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Medicines Safety Update is the drug safety bulletin of the Therapeutic Goods Administration (TGA). It is published in each issue of *Australian Prescriber*. You can also read it and sign up for free Medicines Safety Update email alerts on the TGA website at www.tga.gov.au/adr/msu.htm

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Lamotrigine and serious skin reactions

Summary

Stevens-Johnson syndrome and toxic epidermal necrolysis can develop following lamotrigine administration. Use a lower dose when prescribing lamotrigine with valproate. Advise patients taking lamotrigine to contact their doctor immediately if they experience rash or fever. Discontinue lamotrigine at the first sign of a rash.

Many skin reactions caused by lamotrigine are mild, but serious rashes such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Severe skin reactions occur in 1 in 50–300 children and 1 in 1000 adults taking lamotrigine, and generally appear within the first eight weeks of therapy.[1,2]

As of September 2010, the TGA had received 552 reports of suspected adverse reactions to lamotrigine, 43 (8%) of which were reports of SJS and/or TEN.

SJS and TEN may first present as a prodrome of malaise, fever, headache and cough followed by the sudden appearance of widespread macules, usually on the face, neck and upper trunk, but may appear anywhere on the body. TEN is characterised by widespread bullae which slough over a period of days resulting in large areas of denuded skin.

Although many rashes are mild, there is no way to reliably predict which will develop into serious, potentially life-threatening rashes. Lamotrigine should therefore be discontinued at the first sign of a rash unless the rash is clearly not drug-related.[2]

Many of the cases reported to the TGA involve concomitant use of lamotrigine and valproate, which increases the risk of developing SJS or TEN. Use a lower dose of lamotrigine for patients taking valproate (see the Product Information for details). Avoid high initial doses of lamotrigine and rapid escalation of doses because they also increase the risk of developing a severe skin reaction.

References

1. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2010.
2. Lamictal Product Information. GlaxoSmithKline Australia Pty Ltd. 2010 Feb 3.

Serotonin syndrome

Summary: a reminder

Concomitant use of serotonergic drugs, or use of a single drug in a susceptible patient, can lead to serotonin syndrome which can be life-threatening. The syndrome usually presents as a clinical triad of altered mental status, autonomic dysfunction and neuromuscular excitation, but early signs and symptoms can be mild and easily overlooked. Treatment involves ceasing all serotonergic drugs. Moderate to severe cases usually require hospitalisation and specialist care.

Serotonergic drugs are commonly prescribed in Australia, and carry a risk of serotonin syndrome, especially when used in combination. Any drug that directly or indirectly increases central serotonin neurotransmission at postsynaptic 5-hydroxytryptamine 1A (5-HT1A) and 5-hydroxytryptamine 2A (5-HT2A) can induce serotonin syndrome (see Box 1).

A recent Australian study showed that combinations of drugs with the potential to cause serotonin syndrome are used relatively frequently. In a cohort of over 273 000 elderly war veterans and their dependants, nearly 116 000 (42%) were prescribed at least one serotonergic drug in the period 2000 to 2004. More than 20 000 (8%) had at least one period in which they may have been using two or more serotonergic drugs concomitantly, and over 1800 (0.7%) were dispensed potentially fatal combinations such as a monoamine oxidase inhibitor (MAOI) with a selective serotonin reuptake inhibitor (SSRI), tramadol, or venlafaxine.[1]

Diagnosis

Diagnosis of serotonin syndrome is based on clinical judgement and can be challenging. Mild symptoms can be mistaken for an exacerbation of psychiatric symptoms, and more severe cases for conditions such as neuroleptic malignant syndrome or malignant hyperthermia.

Table 1 lists common clinical features of serotonin syndrome. Generalised hyperreflexia and ankle and ocular clonus suggest a diagnosis of serotonin syndrome because they are not seen in many other conditions.[2,3]

Serotonin syndrome most commonly occurs after a second serotonergic drug is added, or if there has been an inadequate washout interval between changing medicines (see further information, below).[2] It may also be the result of a dose increase or overdose, but may occur even at modest doses in patients with reduced clearance. Dose reduction is recommended in susceptible patients, such as those with hepatic impairment.

