Comparison of the single dose pharmacokinetics of sulphasalazine in rheumatoid arthritis and inflammatory bowel disease

C Astbury, A J Taggart, L Juby, L Zebouni, H A Bird

Abstract
The pharmacokinetics of sulphasalazine and its principal metabolites in rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) were compared. Patients with RA had a significantly greater concentration of plasma sulphapyridine than patients with IBD (medians 14.0 μg/ml and 7.4 μg/ml respectively). Patients with RA also tended to maintain a higher plasma sulphapyridine concentration with time, as determined by the area under the curve (AUC), but a lower plasma sulphasalazine AUC than patients with IBD. It is suggested that more sulphasalazine may be presented to the lower bowel for cleavage to sulphapyridine and 5-amino-salicylic acid in patients with RA than in IBD. Patients with RA may also have impaired metabolism of sulphapyridine as a consequence of their disease. Together these factors may contribute to higher peak circulating sulphapyridine concentrations and may be responsible for the higher incidence of side effects of sulphasalazine treatment in patients with RA than in patients with IBD.

Since its 'rediscovery' by rheumatologists in the late 1970s sulphasalazine has become established as a second line agent for the management of rheumatoid arthritis (RA). Its use in this disease is marred, however, by a high incidence of side effects which may include nausea, vomiting, and headaches. About 20 to 30% of patients with RA develop these adverse effects when treated with 2 g/day of enteric coated sulphasalazine. This contrasts with patients with inflammatory bowel disease (IBD): less than 10% develop these side effects with 2 g/day of plain sulphasalazine.

The occurrence of non-idiiosyncratic side effects to sulphasalazine in IBD has been attributed to high circulating concentrations of total sulphapyridine, and patients who are slow acetylators with a greater plasma concentration of free and total sulphapyridine are more prone to gastrointestinal adverse effects to sulphasalazine both in RA and IBD. Acetylator status cannot be the sole determinant of adverse effects to sulphasalazine because the ratio of fast:slow acetylators in RA without Sjogren’s syndrome, and in IBD, is the same as that observed in the normal white population. Yet patients with RA develop more side effects to sulphasalazine than patients with IBD. The difference in degree of sulphasalazine toxicity between the two disease states may be due to differences in the pharmacokinetic handling of the drug.

Methods
Thirteen patients with classical or definite RA and eight patients with IBD (six with ulcerative colitis, two with Crohn’s disease) were recruited to the study. In patients with RA other second line treatment and non-steroidal anti-inflammatory drugs were discontinued before and throughout the study period. In both disease groups all other drugs were stopped, where possible.

Patients were excluded from the study if they had a history of bowel surgery, sulphasalazine intolerance, had more than two bowel movements a day, or had previously experienced rectal bleeding.

Patients were not allowed to eat or drink after 22.00 hours on the night before the study. On the morning of the study a Teflon coated intravenous cannula was inserted into a forearm vein and a blood sample removed in a tube containing lithium heparin. Plain sulphasalazine 2 g (in four 500 mg tablets) was taken orally with water. Further hourly blood samples were taken until eight hours after sulphasalazine; thereafter blood samples were taken at four hourly intervals until 32 hours after sulphasalazine administration. Blood samples were centrifuged at 550 g for 10 minutes within one hour of collection and the plasma was aliquoted into plain tubes and stored at −20°C until analysis. Dietary restrictions were lifted three hours after receiving sulphasalazine. Plasma sulphasalazine, sulphapyridine and N-acetylsulphapyridine concentrations were determined by high performance liquid chromatography with ultraviolet detection.

Acetylator phenotypes were determined either by a modification of the Bratton and Marshall technique or from the concentrations of free and acetylated sulphapyridine, 24 hours after sulphasalazine administration. Plasma sulphasalazine, sulphapyridine, and N-acetylsulphapyridine concentrations versus time profiles were determined for each patient. Maximum concentration (Cmax) and time to reach this (Tmax) were determined from these profiles. The elimination rate constants (Kel) and plasma half lives (t1/2) of sulphasalazine, sulphapyridine, and N-acetylsulphapyridine were calculated by log linear regression analysis. The areas under the drug concentration versus time curves (AUC) were determined by the trapezoidal rule and extrapolated to infinity.

Results obtained from both sets of patients were compared by the Mann-Whitney U test.

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Results
The groups of patients with RA and IBD were well matched in terms of age, sex, and acetylator status, but patients with RA had a significantly greater serum C reactive protein concentration than the group with IBD (6.5 mg/l and 0.0 mg/l respectively; p<0.01) (table 1).

