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 extraintestinal 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.

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>
<th>Drug</th>
<th>Rate per 1000 person years</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPRD</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>Ransford et al</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>

Autor’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 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 also 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 toxicity 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 d-penicillamine 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.1 The issues raised by our results and their discussion in both our paper and Ratziu’s are being conducted by the British Society of Gastroenterology.

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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.2,3 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 3 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 was on local ablative therapies, treatment with octreotide was initiated (initially 250 µg twice daily followed by long acting octreotide (Sandostatin 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 76153 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.1 Of the octreotide receptors expressed in the liver, octreotide has the highest affinity for SSTR2 compared with the four other isomers of the somatostatin receptors.2 SSTR2 is expressed in HCC3 and has been shown to play a major role in mediating cell cycle arrest.4 Although we were not able to prove SSTR expression in our patient due to tissue preparation in another hospital, high SSTR2 expression in liver tumours 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 all 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 importance question arises of which endoscopic and histopathological diagnostic lesions were found 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 symptoms we were able to disclose CD as the most probable underlying cause of bleeding in four patients. In addition, one patient suffering from Peutz-Jeghers syndrome was diagnosed as also having CD of the small bowel and 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.

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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/stenosis has clearly been excluded;
- the ileal ulcer looks unremarkable 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 stenosing 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,1 please note that in the materials and methods section, under study population, it is clearly stated that all underwent colonoscopies elsewhere, and that judicious use of DEXA scanning is recommended.2

See references

Risk of fracture in coeliac disease

We agree that the risk of fracture in coeliac disease needs to be estimated more precisely and that judicious use of DEXA scanning is appropriate in this group, as it is in the general population. However, as Walters and colleagues (Gut 2003;52:1229–30) and others have clearly shown, bone mineral density does improve following treatment with a gluten free diet, so recommendations to screen all newly diagnosed patients with coeliac disease at diagnosis do not seem judicious.3

Larger studies are needed and one such is in progress. Nevertheless, the small increases in risk which we found are similar to those found in the only other population based study of fracture risk in patients with coeliac disease.4 In the absence of robust data showing a marked increase in the risk of fracture in individuals with coeliac disease, perhaps the onus should be on those making such recommendations5 to provide evidence supporting their efficacy and cost effectiveness.

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References


Sir Francis Avery Jones British Society of Gastroenterology Research Award 2004

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2004 Award. Applications (TWENTY COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years old or less on 31 December 2004 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Glasgow in March 2004. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2003.

British Society of Gastroenterology Hopkins Endoscopy Prize 2004

Applications are invited by the Endoscopy Committee of the British Society of Gastroenterology who will recommend to the Council the recipient of the 2004 Award. Applications (TEN COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

An applicant need not be a member of the Society. The recipient will be required to deliver a 20 minute lecture at the Annual meeting of the Society in Glasgow in March 2004. Applications (TEN COPIES) should be made to the Endoscopy Section Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2003.