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Medicines Safety Update

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Bromhexine-containing cough and cold medicines – risk of allergy and skin reactions

Health professionals are advised that medicines containing bromhexine have been linked to a small risk of severe allergic reactions and severe skin reactions. This information is timely given the arrival of winter and influenza season.

Bromhexine is contained in a number of over-the-counter cough and cold medicines as a mucolytic.

As most of these are schedule 2 medicines, not all have Product Information (PI) or Consumer Medicines Information (CMI) documents.

The TGA reviewed this issue after Europe's Pharmacovigilance Risk Assessment Committee (PRAC) confirmed the previously known risk of severe allergic reactions associated with bromhexine- and ambroxol-containing medicines and also identified a small risk of severe cutaneous adverse reactions (SCARs). SCARs include erythema multiforme, Stevens-Johnson syndrome and acute generalised exanthematous pustulosis.

As a result of the PRAC's finding, in Europe, product information for these products is being updated with warnings regarding these potential adverse events and instructions for patients to stop treatment and seek medical advice if symptoms of SCARs, such as skin swelling or rash, occur.

Ambroxol is a metabolite of bromhexine, but it is not registered for use in Australia.

The TGA has found that similar warnings to those being implemented in Europe are appropriate for bromhexine-containing medicines marketed here.

As of 19 February 2016, 34 cases of hypersensitivity reactions, 10 cases of anaphylactic/anaphylactoid reactions and five cases of SCARs had been reported to the TGA.

Twenty-nine of these cases could not be definitely linked with bromhexine because they involved products with multiple active ingredients or excipients, such as benzoates, which can also cause hypersensitivity, or had confounding factors.

The current PI and package insert for the innovator brand, Bisolvon, already include a warning regarding anaphylactic reactions and skin reactions.

The TGA will be contacting other sponsors of bromhexine-containing products to discuss including similar information in their PI and CMI documents, if they have them.

In the meantime, health professionals are encouraged to advise patients who are using these products of the small risk of these potential adverse events and instruct them to stop using the medicine and seek medical advice if symptoms of SCARs occur.

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

TGA Health Safety Regulation

Lercanidipine and cloudy peritoneal effluent in patients on peritoneal dialysis

Health professionals should consider a reversible medication-induced differential diagnosis for the development of cloudy peritoneal effluent in patients on peritoneal dialysis who are taking lercanidipine and who have no other signs or symptoms of infective peritonitis.

Lercanidipine is a calcium channel blocker (CCB) that acts by blocking the inward current of calcium into cells in myocardial tissue and arteriolar smooth muscle. It is marketed in Australia as Zanidip and various generic brands.

CCBs can be classified as either dihydropyridines or non-dihydropyridines depending on their site of action. Lercanidipine belongs with the dihydropyridines group.

Dihydropyridines act mostly on arteriolar smooth muscle, reducing vascular resistance and blood pressure.[1]

TGA investigation

Investigation by the TGA, including review of medical literature, has found an association between CCBs and the development of cloudy peritoneal effluent (CPE) secondary to elevated triglyceride concentrations (in the effluent) in patients on peritoneal dialysis.

While CPE is not directly clinically significant, it can be confused for infective peritonitis, which is a common and clinically significant complication of peritoneal dialysis.

If this occurs, the patient could be unnecessarily hospitalised and receive empiric antibiotic administration.

The TGA has found that the association between CCBs and CPE is strongest for lercanidipine and manidipine. The latter is not registered for use in Australia.

As of 19 February 2016, there have been four cases of CPE associated with lercanidipine reported to the TGA.

As part of its investigation, the TGA also reviewed a further 23 cases found in international medical literature. There was one case each reported for other CCBs nifedipine, verapamil and diltiazem.

Of the total 27 cases of CPE with lercanidipine, 15 occurred within three days of commencing the medicine.

Information for health professionals

Based on the TGA's findings, health professionals are advised to consider a reversible medication-induced differential diagnosis for the development of cloudy peritoneal effluent in patients on peritoneal dialysis who are taking lercanidipine and who have no other signs or symptoms of infective peritonitis.

Prescribers are also reminded that lercanidipine is contraindicated in patients with severe renal impairment.

The Precautions and Adverse Effects sections of the Product Information (PI) for lercanidipine have been updated with information about CPE.

The turbidity is due to an increased triglyceride concentration in the peritoneal effluent. While the mechanism is unknown, the turbidity tends to resolve soon after withdrawal of lercanidipine.

While the medical literature reviewed suggests the possibility that this adverse event may be a class effect, due to the small number of cases reported for nifedipine, verapamil and diltiazem, there was inadequate evidence at this time to support an update to the PIs for those medicines.

REFERENCE

1. Australian Medicines Handbook. Calcium Channel Blockers. July 2015. Accessed October 2015. Available from: https://amhonline.amh.net.au/chapters/chap-06/antihypertensives/calcium-channel-blockers

Medicine shortages information

The Medicine Shortages Information Initiative provides information about a temporary or permanent disruption to the supply of a prescription medicine. Health professionals and consumers are invited to subscribe to the Medicine Shortages email list to receive an alert when there is new or updated medicine shortage information reported to the TGA.