In both groups of patients sulphasalazine was detected in plasma within one hour of taking the drug and most patients reached peak sulphasalazine concentrations within two to six hours. Sulphapyridine and N\(^4\)-acetylsulphapyridine did not appear in plasma until four to six hours after receiving sulphasalazine. Peak sulphapyridine concentrations were found 12 to 20 hours after sulphasalazine had been taken in most patients. The pharmacokinetic profiles of plasma concentrations of sulphasalazine, sulphapyridine, and N\(^4\)-acetylsulphapyridine versus time from a typical male patient with RA and a typical male patient with IBD are illustrated in figs 1–3 and details of these patients in table 2.

Table 1: Summary of demographic data of patients with rheumatoid arthritis (RA) and patients with inflammatory bowel disease (IBD)

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>4:9</td>
<td>3:5</td>
</tr>
<tr>
<td>Acetylator status (fast:slow)</td>
<td>3:7</td>
<td>4:4</td>
</tr>
<tr>
<td>Age median (years); range</td>
<td>56 (40–75)</td>
<td>51 (32–63)</td>
</tr>
<tr>
<td>Weight median (kg); range</td>
<td>64.5 (46–3–95–4)</td>
<td>69.1 (53.9–94–0)</td>
</tr>
<tr>
<td>C reactive protein median (mg/l); range</td>
<td>6.5 (0–0–124)</td>
<td>0.0 (0–0–3.4)</td>
</tr>
</tbody>
</table>

Table 2: Details of patients illustrated in figs 1–3

Male patient with inflammatory bowel disease
- Disease: ulcerative colitis
- Duration: 6 years
- Acetylator status: slow
- Age: 36 years
- Weight: 74 kg

Male patient with rheumatoid arthritis
- Duration: 18 years
- Acetylator status: slow
- Age: 48 years
- Weight: 64 kg

Table 3: Sulphasalazine, sulphapyridine, and acetylsulphapyridine pharmacokinetic variables (median (range)) in rheumatoid arthritis (RA) and inflammatory bowel disease (IBD)

<table>
<thead>
<tr>
<th></th>
<th>Median (range)</th>
<th>Median (range)</th>
<th>Median (range)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}} ) (µg/ml)</td>
<td>RA</td>
<td>IBD</td>
<td>RA</td>
<td>IBD</td>
</tr>
<tr>
<td>15.6 (5.1–24.5)</td>
<td>2.9 (1.8–24.0)</td>
<td>1.9 (0.4–7.5)</td>
<td>4.0 (2.5–8.6)</td>
<td>0.94 (0.9–4.7)</td>
</tr>
<tr>
<td>p Value</td>
<td>0.04</td>
<td>0.74</td>
<td>0.19</td>
<td>0.74</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (h)</td>
<td>RA</td>
<td>IBD</td>
<td>RA</td>
<td>IBD</td>
</tr>
<tr>
<td>1 (2.0–7.1)</td>
<td>4 (2.5–8.6)</td>
<td>4 (2.5–8.6)</td>
<td>0.10 (0.74–0.97)</td>
<td></td>
</tr>
<tr>
<td>( T_{\text{1/2}} ) (h)</td>
<td>RA</td>
<td>IBD</td>
<td>RA</td>
<td>IBD</td>
</tr>
<tr>
<td>165 (87–252)</td>
<td>10 (0.28–0.35)</td>
<td>10 (0.28–0.35)</td>
<td>0.10 (0.09–0.13)</td>
<td></td>
</tr>
<tr>
<td>( AUC^{*} ) (µg/ml h)</td>
<td>RA</td>
<td>IBD</td>
<td>RA</td>
<td>IBD</td>
</tr>
<tr>
<td>0.07 (0.04–0.12)</td>
<td>0.01 (0.00–0.02)</td>
<td>0.01 (0.00–0.02)</td>
<td>0.01 (0.00–0.02)</td>
<td></td>
</tr>
<tr>
<td>( K_{el} ) (A h(^{-1}))</td>
<td>RA</td>
<td>IBD</td>
<td>RA</td>
<td>IBD</td>
</tr>
<tr>
<td>0.10 (0.09–0.13)</td>
<td>0.01 (0.00–0.02)</td>
<td>0.01 (0.00–0.02)</td>
<td>0.01 (0.00–0.02)</td>
<td></td>
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</table>

\*AcSP=N\(^4\)-acetylsulphapyridine; SASP=sulphasalazine; SP=sulphapyridine; AUC=area under the drug concentration × time curve.
Pharmocokinetics of sulphasalazine in RA and inflammatory bowel disease

A large variation in plasma concentrations of sulphasalazine and its metabolites was observed among patients in both disease groups. Patients with IBD had a tendency to eliminate sulphasalazine more slowly than those with RA, leading to a tendency towards a greater sulphasalazine AUC, but these results failed to reach significance (table 3). Patients with RA had a significantly greater \( C_{\text{max}} \) of sulphapyridine than patients with IBD (medians 14.0 \( \mu \)g/ml and 7.4 \( \mu \)g/ml respectively; \( p<0.01 \); table 3). The sulphapyridine AUC was also greater in RA than IBD, but this failed to reach significance.

