Clozapine and severe constipation

Summary

If left untreated, clozapine-induced constipation can lead to serious, potentially fatal complications including intestinal obstruction, ischaemia and perforation.

While myocarditis and blood dyscrasias are well-known serious adverse effects of clozapine, constipation associated with clozapine can also lead to serious complications if not detected and managed promptly.

A 2008 review of cases that had been published or reported to Australian or New Zealand pharmacovigilance programs described 102 cases of serious clozapine-induced gastrointestinal adverse effects, 28 (27.5%) of which resulted in death. The main presenting symptoms were abdominal pain, abdominal distension and vomiting.

To December 2010, the TGA had received 66 reports of serious gastrointestinal adverse events associated with clozapine, such as intestinal obstruction, paralytic ileus, intestinal ischaemia, intestinal perforation and gastrointestinal necrosis. Thirteen (19.5%) cases had a fatal outcome, although the gastrointestinal adverse event was not necessarily the cause of death in each case.

Constipation associated with clozapine, and with other typical and atypical antipsychotics, is largely due to peripheral anticholinergic effects. Concomitant administration of medicines with anticholinergic activity such as benztropine, tricyclic antidepressants and antipsychotics can contribute to constipation. In a review of 38 French cases of ischaemic colitis and gastrointestinal necrosis associated with treatment with antipsychotics (mostly typical antipsychotics or clozapine), 25 (66%) cases involved treatment with at least one other drug with anticholinergic activity. Fourteen (37%) of the cases reviewed had a fatal outcome; three of these were in patients on clozapine, two of whom were receiving clozapine monotherapy.

Health professionals should counsel patients about the risk of constipation with clozapine and question patients about their bowel movements. Initiate treatment promptly if constipation is suspected or reported. An overview of management of constipation in adults was published in the August 2010 issue of Australian Prescriber.

References

Drug interaction between tamoxifen and antidepressants

Summary

A recent study has suggested a higher death rate amongst women taking tamoxifen for breast cancer who were also using the selective serotonin reuptake inhibitor paroxetine. This is thought to be a result of reduced conversion by cytochrome P450 2D6 of tamoxifen to a major active metabolite. Other studies have not found an association between CYP2D6 inhibitors and poorer outcomes in women taking tamoxifen. Until more conclusive data are available, it may be prudent to avoid, where possible, prescribing antidepressants that inhibit CYP2D6 to women with breast cancer being treated with tamoxifen.

Antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) are commonly used in women with breast cancer to treat major depressive disorder and, off-label, for hot flushes. It is estimated that up to 25% of women with breast cancer suffer from major depressive disorder during the course of their treatment and recovery.1

Tamoxifen is metabolised to one of its major active metabolites, endoxifen, by CYP2D6. Reduced plasma endoxifen levels have been reported with some SSRIs,2 particularly those that are potent CYP2D6 inhibitors, which could result in reduced efficacy of tamoxifen. A recent observational study found an association between use of tamoxifen concurrently with paroxetine (an irreversible CYP2D6 inhibitor) and breast cancer mortality3 but other studies have not found an association between CYP2D6 inhibitors and breast cancer recurrence or death in women taking tamoxifen.4,6

Although evidence from epidemiological studies is conflicting, the mechanism of the effect is biologically plausible, and so caution is warranted when prescribing antidepressants that moderately or strongly inhibit CYP2D6 to women taking tamoxifen (see box). Antidepressants with little or no inhibitory effect on CYP2D6 may be suitable alternatives. It should be noted that some other medicines inhibit CYP2D6, with examples of potent inhibitors including quinidine and cinacalcet.