Marcain Spinal 0.5% Heavy and reports of failed or incomplete spinal anaesthesia

The TGA has investigated recent reports of failed or incomplete spinal anaesthesia with use of Marcain Spinal 0.5% Heavy (bupivacaine hydrochloride anhydrous). The TGA has found that this cluster of reports did not indicate a quality or efficacy issue with the product.

Marcain Spinal 0.5% Heavy is a formulation of bupivacaine hydrochloride monohydrate at a concentration of 5 mcg/mL.

It contains 80 mg glucose per mL solution, resulting in a higher specific gravity than that of the related product Marcain Spinal 0.5%, which does not contain glucose.

These products are also described as being 'hyperbaric' and 'isobaric' respectively, in relation to the specific gravity of cerebrospinal fluid.

Bupivacaine is an amide-type local anaesthetic which causes a reversible blockade of impulse propagation along nerve fibres by preventing neuronal influx of sodium ions.

Marcain Spinal 0.5% Heavy and Marcain Spinal 0.5% are both indicated for the production of spinal anaesthesia.

The Product Information (PI) states that Marcain Spinal 0.5% Heavy is suitable for abdominal surgery lasting 45-60 minutes and urological and lower limb surgery lasting 2-3 hours.

In August 2015, the TGA received notification from one hospital that there had been five occasions where hyperbaric Marcain failed to achieve adequate spinal anaesthesia, despite administration by experienced clinicians.

Three batches of Marcain Spinal 0.5% Heavy were implicated in the reports (batch numbers F0122-1, F0127-1 and F0139-1).

Failed or incomplete spinal blockade can have an impact on patient safety. For example, surgical procedures may be delayed, or conversion to general anaesthetic may be required.

Failure of spinal blockade is a recognised complication of this type of anaesthetic, with incidences suggested in the medical literature of between 2-4% (references are available upon request – email PSAB.Communications@tga.gov.au).

The Australian and New Zealand College of Anaesthetists (ANZCA) published a safety alert about this issue, encouraging clinicians to report any instances to the TGA.

Previous investigations

The TGA had previously investigated similar clusters of reports involving failed spinal anaesthesia with hyperbaric Marcain.

The TGA has tested samples of hyperbaric Marcain in 2000, 2004 and 2009, following reports of failed spinals.

On each occasion the products tested were found to be within specification, and results concurred with those from testing conducted by AstraZeneca.

These investigations were closed out without requiring any further action.

Adverse event reports

The TGA has reviewed adverse event reports recorded in its database.

Most of the cases in the TGA's database are isolated incidents reported by an individual clinician.

The TGA undertook enhanced surveillance of this adverse event for three months after the initial notification of the most recent cluster of reports.

As of 3 November 2015, the TGA received 30 reports of failed or incomplete spinal anaesthesia, each of which can be related to an individual patient. Of these, nine describe a complete absence of spinal blockade, while the remaining 21 reports described incomplete spinal blockade.

TGA findings

The number of reports of complete spinal anaesthesia failure is very small in comparison to the number of ampoules of each implicated batch supplied to the Australian market, and the number of spinal anaesthetics likely to be performed on a regular basis.

The safety alert published by ANZCA has

increased awareness of this potential adverse event and stimulated reporting, but the number of cases reported to the TGA still does not exceed expectations.

AstraZeneca has provided information regarding an internal investigation of this issue, including that testing does not demonstrate a quality issue. Based on previous testing of samples undertaken by the TGA, AstraZeneca's testing of the current implicated batches is considered reliable.

Factors that may cause failure of spinal anaesthesia include insufficient dose, extrathecal injection or leakage to the extradural space, and intrathecal entrapment of the local anaesthetic.

Based on literature reviewed as part of the TGA's latest investigation, spinal anaesthetics resulting in partial blockade most likely reflect variable patient anatomy or technical problems unrecognised by the clinician.

Inadequate height may represent maldistribution of local anaesthetic due to being trapped below the lumbar curve, or due to fibrous structures within the subarachnoid space.

Inadequate density or shortened duration is likely to be due to insufficient dose reaching the nerve roots, either due to the volume of the lumbosacral dural sac or partial misplacement of local anaesthetic.

For complete failures, the literature suggests that this may in rare cases be due to anatomical variation in the form of Tarlov or arachnoid cysts, or inadvertent epidural injection.

Based on these considerations, the TGA has found that there is no evidence of a quality or efficacy issue with Marcain Spinal 0.5% Heavy at this time.

While failed or incomplete spinal anaesthesia is not directly addressed as an adverse event in the PI for Marcain Spinal 0.5% Heavy, clinicians are reminded that 'the safety and effectiveness of Marcain depend on proper dosage, correct technique and adequate precautions'.

The PI also advises that, 'Standard textbooks should be consulted for specific techniques and precautions for spinal anaesthetic procedures.'

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.

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

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