Australian Government
Department of Health
Therapeutic Goods Administration

Medicines Safety Update

Volume 8, Number 4, August-September 2017

In this issue

Lithium level monitoring and toxicity

Health professionals are reminded that early symptoms of lithium toxicity can occur close to or within the serum therapeutic range. You should remain vigilant for potential signs of lithium toxicity, particularly in patients with risk factors.

Lithium, marketed in Australia as Quilonum SR (450 mg sustained release tablets) and Lithicarb (250 mg tablets), is indicated for the treatment of acute mania, hypomania and for the prophylaxis of manic-depressive illness. Lithicarb is also indicated for the treatment of some cases of schizo-affective illness and character or personality disorders in young people with evidence of cyclothymia.

The risk of lithium toxicity is adequately addressed in the Product Information for Quilonum SR and Lithicarb, but a case heard in the Coroners Court of Victoria involving a patient who died in 2013 as a result of lithium toxicity has prompted this reminder. The patient was elderly and had a number of risk factors that increased the potential for this adverse reaction. A delay in attributing early symptoms of toxicity to lithium was also found to have contributed to the patient's death.

Narrow therapeutic index

There are relatively narrow margins between therapeutic and toxic dosages for lithium and therefore regular blood and clinical monitoring is important. In addition, toxicity occurring close to or within the target serum lithium concentration range is a known risk.

Failure to recognise the early signs of toxicity may lead to a delay in treatment and result in poor patient outcomes including, in the worst cases, death.

Symptoms and risk factors

Early symptoms of lithium toxicity are varied and non-specific. They are most likely to occur when serum lithium concentration exceeds 1.5 mmol/L but can occur when serum lithium levels are within the target concentration range. Symptoms/signs can include:

- fine hand tremor
- diarrhoea
- nausea/vomiting
- polyuria
- thirst
- drowsiness
- agitation
- ataxia and muscle weakness
- agitation
- hyperreflexia.

The most important site of toxicity is the central nervous system. Neurological manifestations of lithium intoxication such as ataxia, dysarthria, dysphagia and cognitive impairment may not be fully reversible despite appropriate treatment. Severe toxicity may result in convulsions, myoclonus and coma.

Lithium toxicity can result from a reduction in glomerular filtration, an increase in tubular reabsorption or altered volume of distribution. A

Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)

TGA Health Safety Regulation

number of factors are known to increase the risk of toxicity including:

- impaired renal function
- advanced age (greater than 50 years)
- nephrogenic diabetes insipidus
- dehydration (including fluid loss from vomiting, diarrhoea and excess sweating)
- reduced salt intake
- thyroid dysfunction
- concurrent illness
- medicines that reduce lithium clearance (for example non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, angiotensin 2 receptor antagonists and diuretics).

Additionally, the following factors are also associated with an increase in the risk of neurotoxicity:

- use of a controlled release formulation
- chronic supratherapeutic dosing.

Health professionals are reminded to be vigilant for the potential signs of lithium toxicity, particularly in patients with risk factors. Furthermore, it is recommended that health professionals educate patients and care providers regarding the early symptoms of lithium toxicity and counsel them to seek medical advice if any are suspected.

Adverse event reports

As of 17 May 2017, the TGA has received 58 reports in which lithium was suspected of causing toxicity. Two of these cases resulted in the death of the patient, including the one that was the subject of the aforementioned case heard by the Coroners Court of Victoria.

The serum lithium level was not reported in all cases describing toxicity. For the cases where it was provided, lithium levels ranged between 1.09 and 5.72 mmol/L. In seven cases the lithium level was less than 1.5 mmol/L.

Interactions with other medicines were identified as a contributing factor in 17 cases, and may have played a role in four other cases.

Inappropriate dosing was found to be a contributing cause of toxicity in two cases, and may have contributed to a third case.

