

major problem; this study underlines the importance of considering inflammatory bowel disease.

We thank the many doctors who referred these patients to us and the other physicians at the Hospital for Tropical Diseases for allowing us to abstract case records of patients admitted under their care.

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## Thrombocytopenia associated with ranitidine

We describe a patient who developed thrombocytopenia when his medication was changed from cimetidine to ranitidine. This is believed to be the first report of a haematological side effect of ranitidine. The manufacturers (Glaxo) and the Committee on the Safety of Medicines and Drugs have been informed.

### Case report

A 62 year old man developed thrombocytopenia six weeks after a successful cadaveric renal transplant for hypertensive uropathy. In 1972 a proximal gastric vagotomy had been performed, and cimetidine had been prescribed intermittently since 1977 and continually since 1983. A routine gastroscopy performed three and a half weeks after transplantation showed a friable duodenal cap, and ranitidine 150 mg twice daily was substituted for cimetidine. Despite several postoperative complications—antibiotic associated diarrhoea, two rejection episodes, and a chest infection—platelet counts remained normal until eight days after the start of ranitidine (see figure), although the patient's general condition and renal function remained satisfactory.

Apart from a platelet count of  $<50 \times 10^9/l$ , full blood count, peripheral blood film, and coagulation screen were normal. Bone marrow aspirate and trephine biopsy specimens were cellular with all cell lines represented, but the megakaryocytes showed maturation arrest with marked lack of budding. Platelet associated antibodies were raised: IgG 41 ng/ $10^6$  platelets (normal 2-10) and IgM 9 ng/ $10^6$  platelets (normal  $<2.5$ ). Viral serological titres had not changed; the patient was seropositive for both cytomegalovirus and respiratory syncytial virus before transplantation.

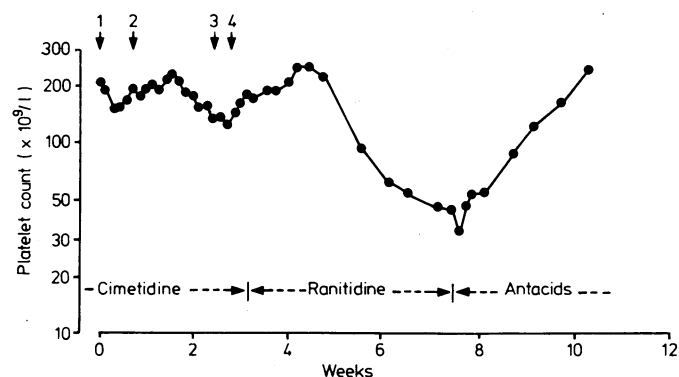
A drug related thrombocytopenia was suspected. His other medication was prednisolone, cyclosporin A, atenolol,  $1\alpha$  calcidol, and frusemide. In view of the known association of  $H_2$  antagonists with thrombocytopenia and because ranitidine had been the most recent change to his drug regimen, it was discontinued and antacids started. There were no haemorrhagic episodes, platelet support was not needed, and two weeks later the platelet count had returned to normal. A further challenge with ranitidine was thought to be unjustifiable clinically or ethically. The platelet associated antibodies have since returned to normal.

### Comments

Cytopenias associated with  $H_2$  receptor antagonists have been reported with cimetidine and metiamide.<sup>1</sup>  $H_2$  receptor blockade per se has no adverse effect on the bone marrow despite earlier suggestions that it interfered with stem cell differentiation.<sup>2</sup> The thiourea moiety of metiamide has been implicated as the cause of its marrow toxicity. Cimetidine, a more potent  $H_2$  antagonist, does not contain this moiety, and patients with marrow suppression induced by metiamide have improved on cimetidine.<sup>1</sup> Ranitidine has no known haematological side effects.<sup>3</sup>

Well over 100 drugs, including cimetidine, have been associated with drug induced thrombocytopenia, although most were isolated instances or

affected very few patients.<sup>4</sup> Concentrations of platelet associated antibodies have been shown to be raised proportionately to the degree of thrombocytopenia and returned to normal with improvement in the platelet count in a recent series of drug induced thrombocytopenias.<sup>5</sup> In our patient raised concentrations of platelet associated antibodies and the temporal association with the thrombocytopenic episode strongly suggest that ranitidine triggered an immune thrombocytopenia. Also, an unrelated cyclical thrombocytopenia would be unlikely in the presence of a cellular marrow.



Clinical course from day of transplant. 1=antibiotic associated diarrhoea, 2=first rejection episode, 3=chest infection (*H influenzae*), 4=second rejection episode.

The antigenic stimulus for the production of platelet associated antibodies probably depends on the drug binding to either platelets or plasma proteins, which then act as haptens.<sup>4</sup> The antibody or antibody-drug complex subsequently produced coats circulating platelets, and possibly developing megakaryocytes, resulting in increased destruction or decreased formation and release. Cimetidine and ranitidine are normally only weakly bound to plasma proteins,<sup>3</sup> and any complex formed is probably only weakly antigenic. Their ability to bind platelets is not known.

Most cases of thrombocytopenia associated with cimetidine have occurred in patients with complex medical histories, usually during an acute exacerbation (commonly septicæmia or renal failure).<sup>1</sup> This prompts the question whether an acute phase response may have an effect on drug binding interactions so as to enhance any potential antigenic stimulus. Whatever the mechanism, ranitidine seems to be one of many drugs that rarely may cause an immunologically mediated thrombocytopenia.

We thank Mr Gordon Williams for his permission to report on his patient.

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### Correction

#### Has mortality related to alcohol decreased in Sweden?

An error occurred in this paper by Anders Romelsjö and Gunnar Ågren (20 July, p 167). In the Methods section the test variable should have read:

$$\text{test variable} = (N_1 - N_2) / \sqrt{(N_1 + N_2)}.$$