

RGH Pharmacy E-Bulletin

Volume 43 (10): September 19, 2011

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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Mirtazapine-related blood dyscrasias

Many psychotropic medications are known to be associated with blood dyscrasias such as leucopaenias and agranulocytosis – implicated agents are known to include clozapine, olanzapine, chlorpromazine, carbamazepine and imipramine. Mirtazapine, a tetracyclic antidepressant, has also been rarely associated with reports of serious blood dyscrasias. The manufacturer's product information acknowledges leucopaenia, granulocytopenia, agranulocytosis, thrombocytopenia, pancytopenia, anaemia, aplastic anaemia, eosinophilia and coagulation disorders as rare but potential adverse effects. It also states that although granulocytopenia or agranulocytosis is reported to occur during treatment with mirtazapine, but that the rate is no greater than that of the background population. In pre-marketing trials, an incidence of agranulocytosis (absolute neutrophil count, $ANC < 0.1 \times 10^9/L$) or severe neutropaenia ($ANC < 0.5 \times 10^9/L$) was observed for 11 of 10000 subjects (0.11%).

Since marketing, several case reports in the literature suggest a possible causal relationship between mirtazapine and blood dyscrasias, and one case documents recurrence of neutropaenia upon rechallenge at a dose of 15 mg daily. Another case concerned a patient who developed pancytopenia.

The onset of neutropaenia and other blood dyscrasias varies but has been documented between 9-61 days after commencement of mirtazapine. This is compatible with a possible hypersensitivity or immune-mediated mechanism, where drug-induced antibodies destroy already committed stem cells, proliferating precursors or mature blood cells. In one case of neutropaenia associated with mirtazapine, a similar response occurred when the patient had previously been prescribed doxepin and amitriptyline, which may suggest that the mechanism is similar for mirtazapine and tricyclic antidepressants.

Management of mirtazapine-related blood dyscrasias involves cessation of mirtazapine and monitoring of total and differential blood cell counts until normalised. Recovery from neutropaenia can take 2-3 weeks as the normal maturation of neutrophils from bone marrow takes about 12 days. All patients with neutropaenia in pre-marketing trials recovered completely when the medication was discontinued, however there have since been a number of fatal cases.

Granulocyte-Colony Stimulating Factor (G-CSF) such as filgrastim has been used to stimulate bone marrow in cases of clozapine-induced agranulocytosis, though its high cost and potential for side effects (fever and bone pain) limit its wider application in this setting.

In one case of mirtazapine-induced neutropaenia the patient's depression was successfully treated with sertraline after blood counts returned to normal, with no adverse effects, and reports of SSRI-induced neutropaenia are much less common than for mirtazapine and TCAs. If an antidepressant is clinically indicated but neutropaenia occurs with mirtazapine, it may be prudent (and reasonable safe) to try a drug from a different class, such as an SSRI, and monitor blood counts closely.

Health professionals should be aware of the potential (though rare) association between mirtazapine and neutropaenia and other blood dyscrasias, and monitor blood cell counts accordingly during treatment. Patients should be advised to report symptoms of fever, sore throat, stomatitis or other signs of infection.

Acknowledgment – This E-Bulletin is based on work by Stephanie Vaughan, Senior Clinical Pharmacist, RGH.

FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@rgh.sa.gov.au
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