Lamotrigine and skin reactions

Lamotrigine is an anti-epileptic medication which may also be used as a “mood-stabiliser” in the treatment of bipolar disorder. It is known to have the potential to cause skin reactions varying in severity from mild rashes to serious, potentially life-threatening reactions such as Stevens-Johnson syndrome and toxic epidermal necrosis. Serious skin reactions occur in about 1 in 1000 adult patients and 1 in 50-300 children, and usually manifest within the first eight weeks of lamotrigine treatment. Other rare but serious side effects of lamotrigine that can present with a rash include multi-organ hypersensitivity syndrome and aseptic meningitis.

Although many lamotrigine-related skin reactions are mild, mild rashes can progress to severe rashes or to systemic involvement and there is no way to reliably predict which will develop into potentially life-threatening reactions. Discontinuation of lamotrigine is therefore recommended at the first sign of rash (unless it is clearly not drug related). If necessary, a specialist opinion should be sought. The majority of rashes reported with lamotrigine resolve on withdrawal, however some patients have developed irreversible scarring and there have been rare cases with fatal outcomes. It is important to note that, as with other anticonvulsant drugs used for the treatment of epilepsy, abrupt discontinuation may provoke rebound seizures. In general, rechallenge with lamotrigine (with lower initial doses and slower escalation) should only be considered if the rash was mild and the potential benefit clearly outweighs the risk.

The main risk factors for serious skin reactions with lamotrigine have been identified as: high initial doses; rapid dose escalation; and concurrent use with sodium valproate (which decreases lamotrigine clearance). A history of anti-epileptic induced rash appears to increase the risk of non-serious rash with lamotrigine.

Dosing guidelines for lamotrigine (which specify initial doses, dose titration schedules, and maintenance doses) have been developed in order to minimise the likelihood of rash occurring and should be followed carefully - clinicians can refer to the Australian Medicines Handbook for details. Dosing varies according to whether lamotrigine treatment is being commenced in: patients taking drugs known not to affect lamotrigine metabolism; patients taking valproate; or patients taking enzyme inducers (e.g. carbamazepine or phenytoin) and not taking valproate. If the effect of concomitant medications on lamotrigine metabolism is unknown, it is safest to use the regimen for patients taking valproate. Recomencement after an interruption to lamotrigine therapy may require re-titration according to the dosing guidelines. The greater the time interval that has elapsed since the previous dose, the more consideration should be given to this.

All patients treated with lamotrigine should be alerted to the risk of developing rash and should be advised to seek medical advice immediately on first sign of a rash or any skin reaction, or any sign of hypersensitivity, such as fever or lymphadenopathy.

Acknowledgment – This E-Bulletin is based on work by Anita Abarno, Clinical Pharmacy Coordinator, RGH.

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

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Psoriatic Arthritis (PsA) is classified as a spondyloarthropathy characterised by spondolytis (inflammation of the vertebral joints), enthesitis (inflammation at the site of muscle insertion into the bone), dactylitis (inflammation of the digits) and synovitis (inflammation of the synovial membrane). Up to 30% of patients with psoriasis go on to develop PsA, with joint inflammation occurring several years (usually around three to six years) after the appearance of skin lesions. PsA has an equal prevalence amongst men and women.

Treatment of psoriatic arthritis usually requires a coordinated approach involving both the rheumatologist and dermatologist, and is aimed at addressing both skin and joint disease, with the aim of an improvement in pain, fatigue, depression and reduction of joint damage which, when managed adequately, will also reduce inflammation-induced artherogenesis and the likelihood of early mortality from cardiovascular disease.

Although most evidence regarding treatment efficacy has been developed in relation to ankylosing spondyloarthritis, rheumatoid and osteoarthritis, nonsteroidal anti-inflammatories (NSAIDS), lower dose corticosteroids and intra-articular injections can be used in milder forms of PsA. Disease Modifying Anti-Rheumatic Drugs (DMARDs) have been shown to have limited efficacy in PsA but are used, in combination or without co-treatment with of Tumour Necrosis Factor (TNF) inhibitors.

TNF inhibitors have been shown to be efficacious against both the psoriatic and arthritic components of PsA. Activated T-cells bearing markers of antigen activation are abundant in the inflamed joint and skin of PsA. Full antigen-induced T-cell activation occurs in a two step fashion: firstly, when the antigen is presented to the T-cell receptor, and then secondly, when antibodies CD80 and CD86 attach themselves to the T-cell via the CD28 molecule. Activation leads to a homeostatic down modulation of the activated T-cells.

