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LETTER TO THE EDITORS

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# Omeprazole does not alter plasma methotrexate clearance

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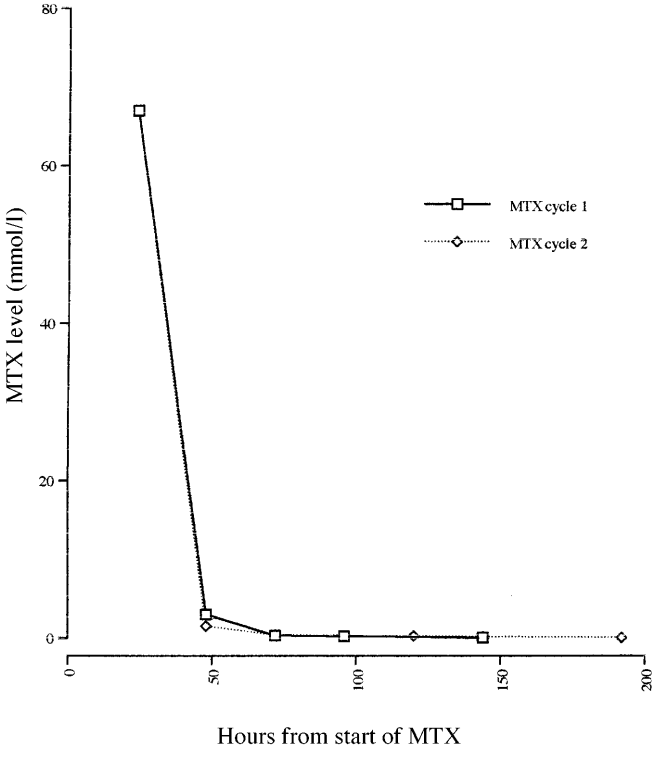
It has been proposed that the commonly prescribed proton-pump inhibitor omeprazole may block the active secretion of methotrexate by the kidney through inhibition of renal tubular $H^+$, $K^+$, ATPase. This could lead to delayed methotrexate clearance and necessitate prolonged folinic acid rescue to avoid systemic toxicity. Alternatively, such an effect could theoretically be exploited to maximise tumour exposure to methotrexate in a disease such as osteosarcoma, where methotrexate levels have been correlated with prognosis [1].

The description by Reid et al. [2] of a patient receiving methotrexate at a dose of 12 g/m$^2$ for osteosarcoma who experienced delayed drug excretion while receiving concurrent omeprazole prompted us to consider a similar mechanism to explain high methotrexate levels in one of our patients.

A 24-year-old man was found to have a chondroblastic osteosarcoma localised to the sacrum. Omeprazole had been taken for 2 months for dyspeptic symptoms. Other treatment included morphine sulfate and laxatives. Chemotherapy began with three cycles of doxorubicin and cisplatin before it was changed to methotrexate at 12 g/m$^2$. A total dose of 20 g was given over 6 h, with urinary alkalinisation using acetozolamide, hydration and folinic acid rescue beginning 24 h after the start of methotrexate administration. Drug levels were first measured at 24 h and were noted to be markedly elevated at 67 mmol/l. The folinic acid dose was adjusted and the methotrexate level fell to $<0.1$ mmol/l by 140 h. Omeprazole was stopped after 72 h and not restarted. At 12 days after the first cycle, a second dose of methotrexate at 20 g was given. Hydration schedules and other medication were identical. The serum level measured at 24 h and subsequent clearance proved identical to that seen in the first course (Figure).

Methotrexate is almost entirely excreted by the kidney, in part through active secretion by cells of the renal tubules. At very high doses, other clearance mechanisms, including hepatic metabolism, may augment this route. Weak organic acids including salicylates, probenicid and vitamin C are known to compete with methotrexate for hydrogen-ion-dependent membrane transport, which may be inhibited by omeprazole. The widespread use of omeprazole and the potentially lethal

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toxicity of methotrexate make any interaction between the two of great significance [3].

Reid et al. [2] reported a single patient in whom prolonged duration of methotrexate excretion was observed in one cycle but not in subsequent cycles after omeprazole had been discontinued. In our patient, no such alteration in methotrexate handling was identified; thus, the contention that omeprazole interferes with methotrexate handling is not supported.

## References


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