Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines

We were interested to read the report by Ransford and Langman of their analysis of yellow card reports of suspected adverse drug reactions for sulphasalazine and mesalazine (Gut 2002;51:536–9). These reports, submitted to the Committee on Safety of Medicines, may provide useful flags to signal unrecognised hazards of drugs. However, as adverse reactions are not always recognised or reported to the regulatory authorities by physicians, these reports usually underestimate the frequency of any adverse drug reaction. Of greater importance, underreporting is usually not random but selective, which may introduce serious bias when comparing different drugs. Various examples have been described previously of drugs that showed substantive differences in reporting rates, which were not substantiated after further research. For this reason, it is recommended that, once there is a signal for a suspected adverse drug reaction, other sources of data are investigated.

We recently initiated a study to quantify the risk of renal toxicity in patients taking aminosalicylate (5-ASA) drugs in the UK. The General Practice Research Database (GPRD) was used for this study, with data collected as part of routine medical practice. The GPRD has previously been demonstrated to be a representative sample of the general population of England and Wales, and the completeness and validity of the GPRD recording of medically significant events is well established. Its data have been used frequently to quantify the risk of adverse drug reactions. Our study population included almost 40,000 patients. We found that the overall incidence of renal damage (which included interstitial nephritis) was rare in patients taking 5-ASA drugs, but was increased relative to control patients (Table 1). The risk of renal toxicity in patients taking mesalazine and sulphasalazine was comparable. Interestingly, we found that the risk of renal disease was related to indicators of severity of inflammatory bowel disease and to concomitant disease and drug treatment. A recent report also suggested that the kidney can be an extratinal target in Crohn’s disease. We presented the results of this study at the recent British Society of Gastroenterology meeting.

Our findings also highlight the substantive underreporting of the data used by Ransford et al (Table 1). Given the selected and incomplete nature of the reports of suspected adverse drug reactions, one needs to establish whether physicians reported cases of interstitial nephritis equally for users of different 5-ASA drugs. The authors did not provide any data for the comparability of the users of the various 5-ASA drugs in the UK. In conclusion, while we agree that renal function should be evaluated and monitored in patients taking 5-ASAs, the results of our large epidemiological study show no difference in renal toxicity between mesalazine and sulphasalazine and that confounding factors can also significantly affect the overall risk. A statistical analysis of suspected adverse drug reaction reports may generate signals but does not provide conclusive evidence of differences in safety between drugs.

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Table 1 Rates of renal events in the General Practice Research Database (GPRD) study and in the study of Ransford et al

<table>
<thead>
<tr>
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<th>Rate per 1000 person years</th>
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</thead>
<tbody>
<tr>
<td><strong>GPRD</strong></td>
<td></td>
</tr>
<tr>
<td>Renal toxicity</td>
<td></td>
</tr>
<tr>
<td>During 5-ASA use</td>
<td>1.2</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>1.2</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>1.7</td>
</tr>
<tr>
<td>Control cohort</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Ransford et al</strong></td>
<td></td>
</tr>
<tr>
<td>During 5-ASA use</td>
<td>0.1</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>0.1</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>0</td>
</tr>
</tbody>
</table>

Author’s reply

We do of course recognise that making deductions from examination of spontaneous adverse reaction reports poses problems from the incomplete nature of the data, and the limited knowledge of biases. Thus we say “spontaneous reporting...cannot be used to determine true rates of reaction”. We also speculate that reporting rates of interstitial nephritis with mesalazine may be high ‘because a specific warning of possible renal toxicity had been issued’.

The comparatively equal values quoted by Logan and van Staa of 1.2 (mesalazine) and 1.7 (sulphasalazine) cases of interstitial nephritis per 1000 patient years are very different from the 29 cases reported spontaneously on yellow cards for mesalazine with none for sulphasalazine in the time period assessed (there are a total of 47 for mesalazine and two for sulphasalazine, a fairly large difference).

