at any rate in vitro, and modifies adjuvant arthritis in rats.2 12 It is also antibacterial and capable of altering gut flora;13 the suggestion has been made that rheumatoid arthritis may be an enteropathic arthropathy.14 The action of sulphasalazine in rheumatoid arthritis might be related to either of these properties.

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Prolongation of canine pancreas allograft survival with cyclosporin A: preliminary report

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Summary and conclusions

Studies were conducted on dogs to test the efficacy of cyclosporin A (CyA) in prolonging normoglycaemia and graft survival after whole-organ pancreas allograft transplantation. Five dogs subjected to pancreactectomy alone served as controls.

Withholding immunosuppression after transplantation (five animals) resulted in the same median duration of survival as occurred in the controls (13 days). Azathioprine and steroids (seven animals) produced median durations of normoglycaemia and survival of 9 and 23 days respectively. Animals given CyA 18 mg/kg/day (five) and 25 mg/kg/day (10), however, showed median durations of normoglycaemia of 18 and 55 days (p < 0.05 and p < 0.02) respectively and median survival times of 36 and 85 days (NS and p < 0.05).

If CyA proved effective in controlling rejection of pancreas allografts in man it would offer useful diabetics in renal failure a more hopeful outlook than conventional immunosuppression.

Introduction

Many children with insulin-dependent diabetes develop complications of their disease, and their life span is greatly reduced. Renal failure accounts for an increasing number of deaths, and after three years the survival of diabetics receiving dialysis is less than half that of non-diabetics receiving dialysis. Cadaveric renal transplantation is also less successful in diabetic patients, with an increased morbidity and a reduction in patient and graft survival. Transplantation of the pancreas has been tried to improve carbohydrate control by producing a more consistent biological release of insulin, but the results of both islet and whole-organ grafting are disappointing. Rejection is difficult to control, and using steroids may disturb carbohydrate metabolism. Thus to find an alternative to steroids in controlling rejection we have tested the non-steroidal fungal metabolite cyclosporin A (CyA).

Materials and methods

Unrelated mongrel dogs were studied. As controls we used five animals (group 1) subjected to total pancreactectomy under general anaesthesia, great care being taken to remove all pancreatic tissue. In the other animals (groups 2-5) total pancreactectomy was followed by transplanting a whole-organ pancreas allograft heterotopically in the right iliac fossa, the donor coeliac axis being anastomosed to the external iliac artery, and the donor portal vein end-to-side to the recipient iliac vein. The main donor pancreatic duct was occluded by direct ligation or by ligation and 2 ml latex duct injection.

In group 2 (five animals) immunosuppression was withheld after transplantation; in group 3 (seven animals) transplantation was followed by treatment with azathioprine 3 mg/kg and prednisolone 1.5 mg/kg daily; in group 4 (five animals) transplantation was followed by CyA alone 18 mg/kg/day, and in group 5 (10 animals) transplantation was followed by CyA 25 mg/kg daily. Normoglycaemia was recorded only when random non-fasting blood sugar concentrations postoperatively remained less than twice the preoperative fasting value.

Results

Transplantation without immunosuppression (group 2) did not prolong survival as compared with pancreactectomy alone, and the median duration of normoglycaemia was four days as compared with less than one (table 1). Animals given azathioprine and steroids (group 3) showed a median period of normoglycaemia of nine days and a median survival of 23 days (p < 0.05; Mann-Whitney two-sample non-parametric test). Animals given CyA, however, both at

References


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