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References

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We have investigated 17 patients with two diphosphonate scans of their hands one year apart as we were also concerned with the value of a single isotope scan. We have calculated the scintigraphical activity of each joint, max-

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We believe our original observation that increased uptake of isotope may be associated with some, but not all erosions, still stands and that isotope uptake probably reflects other processes of acute inflammation unassociated with the development of an erosion.

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Sulphasalazine hepatotoxicity: lack of a hypersensitivity response

SIR. Dr Farr and colleagues report two cases of suspected sulphasalazine hepatotoxicity in rheumatoid patients. The absence of hepatic histology and drug rechallenge, and the failure to exclude other possible explanations (for example extrahepatic biliary obstruction in case 1) makes these presumptive diagnoses based solely on the temporal relation of the biochemical abnormalities to the sulphasalazine administration. The authors fail to clarify the exact timing of these abnormalities in relation to drug administration. Also, in case 2 there was only a twofold rise in an already abnormal alkaline phosphatase level, which had still not returned to its pretreatment level three weeks after the drug was stopped. The case for a drug related phenomenon remains uncertain.

If the hepatic enzyme rises are accepted as probably drug induced, however, there is a more important aspect to note. namely the lack of a clinical hypersensitivity reaction. All but one of the 17 cases in the literature of sulphasalazine hepatotoxicity in inflammatory bowel disease showed such a reaction, comprising fever, lymphadenopathy, and peripheral eosinophilia. We wish to draw your readers’ attention to another rheumatoid patient who developed sulphasalazine hepatotoxicity, in whom this hypersensitivity reaction was also notably absent.

Case history

A 50 year old woman with rheumatoid arthritis developed anorexia, nausea, and upper abdominal pain after 11 weeks of sulphasalazine therapy at a dose of 3 g/day. She was anicteric and had no fever, lymphadenopathy, skin rash, or any stigmata of liver disease. Hepatic transaminases, which had been normal immediately before treatment, were now markedly raised (see Table). There was no history of jaundice, hepatitis contact, or blood transfusion, she had not travelled abroad, and her only other medication was ketoprofen, which she had been receiving for 18 months. Screening for hepatitis A and B, cytomegalovirus, Epstein-Barr, and herpes simplex viruses was negative. Upper abdominal ultrasound was normal, and antibodies to smooth muscle and mitochondria were not detected. A liver biopsy showed a severe acute hepatitis with focal

Table 1  Scintigraphical activity score of rheumatoid joints with new, healed, and unchanged erosions

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<tr>
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<tr>
<td>4</td>
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<td>11</td>
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<tr>
<td>1</td>
<td>128</td>
<td>5</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>117</td>
<td>3</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
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necrosis, an intense inflammatory reaction, and conspicuous numbers of eosinophils. When sulphasalazine was stopped there was an immediate fall in her hepatic transaminases, which returned to normal after 17 days. Rechallenge was not considered justifiable in view of the risk of a potentially fatal reaction. Non-A, non-B viral hepatitis cannot be disproved in this case, but there are morphological clues to a drug induced aetiology, e.g., the prominence of eosinophils, and these, together with the prompt clinical response to drug withdrawal, strongly favour sulphasalazine as the hepatotoxin in this patient.

Thus, not surprisingly, sulphasalazine can cause hepatic damage in rheumatoid arthritis as well as in inflammatory bowel disease. This may be a more frequent problem in the former condition than in the latter and appears to be less frequently accompanied by a clinical hypersensitivity reaction. Rheumatologists using sulphasalazine should be aware of this hepatotoxic potential.

References

SIR, We are glad to see that MacGilchrist and Hunter agreed with our findings that sulphasalazine can cause hepatotoxicity, which may be more common than is generally appreciated in rheumatoid arthritis. Their initial comments about the problems of ‘proving’ a drug cause for hepatotoxicity are, of course, correct—and are indeed well illustrated in their own case since they also felt it unethical to rechallenge.

The Glasgow observations strengthen the hypothesis that sulphasalazine does indeed induce hepatotoxicity. Perhaps these letters will prompt further confirmatory reports which will lead to an acceptable clinical paradigm. This would be helpful in clinical practice even though it cannot be formally proved. The questions of its frequency and of the lack of a clinical hypersensitivity response clearly require further elucidation in relation to the underlying disease, since rheumatoid arthritis may affect both the frequency and the nature of such responses. It may be pertinent that we have now seen a third patient who developed raised liver enzymes while on sulphasalazine therapy for rheumatoid arthritis. In addition, this patient did have signs of a clinical hypersensitivity reaction, as is well described with patients with inflammatory bowel disease. Thus not all rheumatoid patients lack the hypersensitivity response.

Department of Rheumatology, University of Birmingham, Birmingham B15 2TJ

PAUL A BACON
MARGARET FARR
DEBORAH SYMONS

968 Correspondence, Note

Table

<table>
<thead>
<tr>
<th>Liver function tests</th>
<th>Weeks receiving sulphasalazine</th>
<th>Weeks not receiving sulphasalazine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Aspartate transaminase (12–42 IU/l)*</td>
<td>18</td>
<td>609</td>
</tr>
<tr>
<td>Alanine transaminase  (8–55 IU/l)</td>
<td>30</td>
<td>1449</td>
</tr>
<tr>
<td>Alkaline phosphatase (21–130 IU/l)</td>
<td>114</td>
<td>230</td>
</tr>
</tbody>
</table>

*Normal range given in parentheses.

University Department of Materia Medica, Stobhill General Hospital, Glasgow
Gartnavel General Hospital, Glasgow

References

Note

1st Asean Congress of Rheumatology

This congress will be held from 18–21 January 1987 in Jakarta, Indonesia. Further details from the Secretariat, PO Box 34, Palmerah, Jakarta Barat, Indonesia. (See advertisement inside back cover, September issue.)
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A J MacGilchrist and J A Hunter

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