Abatacept competes with the T-cell to bind to CD80 and CD86, thus decreasing serum levels of inflammatory proteins and cytokines implicated in the pathogenesis of PsA. Abatacept is used in the treatment of various arthritic conditions and clinical improvement has been shown in phase I studies involving patients with psoriasis vulgaris. In light of the mode of action in both conditions, it thus was hypothesised it could be used to treat PsA.

In a six-month, multicentre, randomised, double-blind, placebo-controlled, phase II study involving 170 PsA patients, abatacept was well-tolerated and produced the greatest improvement relative to placebo in the dosage range of 10mg/kg, reflected in improved signs and symptoms of arthritis, diminished joint damage, skin lesions, and better physical function and quality of life. Abatacept shows promise as an additional treatment option for PsA, but further studies are warranted as the size and duration of this trial was limited.

Acknowledgment – This E-Bulletin is based on work by Joanna Hogan, Senior Pharmacist, RGH.

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Mirtazapine-related blood dyscrasias

Many psychotropic medications are known to be associated with blood dyscrasias such as leucopaenia 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, granulocytopena, agranulocytosis, thrombocytopenia, pancytopenia, anaemia, aplastic anaemia, eosinophilia and coagulation disorders as rare but potential adverse effects. It also states that although granulocytopena 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, $\text{ANC}<0.1 \times 10^9/\text{L}$) or severe neutropaenia (ANC<$0.5\times10^9/\text{L}$) 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 pancytopena.

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 post-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.

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Drug-induced photosensitivity reactions

Drug induced photosensitivity reactions are a relatively common side effect associated with many medications. These reactions occur via activation of a chemical by ultra-violet or visible light. Many commonly used drugs are implicated (both systemic and topical use), and include amiodarone, NSAIDs, phenothiazines, retinoids, quinolones, sulfonamides, tetracyclines, and thiazides.

Most photosensitive reactions manifest as an exaggerated sunburn on areas of exposed skin; however, some phototoxic reactions may cause a vesicular rash that resembles porphyria cutanea tarda (pseudoporphyria), or other skin conditions, such as lichen planus. Some medications are associated with photosensitive reactions that result in discoloration of the skin; for example, the characteristic blue-grey discoloration that can result from exposure to sunlight during amiodarone treatment. A photosensitive rash to psoralens may resolve with a brown discoloration, and this reaction can be used therapeutically for disorders such as vitiligo.

There are two main types of photosensitive reactions: phototoxic and photoallergic. Phototoxic reactions are the most common form, which occur within minutes to hours after light exposure, and result from direct damage to the skin by a photo-activated medication. The rash is confined to the area of sun exposure, and is dependent on the concentration of drug and the amount of light exposure. Photoallergic reactions occur when repeated exposure to a photoactivated medication results in a cell-mediated immune response. The rash usually occurs within 1–3 days after exposure. Photoallergic reactions occasionally result in a rash that spreads beyond the boundary of light-exposed skin.

A medication history and history of light exposure should be elicited for patients presenting with a rash. Phototesting with ultraviolet or visible light may be required for diagnosis, and also to determine whether the patient can tolerate lower doses of the medication. Most photosensitive reactions are not severe; however, this is dependent on the concentration of medication and the amount of light exposure. Usually, the reaction resolves after the medication is ceased, but this depends on the severity of the reaction and the kinetics of the medication. Some patients develop a persistent light reaction (or chronic actinic keratitis) where the condition persists after drug cessation and can be aggravated by minimal exposure to UV light.

Before treatment with medications commonly associated with photosensitivity, patients should be counselled about the potential for severe skin reactions after exposure to sunlight, and the importance of wearing protective clothing and sunscreen. These measures may be adequate for patients who are required to take medications for a prolonged duration, even after a reaction has occurred. If possible, however, the patient should avoid medication that has caused a skin reaction. If a photoallergic reaction has occurred then the offending medications must be ceased, as reactions of increasing severity may occur upon repeated exposure.

Acknowledgment – This E-Bulletin is based on work by Heather Forbes, Utility Pharmacist, RGH.

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