



Medicines Safety Update

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New warnings on labels of medicines containing neuromuscular blocking agents

Health professionals are advised that new warning statements are being implemented for neuromuscular blocking agent containing medicines. Mandatory warning statements will be included on the container and any outer packaging to mitigate the risk of administration errors.

Neuromuscular blocking agent containing medicines (NMBAs) are used to cause paralysis during anaesthesia.

Errors in the administration of NMBAs present significant risk to patient safety due to potential for unintended paralysis, respiratory arrest, severe permanent harm (including physical and psychological harm) or even death.

Administration errors involving these medicines in Australia can be caused by look-alike selection errors, where two medicines are similar in appearance resulting in the wrong medicine being chosen and administered.

To help address this risk, the TGA has updated [Therapeutic Goods Order No 91 – Standards for prescription and related medicines](#) outlining requirements to include a warning statement on labels of NMBAs.

‘WARNING: Paralyzing agent’ will appear prominently on labels of the primary pack (outer carton) and the container (ampoule or vial) of NMBAs.

On very small containers, the warning statement might be shortened to ‘Warning: Paralyser’ or ‘Paralyser’.

The warning statement will appear in black text on



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TGA Health Safety Regulation

a red background (except on plastic ampoules, on which the warning will appear without a coloured background due to the way these containers are manufactured).

The affected medicines are now specified in Schedule 3 of Therapeutic Goods Order No 91 and include, but are not limited to, the following ingredients:

- suxamethonium
- pancuronium
- vecuronium
- atracurium
- rocuronium
- mivacurium
- cisatracurium.

Medicine sponsors have until September 2020 to make changes to their labels.

Medicines with warning statements on their labels will gradually appear over the next few years as sponsors update their labels and existing stock is used up.

Stock released prior to September 2020 without the warning statement may continue to be sold and used.

These changes complement people-focussed interventions already being undertaken by the Australian and New Zealand College of Anaesthetists, Therapeutic Advisory Groups and the Australian Commission on Safety and Quality in Health Care.

[Further information](#) is available on the TGA website.

Local anaesthetic systemic toxicity

Health professionals are reminded that, while local anaesthetics are sometimes (incorrectly) thought to be without side effects, local anaesthetic systemic toxicity is always a potential complication associated with their use.

Local anaesthetics (LAs) are widely administered in practice by many clinicians, including anaesthetists, general practitioners, surgeons, emergency room providers, dentists, and others.

Routine monitoring of the TGA's adverse event database found a recent increase in reports of local anaesthetic systemic toxicity (LAST). In response to this, we wish to improve awareness of LAST and knowledge about its management.

LAST primarily affects the central nervous system (CNS) and cardiovascular system (CVS), and can be fatal. Major LAST events have decreased since the early 1980s, possibly due to an increase in awareness and routine incorporation of preventative clinical practice measures. These include using the lowest effective dose, safer injection techniques (incremental injecting and pre-injection aspiration), the use of ultrasound guidance, and avoidance of heavy sedation. However, none of these measures are fail-safe.

Symptoms of LAST can include:

- perioral numbness
- metallic taste
- mental status changes including anxiety

- visual changes
- tinnitus
- muscle twitching
- seizures
- loss of consciousness
- hemiparesis (head and neck procedures)
- tachycardia or bradycardia
- hypertension or hypotension
- ventricular arrhythmias and/or asystole.

Risk factors and other considerations

Patient risk factors for developing LAST include:¹

- hyperdynamic circulatory states (pregnancy, uraemia) – increased absorption
- low alpha 1 acid glycoprotein (AAG) (pregnancy, infants under 4 months of age) – increased absorption
- hepatic insufficiency (elderly and infants) – reduced clearance
- topical administration in children (large surface area to weight ratio) – increased absorption
- pregnancy:
 - increased cardiac output (as above)
 - low AAG (as above)
 - venous engorgement increasing absorption during epidural anaesthesia
 - it has been suggested that hormonal changes may cause increased sensitivity of neural tissue and cardiotoxicity²
- metabolic disturbances (acidosis, hypoxia, or hypercarbia)
- carnitine deficiency (increased cardiotoxicity, particularly with bupivacaine)

- concurrent medications (hepatic enzyme inducers/inhibitors).³

Blood concentrations of LA depend on the above patient factors and others, in addition to procedural factors including the area to be anaesthetised, the vascularity of the tissues, the type of block, and the technique used.^{1,3,4,5} Similarly, high plasma levels may be seen as a result of excessive dosage, rapid absorption, or reduced metabolism or elimination.

