based interventions can alleviate distress and minimise the secondary handicap that results from disrupted education and impaired social development.[5]

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Drug points

Severe myalgia from an interaction between treatments with pantoprazole and methotrexate

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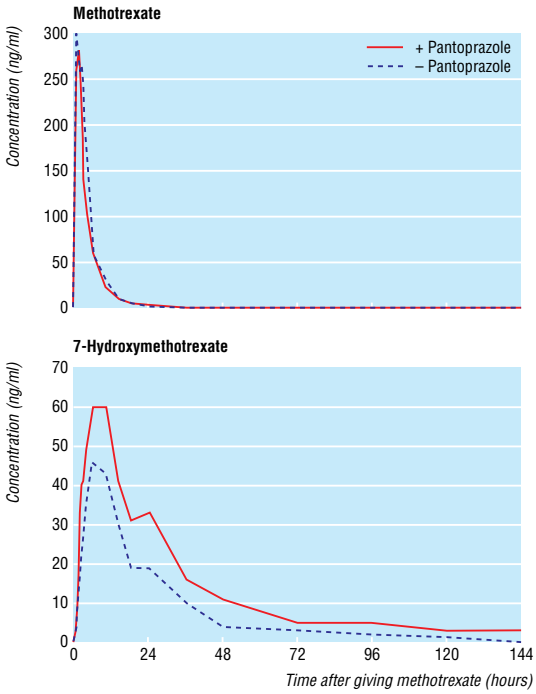
A 59 year old man with a folliculotropic cutaneous T cell lymphoma had been receiving treatment with interferon alfa-2a. After the treatment was discontinued because his tumour had relapsed, he started taking low dose pulse methotrexate (15 mg intramuscularly, once a week). Concomitantly he also had a Barrett oesophagus, which was treated with pantoprazole (20 mg/day, orally), and arterial hypertension, which was treated with atenolol. After the first injection of methotrexate the patient had severe generalised myalgia and bone pain. This led to partial immobility that began three to four hours after the injection and continued—albeit to a lesser degree—for several days. The symptoms recurred over the following four methotrexate cycles. Multiple clinical and laboratory examinations excluded clinical causes such as an underlying focal or disseminated infection and the systemic exacerbation of the cutaneous T cell lymphoma. A drug interaction with methotrexate was suspected because the symptoms arose when the drug was given. After pantoprazole was replaced by ranitidine, the symptoms subsided dramatically and finally disappeared.

The patient was rechallenged with pantoprazole eight weeks later, having given his informed consent. Treatment with pantoprazole was started six days before the weekly dose of methotrexate was given so that the maximum effect could be attained. Serum concentrations of methotrexate and its metabolite 7-hydroxymethotrexate were monitored with and without pantoprazole by a high performance liquid chromatography-fluorescence assay.[1] The two study periods were separated by a washout phase of six weeks. Atenolol, clemastine to treat local itching, and ascorbic acid to treat a temporary deficiency of vitamin C were given concomitantly.

The symptoms reappeared in response to the challenge but did not reappear without pantoprazole. The concentration-time curves (figure) are identical for methotrexate in both periods, but they differ considerably for 7-hydroxymethotrexate. The area under the curve between 0 and 144 h after drug administration was nearly 70% higher for 7-hydroxymethotrexate plus pantoprazole than without pantoprazole (1929 ng·h/ml *v* 1131 ng·h/ml); the half life of 7-hydroxymethotrexate was doubled when methotrexate was given with pantoprazole (81.4 h *v* 36.4 h). This indicates an interaction in renal elimination, rather than a metabolic interaction.

About 30% of all patients discontinue the low dose pulse methotrexate because of adverse effects. Drug interactions contribute considerably to the number of patients who stop using the drug.[2 3] Reactions after dosing occur in about 10-15% of patients with rheumatoid arthritis receiving this treatment.[4 5] This report shows for the first time a link between methotrexate post-dosing reactions and an interaction of 7-hydroxymethotrexate and concomitantly given pantoprazole. The German Federal Institute for Drugs and Medical Devices and the Drug Commission of the German Medical Profession were informed about the case. The manufacturer of methotrexate (Medac GmbH, Wedel, Germany) was not aware of this drug interaction.



Serum concentration of methotrexate and 7-hydroxymethotrexate with and without pantoprazole

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