Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Volume 4, Number 5, October 2013

In this issue

Atomoxetine and suicidality in children and adolescents

Serious adverse events reported to the TGA, including one case involving the death of a child, reinforce the importance of health professionals adequately informing parents and caregivers of the risks of suicidal ideation and behaviour in children and adolescents being prescribed atomoxetine (Strattera).

Atomoxetine is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), as defined by DSM-IV criteria, in children aged 6 years and over, adolescents and adults.

The risks of suicidal ideation and behaviour with atomoxetine are well known and are reinforced in the Product Information in the precautions section, as well as in a boxed warning.

Clinical trials

A greater risk of suicidal ideation was observed in children and adolescents receiving treatment during clinical trials compared with placebo. A pooled analysis of 12 short-term (6–18 weeks) trials (11 in ADHD and one in enuresis) showed the average risk of suicidal ideation in patients treated with atomoxetine was 0.4% (5/1357) compared with 0% (0/851) in patients treated with placebo. One suicide attempt was reported in patients being treated with atomoxetine.

Adverse event data

To July 2013, the TGA received 74 reports of psychiatric disorders associated with atomoxetine. In 65 of these cases, atomoxetine was the sole suspected medicine. Over half of the reported cases (42) were reports of suicidal ideation. Of the 38 reports of suicidal ideation in which the age of the patient was given, 28 reports were in children and adolescents aged 18 years and under. The TGA also received two reports of attempted suicide in children and adolescents and one report of completed suicide in a child being treated with atomoxetine.

Information for health professionals

When considering prescribing atomoxetine in children and adolescents, health professionals should carefully weigh the risks of suicidality against the benefits of atomoxetine therapy.

Patients who are prescribed atomoxetine should be carefully monitored for suicidality, especially in the first few months of treatment and whenever there is a change in dose.

Parents and caregivers should be warned of the risks and alerted to the need to monitor for signs of unusual changes in behaviour or precursors of suicidality, such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania or mania. Parents and caregivers should also be advised of the importance of seeking immediate medical attention if such signs are identified.

Health professionals are encouraged to report all adverse events associated with atomoxetine to the TGA.

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

TGA Health Safety Regulation

MEDICINES SAFETY UPDATE

Rotavirus vaccination and the risk of intussusception

Health professionals are advised that a recently completed study has confirmed that there is an elevated risk of intussusception following the first and second doses of rotavirus vaccines, Rotarix and RotaTeq.

The TGA, working in collaboration with state health authorities, has completed an investigation into this association. Interim results of the investigation were published on the TGA website in February 2011 and in Medicines Safety Update in April 2011.[1]

The final study included data from six jurisdictions (NSW, Victoria, Western Australia, South Australia, Queensland and the Northern Territory) for a three-year period from July 2007 to June 2010.[2] Validated cases of intussusception in children aged 1–12 months were identified from hospital admissions data and, in some states, through the Paediatric Active Enhanced Disease Surveillance System. Vaccination status for each case was obtained from the Australian Childhood Immunisation Register (ACIR). There were 306 cases of intussusception suitable for analysis, of which 260 were recorded to have received rotavirus vaccination.

The association between rotavirus vaccination and the risk of intussusception was examined using a self-controlled cases series (SCCS) method and was confirmed with a matched case-control analysis using matched controls from the ACIR.

Using the SCCS method, there was clear evidence of an elevated risk of intussusception following the first dose of both rotavirus vaccines. There was also some elevated risk of intussusception 1–7 days following the second dose of both vaccines (see Table). There was no evidence of increased risk of intussusception following a third dose of RotaTeq.

