Reversible agranulocytosis in association with cimetidine and hepatic failure

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Summary

A patient is described who developed agranulocytosis in the context of hepatic failure and cimetidine therapy. The close temporal relationship between discontinuation of the drug and granulopoietic recovery is considered to imply a role for cimetidine in the mechanism of the agranulocytosis.

Introduction

There have been several reports of neutropenia in patients taking cimetidine (Ufberg *et al.*, 1977; Klotz and Kay, 1978) but a definite causal relationship between the drug and a blood dyscrasia has not yet been established. This case report concerns an unusually severe degree of reversible neutropenia related to cimetidine therapy which developed in the context of a deterioration of hepatic function.

Case history

A 62-year-old lady with a past history of fibrosing alveolitis and chronic active hepatitis leading to cirrhosis with oesophageal varices, presented to Whittington Hospital with a recurrence of gastrointestinal bleeding in December, 1976. She was given cimetidine 200 mg four times daily for 12 days and cotrimoxazole for a chest infection. The serum bilirubin was 64 $\mu\text{mol/litre}$. During admission and subsequent out-patient follow-up no depression of the peripheral blood neutrophil count was observed.

She was readmitted on 25 June, 1978 with a recurrence of upper gastrointestinal bleeding. Oral cimetidine 200 mg 4 times daily was restarted and the dose increased to 1 g a day on 10 July. She was transfused with 8 units of blood and also received frusemide, neomycin, prednisolone, metoclopramide, cotrimoxazole, vitamin K and lactulose. The neutrophil count was normal (Fig. 1) and serum bilirubin was 118 $\mu\text{mol/litre}$. She was discharged on 19 July

taking cimetidine 1 g/day and prednisolone 7.5 mg/day.

FIG. 1. Neutropenia related to cimetidine therapy—●, leucocytes; ○, lymphocytes; ■, granulocytes. Arrow shows neutrophil count zero on 27 and 28 August.

Her final admission was on 27 July with a 3-day history of haematemesis, buccal ulceration, progressive lethargy and increasing jaundice. On examination she was afebrile with ascites, splenomegaly and oral candidiasis. Investigations: haemoglobin 10.2 gm/dl; white cell count (WCC) $1.1 \times 10^9/\text{litre}$ (100% lymphocytes); serum bilirubin 278 $\mu\text{mol/litre}$; plasma urea 4.5 mmol/litre, plasma sodium 121 mmol/litre and plasma potassium 3.3 mmol/litre.

On the night of admission she developed a fever (39°C) but this resolved following parenteral ampicillin, two previous blood cultures having failed to show

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significant growth. Repeat WCC the next day was 0.6×10^9 /litre (100% lymphocytes) and bone marrow aspiration revealed hypocellularity with almost complete absence of granulopoietic elements. Megakaryocytes and red cell precursors appeared in normal numbers.

In view of the possibility of cimetidine-induced agranulocytosis the drug was discontinued on 28 July. Following this there was a gradual recovery in the peripheral blood neutrophil count (Fig. 1). A second bone marrow aspirate on 3 August was normocellular and demonstrated vigorous but left shifted myelopoiesis. This marrow supported normal growth of granulocyte colonies in agar culture (kindly performed by Dr J. Goldman, Hammersmith Hospital) but unfortunately it was not possible to culture the marrow in the presence of cimetidine.

Although there was a recovery of granulopoiesis, bleeding persisted from the upper gastrointestinal tract uncontrollable by pitressin or Sengstaken tube and the patient died on 7 August. Eleven units of blood had been transfused. Subsequent to stopping cimetidine she had received metoclopramide and cotrimoxazole which did not appear to affect the rising neutrophil count. Other drugs given were frusemide, lactulose, vitamin K, hydrocortisone and neomycin.

Comment

The close temporal relationship between recovery from agranulocytosis and withdrawal of cimetidine, resembling that noted by Ufberg *et al.*, (1977), suggests that the drug may be responsible for a reversible depression of granulopoiesis. Unlike other reports the advent of neutropenia was not precipitate but occurred during the patient's second course of cimetidine when she had been receiving the drug for 32 days.

The clear-cut bone marrow picture indicates that marrow suppression was the cause of the agranulocytosis rather than peripheral neutrophil destruction as postulated by Ufberg *et al.*, (1977).

It is interesting that the agranulocytosis developed in the context of hepatic decompensation since in a series of patients in fulminant hepatic failure treated with cimetidine no instances of neutropenia were noted (MacDougall and Williams, 1978). The urinary excretion of cimetidine following oral administration is variable and has been noted to be as low as 60% in

some cases (Burland *et al.*, 1975). It is therefore possible that individual patients with hepatic failure may demonstrate high blood levels of the drug. Indeed, Dupont *et al.*, (1981) found that a group of patients with cirrhosis treated with 1200 mg/day cimetidine for gastro-intestinal bleeding (a dose similar to that administered to the patient described here) showed significantly higher plasma cimetidine levels than a group of non-cirrhotic patients treated with a similar regime. They advised a dosage of 200–400 mg/day of cimetidine in cirrhotic patients suffering from gastro-intestinal haemorrhage. Sonne *et al.* (1981) reported a normal clearance of cimetidine in patients with compensated cirrhosis but these cases were only treated with 200 mg cimetidine/day and were not bleeding at the time of the study.

It is also possible that the multiple medical problems, including hepatic dysfunction, in this deteriorating patient may have led to a condition of enhanced granulopoietic susceptibility to cimetidine as has been suggested by Freston (1979).

Further investigation is required into levels of plasma cimetidine in patients with hepatic failure on different doses of cimetidine.

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References

- BURLAND, W.L., DUNCAN, W.A.M., HESSELBO, T., MILLS, J.G., SHARPE, P.C., HAGGIE, S.J. & WYLLIE, J.H. (1975) Pharmacological evaluation of cimetidine a new histamine H_2 -receptor antagonist, in healthy man. *British Journal of Clinical Pharmacology*, **2**, 481.
- DUPONT, T., BEAUGRAND, M., BRUNET, J.M., AZOUZ-ABDALLAH, M., BAYLOQ, D., CHAMPAULT, G. & FERRIER, J.P. (1981) Plasma concentrations of cimetidine in cirrhotic and non-cirrhotic patients with upper digestive tract haemorrhage. *Gastroenterologie clinique et biologique*, **5**, 155.
- FRESTON, J.W. (1979) Cimetidine and granulocytopenia. *Annals of Internal Medicine*, **90**, 264.
- KLOTZ, S.A. & KAY, B.F. (1978) Cimetidine and agranulocytosis. *Annals of Internal Medicine*, **88**, 579.
- MACDOUGALL, B.R.D. & WILLIAMS, R. (1978) In: *Cimetidine The Westminster Hospital Symposium* (Ed by Wastell, C. & Lance, P.), p. 180. Churchill Livingstone, London.
- SONNE, J., POULSEN, H.E., DOSSING, M., LARSEN, N.E. & ANDREASEN, P.B. (1981) Cimetidine clearance and bioavailability in hepatic cirrhosis. *Clinical Pharmacology and Therapeutics*, **29**, 191.
- UFBERG, M.H., BROOKS, C.M., BOSANAC, P.R. & KINTZEL, J.E. (1977) Transient neutropenia in a patient receiving cimetidine. *Gastroenterology*, **73**, 635.