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Medicines Safety Update

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In this issue

Measles, mumps, rubella, varicella vaccine

Health professionals are reminded that, to minimise the risk of fever and febrile convulsion, measles, mumps, rubella, varicella vaccine should not be administered as the first dose of measles-containing vaccine to children younger than four years.

Measles, mumps, rubella, varicella (MMRV) vaccine is a combination live virus vaccine for immunisation against these four common childhood illnesses.

While MMRV vaccine is approved for use in children from nine months of age, on 1 July 2013 it was added to the National Immunisation Program (NIP) schedule to be given at 18 months after an initial dose of measles, mumps, rubella (MMR) vaccine at 12 months of age.

Minimising risk

Like most vaccines, MMRV vaccine can cause some mild adverse events. In rare cases, fever after vaccination can lead to febrile convulsions in young children.

MMRV vaccine is only recommended for use as a second dose of measles-containing vaccine. This is because MMRV vaccine administered as a first dose in children aged 9–30 months is associated with an increased rate of fever and febrile convulsions, compared to separate MMR and varicella vaccination.

As described in the postmarketing data section of the Product Information (PI), the attributable risk of febrile convulsions 5–12 days following MMRV vaccination as a first dose of measles-containing vaccine is 3.64/10 000 (95% CI: −6.11;8.30). This equates to one additional case of febrile convulsion per 2747 young children, when compared to MMR or concomitant MMR and varicella vaccination.

When used as the second measles-containing vaccination, there is no indication of an increased risk.

The overall risk of fever and subsequent febrile convulsion in children is greatly reduced by following the NIP schedule of the initial dose of MMR vaccine at 12 months and the second vaccine dose, as MMRV, at 18 months.

Dosage instructions in the PI recommend an interval of six weeks to three months between the first and second vaccine doses. As with other live virus vaccines, under no circumstances should the interval be less than four weeks.

Further information for health professionals is available on the Immunise Australia website.

Adverse events

The TGA continues to receive adverse event reports that suggest MMRV vaccine has been administered as the first dose of measles-containing vaccine in children aged 12 months or younger. In the 12 months to 1 May 2014, the TGA received seven such reports. There were also two reports of MMRV vaccine being given at the same time as other vaccines that contain either MMR or varicella.

Adverse events following immunisation at any age should be reported through the usual reporting mechanisms in your State or Territory or to the TGA.

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

TGA Health Safety Regulation

Fentanyl patches and accidental exposure in children

Health professionals are reminded of the risks of accidental exposure to or ingestion of fentanyl patches, especially for children.

Fentanyl is an opioid analgesic, interacting predominantly with mu-opioid receptors.

Various strengths of fentanyl transdermal delivery system products (patches) are funded under the Pharmaceutical Benefits Scheme as a restricted benefit for 'chronic severe disabling pain not responding to non-narcotic analgesics'.

Like other opioids, at lower doses fentanyl may cause constipation, nausea and vomiting, hypotension, dysphoria and euphoria, urinary retention, blurred vision, impaired cognition and sedation. As the dose increases, it can also cause:

- convulsions
- extreme somnolence progressing to coma
- respiratory depression with the potential for respiratory arrest
- cardiac arrhythmias, circulatory collapse and cardiac arrest.

Non-users who are opiate naïve, and especially children, are at greater risk of very serious adverse events if they are inadvertently exposed to or ingest fentanyl patches, whether they be used or unused.

The Product Information (PI) for fentanyl patches includes instructions to keep the products out of reach of children before, during and after use, as well as other precautionary information. The PI also provides instructions for the safe disposal of patches.

The opiate dose delivered through fentanyl patches is high, with 12 microgram considered approximately equivalent to 45 mg per day of oral morphine. Even used patches can retain high residual levels of the active ingredient (about 60% of the intended dose).[1]

Adverse events

To 1 May 2014, the TGA has received two reports involving fentanyl patches and accidental exposure in children.

The children in these two cases suffered somnolence and loss of consciousness respectively. Both of the children were hospitalised as a result of the incidents.

The TGA is also aware of reports made to the NSW Poisons Information Centre involving accidental exposure to fentanyl patches in children aged younger than five years.

In 2012, the US Food and Drug Administration evaluated a series of 26 cases of accidental exposures to fentanyl patches in children reported over a 15-year period. Of those 26 cases, 10 resulted in death and 12 in hospitalisation. Sixteen of the 26 cases occurred in children two years old or younger.[2]

Information for health professionals

Ensure patients are aware of the risks of accidental exposure to fentanyl patches for non-users and in particular children.

Advise patients to keep fentanyl patches out of reach of children before, during and after use, and to appropriately dispose of patches that have been used or are no longer needed. Specifically, used patches should be folded so that the adhesive side adheres to itself, before being wrapped and disposed of carefully. Unused patches should be returned to the pharmacy for safe disposal.

Fentanyl patches being worn by patients can come into contact with non-users in situations of close contact, and there have been recorded cases of patches being transferred to another person while sharing a bed with a patch wearer.