Being aware of the problems of judging true rates of reaction from spontaneous reports, and knowing that there was (as for interstitial nephritis) a relative paucity of reports for pancreatitis with sulphasalazine, we have recently analysed data from the General Practice Research Database (GPRD) on prior drug exposure in cases of acute pancreatitis. This clearly shows raised odds ratios for mesalazine, but not for sulphasalazine, and with the odds ratio for mesalazine being particularly high in those with first exposure in the prior three months. The finding is consonant with the spontaneous adverse drug reaction data presented by us.

Rates from GPRD for interstitial nephritis, as presented by Logan and van Staa per 1000 patient years, are difficult to relate to individual patient exposures. It would be valuable to have such information. Given that sulphasalazine is the older drug, one would expect longer exposure in each such taker (particularly if it was for inflammatory bowel disease). It would also be valuable to know if the cases of renal damage in sulphasalazine takers identified by Logan and van Staa were in patients with inflam-
matory bowel disease rather than in those with rheumatoid disease, where confounding by use of other agents, notably penicillamine and gold, and complicating renal amyloid, would need to be borne in mind. Differences between our findings may be resolved in due course by current surveillance studies being conducted by the British Society of Gastroenterology.

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Worsening of steatosis and fibrosis progression in hepatitis C
We thank Ratziu et al for their interest in our work.1 To grade steatosis, we used the Metavir scoring system, shown by their group to be accurate and reproducible.2 Worsening was characterised by an increase in the amount of lipids in hepatocytes, as defined in this grading system. As emphasised in our paper, our main finding was that worsening of steatosis was the only independent factor associated with fibrosis progression in multivariate analysis. This study was observational and not aimed at establishing causal links, a goal that requires a combination of prospective clinical studies and careful in vitro experiments. Ratziu’s discussion of our data is interesting but remains purely speculative.3 The issues raised by our results and their discussion in both our paper and Ratziu’s letter are currently being addressed through appropriate studies in our centre.

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References

Complete regression of advanced HCC with long acting octreotide
Various therapeutic approaches for unresectable hepatocellular carcinoma (HCC) have been suggested in recent years. However, major advances concerning tumour regression or patient survival were not achieved. A few trials have assessed the effect of the somatostatin analogue octreotide in advanced HCC with divergent results.1,2 The latter might be due to expression of somatostatin receptor type 2 (SSTR2) in some but not all patients with HCC.1,3 Here, we describe a patient with advanced HCC who was treated with long acting octreotide, which resulted in complete and prolonged regression of the tumour.

The patient was diagnosed with HCC after a suspect nodule was detected in the abdominal ultrasound. Laboratory testing revealed a highly increased alpha fetoprotein (AFP) level and positive hepatitis C virus antibodies. Computed tomography (CT) of the liver displayed multiple tumours (maximum diameter 5 cm) in segment seven and two smaller nodules in segments six and one. Histology of an ultrasound guided biopsy revealed HCC. Due to the advanced stage of the tumour, surgical resection was not feasible. As the patient refused all local ablative therapies, treatment with octreotide was initiated (initially 250 µg twice daily followed by long acting octreotide (Sandostat Lin LAR) 10 mg monthly). Four months later a 50–70% reduction in the size of the multifocal tumours was demonstrated by CT. Furthermore, complete regression of the formerly described tumours was noted 10 months after initiation of octreotide therapy. This was paralleled by normalisation of the formerly elevated AFP values (33.1 ng/ml to 7615.3 ng/ml). Octreotide receptor scintigraphy performed after 12 months and 19 months of therapy did not reveal any suspicious enhancement. However, after 13 and 19 months a gradual increase in AFP levels from 37 to 223 ng/ml and a new suspicious liver nodule by CT scan was observed. To date, the patient has not experienced any tumour associated symptoms or drug related side effects and has been in excellent condition during the 22 months of treatment.

The survival improving treatment effects of octreotide described by Kouroumalis and colleagues were not confirmed in a subsequent randomised placebo controlled trial.4 Of the octreotide receptors expressed in the liver, octreotide has the highest affinity for SSTR2 compared with the four other isoforms of the somatostatin receptors.5 SSTR2 is expressed in HCC,6 has been shown to play a major role in mediating cell cycle arrest.7 Although we were not able to prove SSTR expression in our patient due to tissue preparation in another hospital, high SSTR2 expression in primary liver cancer might be the reason for the unusual beneficial clinical course. The recent increase in AFP levels could reflect the ability of the tumour cells to escape somatostatin receptor treatment, possibly by downregulation or mutation of the respective receptor.