There were no significant differences in any of the pharmacokinetic variables obtained for \( N^4 \)-acetyl sulphasalazine between the two disease groups.

**Discussion**

Although the enteric coated formulation of sulphasalazine is generally prescribed in both IBD and RA, the uncoated version was used in this investigation. Plain tablets were used to minimise the chances of any difference in the rate of dissolution of the enteric coating in the two disease states. The plain tablets were given once only and patients were able to tolerate any gastrointestinal discomfort that might have occurred.

Previous studies in IBD have indicated that high circulating concentrations of sulphapyridine (free and total) may be responsible for the toxic effects of sulphasalazine.\(^{15,21}\) This investigation has shown that patients with RA have a significantly greater \( C_{\text{max}} \) of sulphapyridine than patients with IBD. There was also a tendency for patients with RA to eliminate parent sulphasalazine more rapidly than patients with IBD and hence have a lower sulphasalazine AUC. Although the multiple dose pharmacokinetics of sulphasalazine were not determined, these results may be of clinical importance if extrapolated to cover a period of repeated dosing with the drug.

It has been suggested that about one third of an oral dose of sulphasalazine is absorbed as the parent compound\(^{22}\) and most of this is eliminated in the bile. A more rapid presentation of recirculated sulphasalazine to the colon in patients with RA compared with those with IBD, together with unabsorbed sulphasalazine, may lead to increased bacterial cleavage of the compound to sulphapyridine and 5-aminosalicylic acid, and hence increased plasma sulphapyridine concentrations. Furthermore, a feature of IBD is increased gut motility; patients with RA have a tendency towards constipation, although the bowel habits of the patients with RA were not discussed. It has been observed that the bioavailability of sulphapyridine from sulphasalazine is reduced when intestinal transit time is accelerated.\(^{23}\) It has also been shown that during relapse patients with ulcerative colitis have a lower plasma concentration of sulphapyridine, and it has been postulated that an inflamed colon may absorb sulphapyridine inefficiently.\(^{17}\)

If the bioavailability of sulphapyridine from sulphasalazine is greater in RA than IBD then it may be reasoned that the \( C_{\text{max}} \) and AUC of \( N^4 \)-acetyl sulphapyridine, the principal metabolite of sulphapyridine, should be correspondingly greater. This, however, was not observed. Sulphapyridine and \( N^4 \)-acetyl sulphapyridine are also metabolised at the 5' position of the pyridine ring, followed by subsequent glucuronidation. These metabolites appear only transiently in plasma and are rapidly excreted by the kidneys; they were not detected in plasma samples obtained from the patients with RA or IBD. The hydroxylation reaction is mediated by cytochrome P-450 in the liver, but in inflammatory states the activity of this mixed function oxidase system is depressed. This has been attributed to the cytokines interleukin-1, interleukin-6, and tumour necrosis factor, which stimulate hepatocytes to synthesise acute phase proteins and suppress cytochrome P-450 mediated drug metabolism.\(^{24}\)

The patients with IBD who participated in this investigation all had mild disease, and only one of the eight patients had a slightly increased serum C reactive protein concentration. It has been suggested that measurement of serum C reactive protein gives an objective indication of inflammation in Crohn's disease.\(^{25}\) Impaired hydroxylation, especially in patients who are slow acetylators, may give rise to particularly high circulating sulphapyridine concentrations. Cytochrome P-450 may also mediate the sulphoxidation of 5-carboxymethylcysteine and the incidence of poor sulphotransferases has been reported to be greater in patients with RA than in normal, healthy subjects.\(^{26}\) Furthermore, poor sulphotransferases have been shown to be more prone to adverse effects from sodium aurothiomalate and D-penicillamine than extensive sulphotransferases.\(^{26,28}\) Thus suppression of drug metabolism by the hepatic mixed function oxidase system as a result of disease may help to explain the high prevalence of toxic reactions to sulphasalazine and other drugs in patients with RA.

A possible reduced capacity to hydroxylate sulphapyridine, coupled with an increased absorption of sulphapyridine after sulphasalazine administration, may lead to higher systemic sulphapyridine concentrations in patients with RA than in patients with IBD and may be responsible for the higher incidence of adverse effects to sulphasalazine treatment in RA.
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