Risk–benefit consideration

Prior to the introduction of rotavirus vaccination, there were an estimated 10 000 hospitalisations annually in children under five years due to rotavirus gastroenteritis. Since the introduction of Rotarix and RotaTeq onto the National Immunisation Program, emergency department visits for acute gastroenteritis in young children have declined and hospitalisations for rotavirus gastroenteritis in the under-five year age group have been reduced by over 70%.[3,4]

Based on the established benefits of rotavirus vaccination and the rare occurrence of intussusception, both the World Health Organization and the Australian Technical Advisory Group on Immunisation have recommended the continued use of rotavirus vaccine for infants.

Information for health professionals

Health professionals are advised that information about the risk of intussusception following rotavirus vaccination has been added to the postmarketing adverse events sections of the Product Information of Rotarix and RotaTeq.

Health professionals should advise parents and caregivers of the risks and signs of intussusception, and the importance of seeking early medical attention if they suspect their child has intussusception.

Further information is available on the Immunise Australia website and in the Australian Immunisation Handbook.

REFERENCES

1. Therapeutic Goods Administration. Rotavirus vaccination and risk of intussusception: investigation of a possible safety signal. Med Saf Update 2011;2.
2. Carlin JB, Macartney K, Lee KJ, Quinn HE, Buttery J, Lopert R, et al. Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's national immunisation program. Clin Infect Dis 2013 Aug 30. doi: 10.1093/cid/cit520.
3. Macartney KK, Porwal M, Dalton D, Cripps T, Maldigri T, Isaacs D, et al. Decline in rotavirus hospitalisations following introduction of Australia's national rotavirus immunisation programme. J Paediatr Child Health 2011;47:266-70.
4. Lambert SB, Faux CE, Hall L, Birrell FA, Peterson KV, Selvey CE, et al. Early evidence for direct and indirect effects of the infant rotavirus vaccine program in Queensland. Med J Aust 2009;191:157-60.

Table
Relative risk of intussusception after first and second dose of Rotarix and RotaTeq

	Relative risk – dose 1		Relative risk – dose 2
	Day 1–7	Day 8–21	Day 1–7
Rotarix (95% CI)	6.8 (2.4–19.0) p<0.001	3.5 (1.3–8.9) p=0.01	2.8 (1.1–7.3) p=0.03
RotaTeq (95% CI)	9.9 (3.7–26.4) p<0.001	6.3 (2.8–14.4) p<0.001	2.8 (1.2–6.8) p=0.02

CI confidence interval

MEDICINES SAFETY UPDATE

Drug-induced liver injury

Drug-induced liver injury (DILI) has been associated with a wide variety of drugs, including prescription, over-the-counter and complementary medicines, and poses a diagnostic and management challenge for health professionals. Early recognition is important to minimise injury.

Because there is no pathognomonic injury type associated with DILI, the diagnosis is often one of exclusion. However, it should be included in the list of differential diagnoses in any patient with new-onset liver disease and in any patient with deterioration of existing liver disease after the recent addition of a new drug.[1]

Important differential diagnoses include viral hepatitis, alcoholic liver disease, autoimmune disorders, liver congestion from cardiac failure, liver injury from shock or septicaemia, and biliary tree disorders. Rarer infiltrative liver diseases, such as haemochromatosis and Wilson's disease, may also require exclusion.

Table
Some drugs commonly known to cause elevated liver enzymes *

Pattern of abnormality	Examples of drugs associated
Hepatocellular	Antibiotics: isoniazid, rifampicin
	Antifungals: ketoconazole, itraconazole, fluconazole
	Antivirals: zidovudine, didanosine, nevirapine, ritonavir, indinavir
	Anticonvulsants: phenytoin, carbamazepine, sodium valproate, phenobarbitone
	Antihypertensives: captopril, enalapril, lisinopril, losartan
	Antidepressants: amitriptyline, imipramine, trazodone, venlafaxine, fluoxetine, paroxetine, duloxetine, sertraline, bupropion
	Anti-inflammatories: ibuprofen, indomethacin, diclofenac, sulindac
	Statins
Mixed hepatitis/ cholestasis	Antibiotics: amoxycillin/clavulanic acid, trimethoprim/ sulfamethoxazole, clindamycin
	Immunosuppressive: azathioprine
Cholestatic	Antibiotics: erythromycin, nitrofurantoin, rifampicin, amoxycillin/clavulanic acid
	Antidepressants: duloxetine, mirtazapine, tricyclic antidepressants
	Antiplatelets: clopidogrel

* Note: this list is not comprehensive

Causes

Determining the cause of liver injury is often complex, as initial symptoms may be non-specific, the date of commencement of drugs may not be clearly recalled, and the picture may be confounded by underlying disease processes.