Box 1

Drugs that may contribute to serotonin syndrome [2,3]

Antidepressants
SSRIs
MAOIs (reversible and irreversible)
Tricylic antidepressants
SNRIs

CNS stimulants
Amphetamines and derivatives such as MDMA (ecstasy)

Opioids
Tramadol
Pethidine
Dextromethorphan
Fentanyl

Other
Lithium
St John's wort
Tryptophan

SSRI selective serotonin reuptake inhibitor
MAOI monoamine oxidase inhibitor
SNRI selective noradrenaline reuptake inhibitor

Table 1

Clinical features of serotonin syndrome [2–4]

Altered mental status
Confusion, agitation, restlessness, excitement
Autonomic dysfunction
Tachycardia, hypertension, hyperthermia, sweating, mydriasis, flushing, shivering
Neuromuscular excitation
Hyperreflexia, hypertonia, ataxia, tremor, clonus (spontaneous, inducible or ocular)

Treatment

Awareness of the possibility and supportive care are the most important treatments of serotonin syndrome. In most cases symptoms will improve when the serotonergic agents are ceased. Milder cases will usually resolve in 1–3 days. Moderate to severe cases usually require hospitalisation for haemodynamic stabilisation, sedation, temperature control and hydration. Serotonin antagonists such as cyproheptadine and chlorpromazine may be administered, and benzodiazepines may be required to manage agitation.

Further information

Isbister GK, Buckley NA, Whyte IM. Serotonin toxicity: a practical approach to diagnosis and treatment. Med J Aust 2007;187:361-5.

For information about switching between antidepressants:

Washout or taper when switching antidepressants. Aust Adv Drug React Bull 2009;28:19.

Therapeutic Guidelines: Psychotropic. Version 6. Melbourne: Therapeutic Guidelines Ltd; 2008.

Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2010.

References

1. Ringland C, Mant A, McGettigan P, Mitchell P, Kelman C, Buckley N, et al. Uncovering the potential risk of serotonin toxicity in Australian veterans using pharmaceutical claims data. Br J Clin Pharmacol 2008;66:682-8.
2. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352:1112-20.
3. Isbister GK, Buckley NA, Whyte IM. Serotonin toxicity: a practical approach to diagnosis and treatment. Med J Aust 2007;187:361-5.
4. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter serotonin toxicity criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM 2003;96:635-42.

Drug-induced acute akathisia

Summary

Acute drug-induced akathisia is a relatively common extrapyramidal side effect that can be associated with poor outcomes. Clinicians are reminded to be vigilant to the signs and symptoms of akathisia, particularly in patients taking typical or atypical antipsychotics.

While acute akathisia is seen with typical antipsychotics, it can also occur with atypical antipsychotics, antidepressants (such as selective serotonin reuptake inhibitors (SSRIs)), antiemetics, calcium channel blockers and other medicines.

Akathisia is frequently distressing for patients and in psychiatric settings has been associated with poor medication compliance, agitation, and exacerbations of psychiatric symptoms.[1] Akathisia can be mistaken for anxiety or agitation related to affective or psychotic disorders, which can result in a changes to antipsychotic therapy that worsen the akathisia. A combination of akathisia, depressive symptoms and impulsiveness may contribute to aggressiveness and suicidality in some patients with akathisia.[2]

How common is antipsychotic-induced akathisia?

In the Clinical Antipsychotics Trial of Intervention Effectiveness (CATIE) study, it was estimated that 26–35% of people taking an atypical antipsychotic experienced akathisia each year, compared with 35% taking the typical antipsychotic perphenazine*.[3]

To September 2010 the TGA had received 197 reports of akathisia in which a range of medicines were suspected, including antipsychotics, antidepressants, and antiemetics. An antipsychotic medication was suspected in 62% of reports while more than one drug was implicated in 24% of reports.

Patients with bipolar affective disorder, particularly bipolar depression, may be at a higher risk of developing akathisia with antipsychotics than patients with schizophrenia.[4] Other risk factors include higher antipsychotic doses, high-potency antipsychotics, rapid dose escalation, and psychotropic drug combinations.

Diagnostic issues

The essential underlying feature of akathisia is a subjective feeling of 'inner' restlessness and the drive to move. This can result in significant distress. Objective motor signs of restlessness usually take the form of semipurposeful repetitive movements (e.g. fidgety movements). The subjective component may predominate with there being little or no apparent motor restlessness. The diagnosis of akathisia is a clinical one and can be rapidly assessed (see Box 2). A standardised screening tool, such as the Barnes Akathisia Rating Scale, can aid in diagnosis and monitoring.[5]

Persistent and tardive forms of akathisia can also occur.

