

RGH Pharmacy E-Bulletin

Volume 25 (9): April 9, 2007

A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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Folate supplementation and methotrexate in rheumatoid arthritis

Methotrexate is a folic acid antagonist with cytotoxic, immunosuppressive and anti-inflammatory actions. Due to its ease of use, low cost and favourable efficacy/toxicity profile, it has become established as the most commonly used disease-modifying anti-rheumatic drug (DMARD) for the treatment of rheumatoid arthritis (RA). However, despite its proven efficacy in RA, it has been reported that up to 30% of patients discontinue methotrexate therapy within the first year of treatment due to toxicity.

As a folate antagonist, the toxicity of methotrexate may be broadly divided into those effects likely to be caused or exacerbated by folate depletion and those unaffected by folate balance. It is thought that adverse effects including gastrointestinal intolerance, bone marrow toxicity and alopecia may be attributable to depletion of folate and indeed these effects are similar to those seen in folate deficiency states. Folate deficiency is recognised as a risk factor for methotrexate toxicity and so it might be expected that supplementation with folic acid may be beneficial in minimising these adverse effects.

Whilst the theoretical basis exists, there is as yet no consensus regarding how best to achieve folate supplementation for patients taking low dose methotrexate. One author has suggested that “there seem to be as many different regimes of folic acid administration as there are rheumatology departments”. Researchers have investigated the adverse effects that are alleviated by folate supplementation, and compared folic acid with folinic acid as well as weekly with daily dosing schedules. There has also been research to determine whether the benefit seen with folate supplementation occurs at the expense of methotrexate efficacy.

A review published in 2004 summarised the available literature and made a recommendation for folic acid supplementation. The authors concluded that folic acid supplementation for RA patients taking methotrexate is likely to reduce the incidence of liver function test abnormalities and may reduce the incidence of gastrointestinal intolerance and stomatitis. There is also some evidence that leucopaenia may be lessened although the background incidence of this is low. Folinic acid is no more effective than folic acid in the prevention of methotrexate-related side-effects, is considerably more expensive and may in fact reduce the effectiveness of methotrexate at higher doses. Without reference to specific evidence, the authors recommend a single dose of 5 mg of folic acid once per week, taken on the morning after methotrexate dosing.

On the basis of current evidence, folic acid improves methotrexate continuation rates without compromising efficacy. It is inexpensive, has essentially no side-effects and should be considered for all patients receiving methotrexate for the treatment of RA. The current evidence base is insufficient to determine the optimum dose for supplementation and weekly doses ranging from 5mg to 27.5mg have been demonstrated to be effective in reducing methotrexate side effects without compromising efficacy. Further studies are required to provide evidence for the choice of dose, frequency and timing.

Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. *Rheumatology* 2004;43:267-71.

Acknowledgment – This E-Bulletin is based on work by Anna McClure, Clinical Pharmacy Coordinator, RGH

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