

RGH Pharmacy E-Bulletin

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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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Serious drug interactions with medications used for gout

Gout is a metabolic disease with symptoms arising from the deposition of monosodium urate crystals in joints and connective tissue tophi. Colchicine does not affect uric acid levels, but reduces the inflammatory reaction to urate crystals. It may be used for pain relief in the acute treatment of gout and/or at lower doses for prophylaxis when urate-lowering treatment is initiated. Allopurinol is a xanthine oxidase inhibitor used to prevent gout attacks, acting by reducing urate levels through inhibition of the metabolism of xanthine to uric acid.

The oral bioavailability of colchicine is 25 to 50%, however this may be increased by medications that inhibit P-glycoprotein transport. 10 to 20% of the drug is excreted in the urine and dose reduction is required in patients with creatinine clearance less than 50 mL/minute (creatinine clearance of less than 10mL/minute is a contraindication to use). The hepatic metabolism of colchicine is mainly by the cytochrome P450 isoenzyme CYP3A4. Medications that inhibit CYP3A4 include clarithromycin, erythromycin, fluconazole, ketoconazole, diltiazem, verapamil, fluvoxamine and ritonavir. Coadministration of colchicine with such medications will increase its levels in the blood and may contribute to toxicity, particularly in predisposed patients such as those with renal impairment. For this reason it is recommended that the combination of colchicine with CYP3A4 inhibitors be avoided if possible, and if this cannot be avoided careful monitoring must be undertaken, particularly in those with renal impairment. Serious toxic effects of colchicine can include blood dyscrasias (e.g. neutropenia, thrombocytopenia, pancytopenia, leukopenia, agranulocytosis) due to bone marrow suppression and multi-organ failure.

In the case of clarithromycin the interaction with colchicine may be fatal and the combination should be avoided. Clarithromycin is a macrolide antibiotic used in the treatment of respiratory tract infections and as a part of *Helicobacter pylori* eradication regimens. It is known to be a strong inhibitor of CYP3A4 and also inhibits P-glycoprotein. Case reports of the interaction between clarithromycin and colchicine have included patients taking doses of 1mg to 1.5mg daily. A retrospective study published in 2005 showed that in 88 inpatients who had received clarithromycin and colchicine concomitantly nine deaths occurred. Factors found to be associated with an increased risk of death in these patients included longer duration of overlapping therapy with colchicine and clarithromycin, the presence of baseline renal impairment and the development of pancytopenia.

Allopurinol reduces the metabolism of azathioprine through inhibition of xanthine oxidase. Azathioprine is a cytotoxic immunosuppressant used in the prevention of organ transplant rejection and in many autoimmune diseases including severe rheumatoid arthritis. It exerts its effect after being metabolised to mercaptopurine, and following this it is normally converted to an inactive compound by xanthine oxidase which is then excreted. Concurrent use with allopurinol can cause mercaptopurine to accumulate and can result in myelosuppression and pancytopenia. If possible the combination of these medications should be avoided. If it is necessary for a patient to receive both, a reduction in the azathioprine dose to one-quarter to one-third of normal is essential. Close monitoring of the patient, including complete blood counts, is required. It is also important to note that mercaptopurine itself is sometimes used instead of azathioprine, and the same precautions are necessary with respect to the use of azathioprine.

Finally, it is important to note that Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are sometimes used in the management of acute gout, and have a range of significant drug interactions. Important examples include the elevation of serum lithium concentrations with concurrent use of NSAIDs, and the increased risk of acute renal impairment when NSAIDs are co-prescribed with ACE inhibitors.

This E-Bulletin is based on work by Liz Learhinan, Senior Clinical Pharmacist, RGH

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