There is a wide spectrum of presentations of DILI, ranging from mild asymptomatic elevation of liver function tests to serious DILI with acute fulminant hepatic failure.

Liver injury associated with medicines occurs via two mechanisms. The pathogenesis involves either direct biochemical effects or the stimulation of an immune response by the toxic drug or metabolite.[1]

Hepatotoxins

Most significant hepatotoxins cause a hepatocellular pattern of injury, but cholestasis and mixed-pictures can also be drug-induced.[2] However, individual drugs that cause liver injury tend to cause patterns of injury and latency periods characteristic of that drug. Exceptions include amoxycillin/clavulanic acid, which can produce more than one pattern of injury.[3]

Examples of drugs known to cause elevated liver enzymes are in the Table. These drugs are also included in a list of substances most implicated in DILI-Acute Liver Failure (ALF).[4] Caution should be exercised and more regular liver monitoring undertaken when combining two or more drugs known to cause ALF in vulnerable patients, such as the elderly, those on polypharmacy, those with potential liver ischaemia, or those with existing liver disease.

Latency periods can be short (hours to days), intermediate (1–8 weeks) or long (1–12 months or more). In rare cases, the reaction can occur after the drug is ceased.

Diagnosis

Alanine transferase (ALT) and alkaline phosphatase are considered the most useful of the liver function tests to determine the type of hepatic injury but, despite a high sensitivity, they carry a low specificity for predicting serious hepatotoxicity. ALT values that are within the reference range at baseline and rise two- to threefold should lead to enhanced vigilance in terms of more frequent monitoring. ALT values 4–5 times higher than the reference range should lead to prompt discontinuation of the drug.[3]

Bilirubin levels twofold greater than baseline, when accompanied by a rise of ALT of more than threefold, indicate a more severe liver injury has already occurred and must prompt investigation. If a drug is suspected to be the causative agent, it should be promptly discontinued.

Because the diagnosis and prediction of a serious DILI is difficult, recent research has focused on the role of biomarkers, such as micro-RNAs.

Treatment

Treatment of DILI is largely supportive. Most events resolve with the withdrawal of the causative agent. While the time to recovery can take a few days to a week, more commonly there is improvement on cessation of the drug with slower resolution over several weeks to months. In very rare cases, liver injury is permanent and a liver transplant is required.

It is advised that a drug suspected of causing liver injury should not be re-introduced, as the subsequent reaction may be more severe than the initial one, especially if the reaction was hypersensitivity related. In cases where a number of possible medicines could have been involved, careful consideration should be given to recommencement of the medicines, together with careful monitoring.

Health professionals are encouraged to report all cases of liver injury associated with prescription, over-the-counter and complementary medicines to the TGA.

REFERENCES

1. Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterol 2008;135:1924-34.
2. Kaplowitz N. Drug-induced liver injury. Clinc Infect Dis 2004;38 Suppl 2:S44-48.
3. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. US Food and Drug Administration. 2009.
4. Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010;52:2065-76.

FURTHER READING

Mehta N. Drug-induced hepatotoxicity. Medscape. 2012.

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. US National Library of Medicine. 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 and with the October issue of *Australian Prescriber*
- **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 Office of Product Review 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 Office of Product Review at ADR.Reports@tga.gov.au or 1800 044 114

Medicines Safety Update is written by staff from the Office of Product Review