Correspondence

Inhibitory effect of sodium aurothiomalate on a chronic inflammatory model in the rat

SIR. The effects of gold salts in adjuvant arthritis have for a long time been subject to discussion, and in a recent report the authors found that pretreatment of rats for three months with sodium aurothiomalate (NATM) exacerbated the severity of the subsequent adjuvant arthritis. Like other workers we have found it possible to inhibit adjuvant arthritis in the rat with NATM, and the experiment described here may be of interest.

Male Wistar rats (OLAC) initially weighing 190–240 g received an injection into the right hind paw of 0.5 mg dead Mycobacterium tuberculosis cells in 0.1 ml mineral oil. NATM 13.5 or 3.4 mg/kg was administered by injection into the thigh muscle daily for 14 days, starting at the time of adjuvant injection, the site being alternated between left and right limbs to reduce the risk of necrosis. Controls received intramuscular saline, and another group of animals were given indomethacin 2 mg/kg orally. The disease was monitored regularly for 28 days by measurement with calipers of the injected paw depth and by a subjective scoring system after the onset of secondary arthritis. A count was made of the affected joints of all four limbs and the ears and tail, with a weighting being given for severity of inflammation such that the theoretical maximum score for each animal was 28. The person performing the measurements was aware of the treatment of each group. Bodyweight changes were recorded throughout the experiment, and at termination the post-mortem thymus and spleen weights were measured.

The effects of NATM on the arthritis are summarised in Table 1 and show a dose-related inhibition of both the injected paw depth and the arthritis score. With NATM, unlike indomethacin, no antagonism was seen of the acute paw swelling at day 3. At day 28 the animals which had received NATM 13.5 mg/kg showed an enhanced bodyweight gain over arthritic control animals, and both doses of NATM showed a reversal of disease-associated organ weight changes (Table 2).

Table 1 The effect of NATM on adjuvant-induced arthritis

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg/kg) and route</th>
<th>Mean right paw depth (mm±SE)*</th>
<th>Mean change in body weight from day 0 (g±SE)</th>
<th>Mean arthritis score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 3</td>
<td>Day 14</td>
<td>Day 28</td>
<td>Day 3</td>
</tr>
<tr>
<td>Saline</td>
<td>—</td>
<td>6.5</td>
<td>8.6</td>
<td>10.5</td>
</tr>
<tr>
<td>IM</td>
<td>±0.2</td>
<td>±0.4</td>
<td>±0.5</td>
<td>±0.5</td>
</tr>
<tr>
<td>NATM 13.5</td>
<td>±0.2</td>
<td>6.5</td>
<td>7.6†</td>
<td>8.6†</td>
</tr>
<tr>
<td>IM</td>
<td>±0.2</td>
<td>±0.4</td>
<td>±0.5</td>
<td>±0.5</td>
</tr>
<tr>
<td>NATM 3.4</td>
<td>±0.2</td>
<td>6-4</td>
<td>7.2†</td>
<td>8-9†</td>
</tr>
<tr>
<td>IM</td>
<td>±0.2</td>
<td>±0.4</td>
<td>±0.5</td>
<td>±0.5</td>
</tr>
<tr>
<td>Indomethacin 2</td>
<td>±0.2</td>
<td>±0.4</td>
<td>±0.5</td>
<td>±0.5</td>
</tr>
<tr>
<td>p.o.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Normal uninflamed paw = 4.5 mm.

†p<0.05 | Difference from control.
‡p<0.01 | Student's t test.
§p<0.001 | Mann-Whitney U test.
IM=intramuscularly; p.o.=orally.

Compounds administered days 0–13 inclusive.

Each group consisted of eight rats and there were no deaths.
A recent review has suggested that reports of gold salts being inhibitory to adjuvant arthritis following parenteral administration may be explained by counterirritancy. While we cannot completely preclude this possibility, the following points seem relevant. The injection sites were examined daily and no signs of irritation or necrosis were observed, the animals were not distressed, and there were no adverse effects on bodyweight gain. NATM had no effect on the acute indomethacin-sensitive inflammation at day 3, but the secondary arthritis was inhibited in a dose-dependent manner, with the activity being maintained for 14 days after cessation of dosing. Finally, the systemic non-inflammatory disease was modified, with NATM reversing the thymic regression and splenic hypertrophy seen in adjuvant arthritic rats.

These results are similar to those obtained by Walz et al., who in addition showed a correlation between antiarthritis activity and serum gold levels. It appears that under certain conditions adjuvant-induced arthritis in the rat can be used to evaluate the efficacy of gold salts.

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References
3 Sofia R D, Knoblock L C, Douglas J F. Effect of concurrent administration of aspin, indomethacin or hydrocortisone with gold sodium thiomolate against adjuvant-induced arthritis in the rat. Agents Actions 1976; 6: 728-34.

Hypogammaglobulinaemia associated with gold therapy

Sir, The recent report of two patients with hypogammaglobulinaemia associated with gold therapy prompts me to report the case of a man with seronegative rheumatoid arthritis who developed hypogammaglobulinaemia while on gold therapy. The development of hypogammaglobulinaemia coincided with a complete clinical remission. His immunoglobulin levels have returned to normal, and he has remained in remission for nearly five years.

The patient was well until 1976 when at age 46 he developed a symmetrical polyarthritis. The latent fixation test was negative. In April 1978 despite salicylate therapy and naproxen 250 mg twice a day, he still had persistent active synovitis of the wrists, metacarpophalangeal joints, proximal interphalangeal joints, knees, and metatarsophalangeal (MTP) joints. The latex test was again negative. Radiographs of the hands were normal, but the feet showed small erosions of the right third and left fifth MTP joints. The serum IgG level was raised, and serial levels are shown in Table 1. He was started on sodium aurothiomalate 50 mg intramuscularly (IM) weekly, and by December 1978 he was markedly improved with only synovitis of both wrists. However, serum levels of IgA and IgM had fallen below normal levels. He was continued on gold 25 mg IM monthly and was seen again in January 1980 when he was in complete remission. However, his serum IgG level had fallen below normal. Gold was discontinued as were the salicylates and naproxen, and his immunoglobulin levels returned to normal. No infections occurred during the course of his illness. He remains in clinical remission, and radiographs of his hands and feet remain unchanged.

It is interesting to speculate whether there is a relationship between the development of hypogammaglobulinaemia and the excellent response to gold seen in this patient.

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Reference

Non-steroidal anti-inflammatory drugs and adverse renal effects

Sir, We read with interest the report by Sellars et al. of the induction of nephrotic syndrome and renal impairment by non-steroidal anti-inflammatory drugs.