To the best of our knowledge, complete and prolonged regression of advanced HCC with normalised AFP levels during octreotide treatment has not been described previously. Based on our observation and the divergent results of recent studies, forthcoming trials evaluating the effect of octreotide in advanced HCC might additionally stratify patients according to the respective somatostatin receptor expression profile of tumour cells.

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References

Diagnosing small bowel Crohn’s disease with wireless capsule endoscopy
We read the article by Fireman et al (Gut 2003;52:390–2) with great interest. We agree that full visualisation and imaging of the entire length of the small bowel is unsatisfactory at present and that capsule endoscopy (CE) is a novel technique and can be considered as a promising new approach for the diagnosis of obscure disease located in the small bowel.

The authors diagnosed Crohn’s disease (CD) in 12 of 17 patients with clinically suspected CD according to the findings of CE. The authors state that the majority of diagnostic lesions were located in the distal ileum. At least one colonoscopy had been performed prior to CE in four of these patients. Unfortunately, the investigators do not report whether or not they were able to explore the terminal ileum in all of these patients. Hence the important question arises of which endoscopic and histological findings had been observed in the terminal ileum of these 15 study patients prior to CE, and whether this clinical information may have affected the interpretation of the CE findings in this investigational setting. Furthermore, the authors did not compare their non-diagnostic x-ray findings with the CE results.

To date, we have performed a total of 130 capsule endoscopy procedures. In 50 patients with obscure gastrointestinal bleeding, we were able to disclose CD as the most probable underlying cause of bleeding in four patients. In addition, one patient suffering from Peutz-Jegher’s syndrome was diagnosed as also having CD of the small bowel. We performed CE in eight patients in whom the diagnosis of CD had been established prior to CE to “stage” the small bowel for additional lesions that could influence treatment decisions. In the majority of our patients we found that the main pathological lesions were located in the terminal ileum. We were however able to confirm most CD lesions histologically by applying a second ileocolonoscopy with special emphasis on the small bowel biopsies in most of these patients, which allows for a greater diagnosis validity.
as small bowel ulcerations obtained with CE may also be caused by non-steroidal anti-inflammatory drug abuse, ulcerative ileitis, or coeliac disease. Hence from our experience we strongly recommend that patients with suspected CD should initially undergo careful ileocolonoscopy with close inspection of as much as the ileum as possible, and acquisition of multiple ileal biopsies to histologically establish CD prior to therapy. We believe that at present CE is only clinically indicated in patients with signs and symptoms suggestive of small bowel CD in whom:

- a stenosis/stricture has clearly been excluded,
- the terminal ileum looks unrewardable on endoscopy, or
- the ileum cannot be intubated for technical reasons.

The present study does not elucidate whether CE is really superior to conventional endoscopy plus histological assessment, which must still be considered the gold standard for the diagnosis of CD. As there is a substantial risk of capsule retention in the gastrointestinal tract in patients with stenotic CD, it should be determined if the benefits of CE findings outweigh the risks of this otherwise remarkable novel technique in individual patients.

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Authors’ reply

We thank Drs Schulmann, Hollerbach, and Schmiegel for their interest in our paper on the subject of diagnosing small bowel Crohn’s disease with wireless capsule endoscopy.1 Regarding colonoscopy,2 please note that in the materials and methods section, under study population, it is clearly stated that all underwent colonoscopies elsewhere, at most six months prior to entering the study, and this statement is repeated in the first paragraph of the results section. As these patients came to us from other medical centres with the results of their previous colonoscopies, we sent the results of capsule endoscopy (CE) to their own physicians (Re: exploration of the terminal ileum). In the results section, we state that six patients underwent ileoscopy which was normal. We appreciate the experience of your group and agree with your indications against indications for the CE study.

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Reference