Peptic ulcer in rheumatoid arthritis

Sir, A report appeared recently in the Annals of 230 patients with arthritis, 185 with rheumatoid arthritis (RA), who were found to have ‘peptic ulcer’ associated with non-steroidal anti-inflammatory drug (NSAID) treatment in an uncontrolled fashion.1 Fifty-six of those patients with RA were then reported to be treated for up to 12 weeks with ranitidine, with a cumulative 90% healing rate of peptic ulcers.

We have recently reported on 238 patients with RA in a double blind, endoscopy controlled study with the prostaglandin E2 analogue misoprostol v placebo.2 Over 20% of the patients in that study receiving therapeutic doses of aspirin were found to have ulcer crater disease. With continuing aspirin treatment over a three month period 70% of the ulcer craters persisted in the group receiving placebo, with bleeding on several occasions. Over 70% of the ulcer craters resolved with misoprostol treatment. In a subsequent paper we reported over 500 patients with osteoarthritis who were screened by endoscopy; 25% were found to have ulcer crater disease.3 Of the 75% without ulcer crater disease, over 20% went on to develop ulcer craters in the placebo group, while maintaining their usual NSAIDs (naproxen, ibuprofen, piroxicam). The half, receiving therapeutic doses of misoprostol, however, did not develop ulcers over the three months of the study, with the exception of a small percentage. These two large multicentre studies indicate the importance of controlled trials and a large data base when considering such complex issues as whether RA has a unique potential for ulcer crater disease compared with a non-systemic disease such as osteoarthritis. We have previously reviewed accumulating reports that there is as yet no conclusive evidence to indicate that patients with RA are more prone to ulcer disease than those with osteoarthritis in association with extended NSAID treatment.4 5 This review included a one year study of 101 patients receiving an H2 antagonist, cimetidine, compared with those receiving placebo. There was no significant difference between the two groups in mucosal lesion progression, and over 20% ulcers were found at baseline in that study.6 This contrasts with the report of Farah et al of uncontrolled ranitidine treatment, though a different H2 receptor/antagonist was used and the dosage schedule was also different.

Furthermore, another article reported in the Annals on prostaglandin E2 treatment for RA was an uncontrolled trial with only 12 patients.7 The authors correctly admit that ‘doctor’s bias and possible placebo effects or a spontaneous improvement in disease activity’ may explain the suggested improvement in RA associated with that short six week trial. This experience was not confirmed by our double blind study of 238 patients with RA, in which there was no difference in any of the usual clinical and laboratory parameters between those receiving prostaglandin or placebo.2

We have previously considered the importance of separate terminology for NSAID gastropathy as distinct from classic peptic ulcer disease on the basis of apparent differences in pathophysiology (NSAID prostaglandin inhibition of hyperacidity), anatomic location (primarily antral, prepyloric v duodenal), demographics (more often elderly women than younger men), and even differences in clinical pattern (often asymptomatic NSAID gastropathy and universal responsiveness to H2 receptor antagonists of acid peptic disease).8 Non-steroidal anti-inflammatory drug gastropathy is not a new iatrogenic disorder,9 rather, we are newly coming to realistic terms with this problem as it assumes dimensions affecting public health and now requires class labelling of NSAIDs for ‘risk of gastrointestinal ulcerations, bleeding, and perforation’ by the US Food and Drug Administration. We have recently reported that this difficult to recognise, difficult to prevent threat of common NSAID treatment now requires a responsible response from present medical practice.10

Arthritis Center Ltd, Phoenix, Arizona, USA

SANFORD H ROTH

References

Sir, We would agree with the comments which Dr Roth makes but would point out that our own study was not set
up as a double blind, controlled endoscopy study comparing
an ulcer healing agent with placebo. As can be seen from
our paper¹ the study described was in two parts, the first
being a survey of patients routinely attending a rheumato-
logy outpatient clinic and the second phase of the study
consisting of a report of the effects of an ulcer healing
agent on non-steroidal anti-inflammatory drug (NSAID)
induced peptic ulceration with the NSAID continued
throughout treatment. The discrepancy between the preva-
ience of peptic ulceration in our patient population
compared with that described by Dr Roth could possibly
be due to patient selection and the type of population
studied. In our own study we showed that smoking was an
important risk factor in the development of the peptic
ulceration in the rheumatoid population and yet this is a
variable which is not always taken into account in
previously reported studies of the prevalence of peptic
ulceration in rheumatic disease. We would entirely agree
with Dr Roth's comments that separate terminology
should be used for NSAID gastropathy as one of the
problems of multicentre studies is the standardisation
of the criteria for gastric ulceration and the grading of
mucosal lesions in this group of patients. Whether
rheumatoid arthritis itself may predispose to peptic ulcer-
ation is an open question, and further studies with large
numbers of patients whose demographic characteristics are
carefully standardised will be required to answer this.

Centre for Rheumatic Diseases,  
Royal Infirmary,  
Glasgow G4 0SF

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Hepatitis induced by
non-steroidal anti-inflammatory
drugs

Sir, We read with interest the letter by Llorca et al entitled
'Changing the class of NSAID in cases of hepatotoxicity'.¹
We would like to draw attention to the incidence and
clinical features of this side effect.

In 1985 the French drug surveillance centres collected 56
cases (37 women and 19 men) of hepatitis associated with
non-steroidal anti-inflammatory drug (NSAID) adminis-
tration.² They consisted of acute cytolitic (24), acute
cholestatic, (nine) or mixed (15) hepatitis. The remainder
included subclinical biochemical abnormalities such as an
increase of serum aminotransferase (four) or serum
alkaline phosphatase (four). Most patients recovered after
the drug was stopped. Three patients died, however, of
fulminant hepatitis due to pirprofen (two cases) and
niflumic acid (one case).

Moreover, this study allowed the classification of
NSAIDs according to the incidence of hepatitis, expressed
as the number of cases by months of treatment (Table 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence of hepatitis</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1/50 000</td>
<td>Oxyphenbutazone, isoxicam, pirprofen, sulindac</td>
</tr>
<tr>
<td>2</td>
<td>1/100 000 to 1/100 000</td>
<td>Fenbufen, Ibuprofen, indomethacin, ketoprofen</td>
</tr>
<tr>
<td>3</td>
<td>1/500 000</td>
<td>Diclofenac, piroxicam</td>
</tr>
<tr>
<td>4</td>
<td>1/1500 000</td>
<td>Flurbiprofen, sodium naproxen, niflumic acid, tiaprofenic acid</td>
</tr>
</tbody>
</table>

Finally, hepatitis is a relatively rare side effect, but it has
been reported to occur with almost all the NSAIDs
commonly in use.³ Although NSAID hepatotoxicity cannot
be predicted, the following measures may limit its serious-
ness: (a) If clinical signs appear, even non-specific ones
such as asthenia, fever, abdominal pain, or vomiting,
the administration of NSAIDs should be interrupted and a
serum liver test should be carefully carried out, especially
if these signs are unusual for the patient; (b) In a patient
with a history of NSAID induced hepatitis the readminis-
tration of the same drug must be strictly avoided. As cross
hepatotoxicity between different NSAIDs of the same
chemical class has been reported⁴ an NSAID of a different
chemical structure should be used.¹

Centres de Pharmacovigilance  
de Nancy et Paris,  
Fernand Widal et  
INSERM U 24,  
Paris, France  
PATRICK NETTER  
ANNE CASTOT  
DOMINIQUE LARREY  
PATRICK CARLIER  
BERNARD BANNWARTH  
PHILIPPE TRECLOT

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S H Roth

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