New precautions for hyoscine butylbromide ampoules

Health professionals are reminded that parenteral administration of hyoscine butylbromide can cause tachycardia, hypotension and anaphylaxis and therefore it should be used with caution in patients with pre-existing cardiac conditions. Hyoscine butylbromide is marketed in Australia as Buscopan.

Hyoscine butylbromide is an antispasmodic. Its anticholinergic spasmolytic effect is based both on competitive inhibition of the parasympathetic activation of smooth muscle mediated through muscarinic receptors and, more markedly, through ganglionic blockade of neural transmission.

Hyoscine butylbromide ampoules, administered by intramuscular or slow intravenous injection, are used to treat spasm of the gastrointestinal tract, biliary spasm and renal spasm, and as a diagnostic aid in radiology.

The Australian Product Information (PI) for hyoscine butylbromide lists tachycardia, decreased blood pressure and anaphylaxis as potential adverse effects, but the PI is now being updated to include a stronger warning in the precautions section because these adverse events can be more serious in patients with cardiac conditions.

The updated PI will advise that hyoscine butylbromide ampoules should be used with caution in patients with pre-existing cardiac conditions, such as cardiac failure, coronary heart disease, cardiac arrhythmia or hypertension, and in cardiac surgery. Monitoring of these patients is advised and emergency equipment and personnel trained in its use must be readily available.

Australian adverse event reports

There are 28 cases describing tachycardia and/or hypotension relating to use of hyoscine butylbromide in the TGA's adverse events database. An additional four cases describe anaphylactic reactions. There is insufficient clinical information provided to determine whether or not these reactions occurred in people with pre-existing cardiac conditions. None of these cases reported death, cardiac arrest or myocardial infarction.

Off-label prescribing

Health professionals are encouraged to use caution when considering 'off-label' prescribing and to clearly communicate the potential risks and benefits with patients and/or their carers before deciding on a treatment. The TGA also urges you to report any adverse events that occur during off-label use.

Off-label prescribing refers to the use of a registered medicine outside of the indications, dose, route of administration or patient group set out in the TGA-approved Product Information (PI).

The TGA is responsible for ensuring that medicines available for supply in Australia are safe and fit for their intended purpose. The approved indications, as described in the medicine's PI, have been evaluated for safety and efficacy by the TGA.

The TGA recognises that off-label prescribing may be clinically appropriate in some circumstances, but recommends that such use only be considered when other options are unavailable, exhausted, not tolerated or unsuitable.

Prescribers should discuss the risks and benefits of the proposed treatment with the patient and/or their carers so that they are capable of providing informed consent.

Additionally, the treatment, including its effectiveness and potential adverse events, should be monitored.

In situations where the PI for a medicine is updated in a way that makes continued use 'off label', the patient should be informed so they can participate in the decision regarding treatment options.

FURTHER READING

Council of Australian Therapeutic Advisory Groups: Rethinking medicines decision-making in Australian Hospitals – Guiding principles for the quality use of off-label medicines. November 2013.

Australian Medical Association: Lots to consider in going off-label. Australian Medicine. February 2014.

NPS MedicineWise: Off-label prescribing. Australian Prescriber. December 2013.

What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, and herbal, traditional or alternative remedies. We particularly request reports of:

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website
- **online** at www.tga.gov.au
- **by fax** to 02 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For more information about reporting, visit www.tga.gov.au or contact the TGA's Pharmacovigilance and Special Access Branch on 1800 044 114.

DISCLAIMER

For the latest safety information from the TGA, subscribe to the TGA Safety Information email list via the TGA website

For correspondence or further information about Medicines Safety Update, contact the TGA's Pharmacovigilance and Special Access Branch at ADR.Reports@tga.gov.au or 1800 044 114

Medicines Safety Update is written by staff from the Pharmacovigilance and Special Access Branch

Editor:
Dr Jane Cook

Deputy Editor:
Mr Michael Pittman

TGA Principal Medical Adviser:
Adj Prof Tim Greenaway

Contributors include:
Dr Claire Behm
Mr Andrew Case
Dr Abby Krishnamoorthy
Dr Grant Pegg