References


Box

Antidepressant CYP2D6 inhibitors7,8 *

<table>
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<th>Potent inhibitors</th>
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<tr>
<td>Bupropion†</td>
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<td>Fluoxetine</td>
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<td>Paroxetine</td>
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<th>Moderate inhibitors</th>
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<tr>
<td>Duloxetine</td>
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<td>Sertraline (mild inhibitor at doses &lt; 100 mg/day)</td>
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* The information provided is a guide only. The precision in categorising the strength of CYP2D6 inhibition is limited for some antidepressants.
† Not registered in Australia for the treatment of depression
Methysergide and retroperitoneal fibrosis

Summary

Retroperitoneal fibrosis is a well recognised adverse effect associated with long-term uninterrupted use of methysergide. To reduce the risk of this adverse effect, withdraw methysergide for 3 to 4 weeks at least every 6 months. Reduce the dose gradually during the last 2 to 3 weeks of each course to avoid rebound headache.

Methysergide (Deseril) is an ergot alkaloid derivative indicated for prophylaxis of migraine, cluster headaches and other vascular headaches. It is considered the most potent of the prophylactic drugs for migraine and may be effective when first- and second-line therapies fail. The most well-known serious adverse effect of methysergide is retroperitoneal fibrosis, which is usually associated with uninterrupted use for longer than six months, although cases have been reported with continuous use for less than six months. Pleuro-pulmonary fibrosis and fibrotic changes of the pericardium and cardiac valves have also been associated with methysergide in a small number of patients. Intermittent use of methysergide is recommended to reduce the risk of fibrotic complications.

The TGA has recently received two reports of retroperitoneal fibrosis where methysergide was suspected, bringing the total number of reports received, to December 2010, to 22. A 37-year-old woman who received methysergide uninterrupted for 16 months developed acute renal failure and required bilateral ureteric stents. In the second report, a 43-year-old woman who received methysergide uninterrupted for 30 months developed acute renal failure and required bilateral nephrostomy.

Methysergide should be withdrawn for 3 to 4 weeks after every six months or less of continuous use. The withdrawal should be gradual, over 2 to 3 weeks, to avoid rebound exacerbation of migraine. Symptoms and signs such as general malaise, backache, girdle or flank pain, dysuria, oliguria, increased blood nitrogen or vascular insufficiency of the lower limb should raise the suspicion of retroperitoneal fibrosis.

References

2. Deseril Product Information. Link Medical Products Pty Ltd. 2009 Apr 9.

Thank you for your reports

The TGA received over 17 000 adverse reaction reports in 2009–10, which was an increase of more than 7000 reports from 2008–09. The increase in report numbers was largely attributable to the H1N1 influenza vaccination program, which used a variety of strategies to encourage consumers and health professionals to report adverse events, facilitating close monitoring of the vaccine’s safety (see Medicines Safety Update Issue 4, August 2010). General practitioners contributed 1720 reports and pharmacists 790 reports.

The TGA thanks all those who have reported suspected adverse reactions – your reports are essential to early detection and investigation of potential safety signals. Please continue to report adverse events that might be related to a medicine or vaccine, particularly those that are serious or associated with new medicines or possible interactions (see ‘What to report?’ on page 25). There is no need to be certain that a drug caused the reaction – a suspicion is reason enough to report, and contributes valuable information to our medicines safety monitoring activities. Similarly, please report adverse effects that you consider to be known as these reports can contribute to a greater understanding of a medicine’s safety profile.

Thank you for your reports
Suspected adverse reactions to vaccines: a reminder to report

Adverse events following immunisation (AEFIs) are notifiable conditions by healthcare providers in the Australian Capital Territory, New South Wales, Northern Territory, Queensland, South Australia, Victoria and Western Australia, and must be reported directly to the relevant health authority. In Tasmania, immunisation providers should report directly to the TGA. State and territory health authorities forward AEFI reports to the TGA.

Healthcare providers should report AEFIs promptly, and encourage consumers to report suspected adverse effects to their doctor, immunisation provider, state health authority or directly to the TGA (see ‘What to report?’ below). For health authority contact details and further information about the adverse effects of vaccines, see the Australian Immunisation Handbook (www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/handbook-home).

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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.

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

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