If a fentanyl patch adheres to a non-user, it should be removed immediately.

Advise patients to contact a doctor immediately in any case of suspected exposure to or ingestion of fentanyl patches.

Toxicological advice is available from the Poisons Information Centre's 24-hour phone line on 131 126.

REFERENCES

1. NPS MedicineWise. NPS Radar: Fentanyl patches (Durogesic) for chronic pain. 2006.
2. U.S. Food and Drug Administration. Drug alerts and statements. FDA Reminds the Public about the Potential for Life-Threatening Harm from Accidental Exposure to Fentanyl Transdermal Systems ("Patches"). 2012.

MEDICINES SAFETY UPDATE

Zolpidem (Stilnox) and next-day impairment

Following completion of a safety review, the TGA reminds health professionals treating patients with zolpidem of the risk of next-day impairment.

Zolpidem (Stilnox) is an imidazopyridine with relative selectivity for the type 1 benzodiazepine receptor subtype. It has been registered in Australia for the short-term treatment of insomnia in adults since 1999.

Currently marketed presentations for Stilnox and Stilnox CR are:

- Stilnox 5 mg tablets
- Stilnox 10 mg tablets
- Stilnox CR 6.25 mg modified-release tablets
- Stilnox CR 12.5 mg modified-release tablets

There are also generic brands of zolpidem 5 mg and 10 mg marketed in Australia.

The Product Information (PI) for zolpidem includes a precaution regarding the drug's effect on the patient's ability to drive and use machinery. It warns that patients should not drive or operate machinery for eight hours after taking the drug and that drowsiness may continue the following day.

The PI also includes a black box warning that, among other things, advises health professionals to use caution when this drug is used with other central nervous system (CNS) depressant drugs.

Black box warning in zolpidem Product Information

Zolpidem may be associated with potentially dangerous complex sleep-related behaviours which may include sleep walking, sleep driving and other bizarre behaviours. Zolpidem is not to be taken with alcohol. Caution is needed with other CNS depressant drugs. Limit use to four weeks maximum under close medical supervision.

Minimising risk

The benefit–risk profile for zolpidem remains positive.

However, based on the findings of its safety review, the TGA recommends that patients being treated with zolpidem-containing products should take the lowest effective dose. Zolpidem should be taken in a single dose just before bedtime and should not be taken again during the same night.

The daily dose of zolpidem for adults must not exceed 10 mg, or 12.5 mg for the modified-release tablet, while elderly and debilitated patients, who may be particularly sensitive to the effects of zolpidem, should not exceed 5 mg, or 6.5 mg for the modified-release tablet.

Adverse events

As at 1 May 2014, the TGA had received 1360 adverse event reports relating to zolpidem-containing products.

Some of these adverse events were indicative of next-day impairment or the potential for next-day impairment in patients taking therapeutic doses of zolpidem.

Information for health professionals

Discuss the risk of next-day impairment, as well as other risks, with patients before prescribing zolpidem.

Ensure that patients understand the importance of not exceeding the recommended daily dose. Advise them to take zolpidem just before going to bed and not to re-administer during the same night.

Advise patients to avoid driving or any other activity requiring mental alertness, such as operating machinery, for at least eight hours after taking zolpidem and explain that drowsiness may continue the following day.

Please report to the TGA all adverse events involving zolpidem. This will assist in the continued monitoring of this drug.

The TGA is working closely with the sponsor to update the PI with further information about the risk of next-day impairment.

FURTHER READING

European Medicines Agency. CMDh endorses new advice to minimise risk of next-morning impaired driving ability and mental alertness with zolpidem. 2014 Apr 25.

MEDICINES SAFETY UPDATE

Diclofenac and arteriothrombotic events

The Product Information documents for prescription-only diclofenac have been updated to provide further information about the increased risk of arteriothrombotic events.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID). Prescription-only products are available in oral and rectal forms.

Information regarding arteriothrombotic events was previously included in the precaution and adverse reaction sections of the Product Information (PI). However, the updated PI includes details from meta-analyses of individual participant data from randomised trials by the Coxib and traditional NSAID Trialists' Collaboration that estimated, in comparison with placebo, use of diclofenac caused about three additional major vascular events per 1000 patients per year. This information was derived from trials involving long-term (more than 28 days) treatment with high-dose diclofenac (150 mg/day).[1]

You should discuss with patients the benefits and risks associated with this drug before prescribing it. Educate patients regarding the signs and symptoms of arteriothrombotic events.

To minimise risks, the lowest effective daily dose should be used for the shortest duration necessary to control symptoms. Patients with cardiovascular disease or other risk factors may be at greater risk. The TGA is undertaking a review of all NSAIDs with regard to their association with cardiovascular risks.

REFERENCE

1. Coxib and traditional NSAID Trialists' Collaboration, Bhala N, Emberson J, Merhi A, Abramson S, Arber N, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382:769-79.

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.

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