Differential diagnoses include restless legs syndrome, drug withdrawal states, tardive dyskinesia, neurological disorders (such as Parkinson's disease, subthalamic lesions), rebound reactions from abrupt withdrawal of psychotropic medication and the activation syndrome sometimes seen with initiation of certain psychotropic drugs (such as partial dopamine agonists, SSRIs, and the serotonin and noradrenaline reuptake inhibitors).

Box 2

Brief clinical assessment for akathisia [1,5]

Ask about:

- feeling of inner restlessness
- desire to walk or pace
- difficulty sitting or standing still
- related distress

Observe for restless movements, such as:

- fidgety movements
- leg swinging while sitting
- rocking from foot to foot
- pacing

Preventing and managing antipsychotic-induced akathisia

To minimise the risk of akathisia, avoid polypharmacy, titrate the antipsychotic dose slowly and use the lowest effective dose.

Antipsychotic-induced akathisia can be managed by stopping unnecessary contributing medicines, reducing the dose or switching to an antipsychotic less likely to cause akathisia.

Some anticholinergic medicines (e.g. benztropine, benzhexol) are registered in Australia for the treatment of drug-induced extrapyramidal symptoms. Lipophilic beta blockers and benzodiazepines are sometimes used in specialist settings to treat antipsychotic-induced akathisia, but are not registered in Australia for this indication.

References

1. Bratti IM, Kane JM, Marder SR. Chronic restlessness with antipsychotics. Am J Psychiatry 2007;164:1648-54.
2. Poyurovsky M. Acute antipsychotic-induced akathisia revisited. Br J Psychiatry 2010;196:89-91.
3. Miller DD, Caroff SN, Davis SM, Rosenheck RA, McEvoy JP, Saltz BL, et al. Extrapyramidal side-effects of antipsychotics in a randomised trial. Br J Psychiatry 2008;193:279-88.
4. Kumar R, Sachdev PS. Akathisia and second-generation antipsychotic drugs. Curr Opin Psychiatry 2009;22:293-9.
5. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672-6.

* not registered in Australia

Unintended pregnancy due to interaction between etonogestrel implant (Implanon) and carbamazepine

Summary

An interaction between hepatic-enzyme-inducing medicines, such as carbamazepine, and etonogestrel implant (Implanon) can lead to contraceptive failure. Depending on the length of co-administration, patients should be instructed to use a barrier method in addition to Implanon, or Implanon should be removed and another non-hormonal contraceptive method used.

Interactions between hormonal contraceptives and other medicines leading to a decreased contraceptive effect are well recognised.[1] For example, carbamazepine can reduce the efficacy of oral and implantable hormonal contraceptives by inducing cytochrome P450 enzymes, which increases clearance of sex hormones.

Implanon is a long-acting progesterone-only contraceptive implant that contains etonogestrel. To August 2010, the TGA had received 32 reports describing contraceptive failure leading to unintended pregnancy due to a suspected interaction between Implanon and carbamazepine.

Women taking hepatic-enzyme-inducing drugs should use a barrier method in addition to Implanon during the time of concomitant drug administration and for 28 days after discontinuation (see Box 3).[2] In women on long-term treatment with hepatic-enzyme-inducing drugs, remove Implanon and recommend a non-hormonal method instead.[2]

References

1. Implanon: interactions and failure of contraception. Aust Adv Drug React Bull 2007;26:4.
2. Implanon Product Information. Schering-Plough Pty Ltd. 2009 Feb 10.

Box 3

Medicines that may decrease the efficacy of Implanon [2]

- Barbiturates
- Griseofulvin
- Nelfinavir *
- Oxcarbazepine
- Phenytoin
- Primidone
- Rifabutin
- Rifampicin
- Ritonavir
- St John's wort
- Topiramate

* not registered in Australia

What to report? You do not need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, 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
- birth defects

Reports may be submitted:

- **using the 'blue card'** available from the TGA website (www.tga.gov.au/adr/bluecard.pdf) and in the April, August and December issues of *Australian Prescriber*
- **online** on the TGA website (go to www.tga.gov.au and click on 'report a problem' on the left)
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For further information, please contact the TGA's Office of Product Review on 1800 044 114.

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