The effects of systemic overdose and unintentional intravascular injection may involve the CNS and/or the CVS. Inadvertent subarachnoid injection may lead to CNS depression, respiratory arrest and cardiovascular collapse.

Certain local anaesthetic procedures such as injection in the head and neck region, including retrobulbar, dental and stellate ganglion blocks, may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used. The side effects may be similar to the systemic toxicity seen with unintentional intravascular injections of larger doses.

For major nerve blocks the dosage should be adjusted to the site of administration and patient status. Interscalene and supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions regardless of the local anaesthetic used.

Peripheral nerve blocks have been associated with a higher rate of LAST, and particularly of serious LAST events (seizures or unconsciousness).^{1,3,4}

Incidence rate

A review of data from the Australian and New Zealand Registry of Regional Anaesthesia (AURORA) included data from approximately 25,300 peripheral nerve blocks performed from 2008 to 2012.⁶

The overall incidence of minor and major LAST events was 0.87 per 1000 blocks.

Major LAST events occurred in 8 patients (0.31 per 1000), including 7 cases of major CNS events (0.28 per 1000), and 1 case of cardiac arrest.⁶

Patient management

The clinical presentation of LAST is highly variable. LAST should be suspected whenever physiological changes occur after administration of any LA.

The literature classically describes LAST as occurring

soon after injection and progressing through CNS excitation, CNS inhibition, CVS excitation and in extreme cases CVS inhibition and arrest.¹ However, a 2009 review of 93 reported LAST events following regional anaesthesia over 3 decades, found only 60% of reported cases followed this classic presentation.⁷ In the remaining 40% of cases, onset was delayed or involved only cardiovascular effects, without any signs of CNS toxicity.⁷

Careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness should be accomplished after each local anaesthetic injection.

Restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of CNS toxicity.

LAST is a medical emergency and should be recognised and treated as early as possible.

When any LA agent is used, resuscitative equipment and drugs, including oxygen, should be immediately available in order to manage possible adverse reactions involving the cardiovascular, respiratory or central nervous systems. This is especially important in outpatient clinic settings.

It is also recommended that an intravenous cannula be inserted prior to any major peripheral block. Avoidance of hypoxia and acidosis should be a priority.

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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.

Off-label use of atropine

Health professionals are advised to exercise extreme caution if considering off-label prescribing of atropine eye drops to treat hypersalivation. This follows the death of an adult patient in 2014 that has been attributed to accidental oral ingestion of a toxic quantity of atropine eye-drop, which had been prescribed off-label for sublingual administration.

When formulated as eye drops, atropine is indicated for the treatment of mydriasis and cycloplegia (typically administered by health professionals to assist with examination of the retina).

The Coroner reviewing the 2014 death found that atropine had been prescribed off-label to treat hypersalivation (a side effect of other medications being used). The eye drops were intended by the prescriber to be self-administered by the patient with two drops under the tongue (frequency of administration was not stated in the Coroner's report).

The coronial inquest included expert opinion from a toxicologist, who determined that the concentration of atropine found in the patient was 50-100 times the

expected therapeutic dose, based on the prescribed dosing instructions. It was noted that the plastic dispenser bottle was very easy to empty with a gentle squeeze and that the dose taken by the deceased was at least 6-8 ml of the solution.

The TGA's toxicology evaluation determined that higher systemic exposure is expected from sublingual administration of atropine eye drops compared with oral administration (tablets) due to bypassing of first-pass metabolism. As a result, toxicity is expected to be seen at lower sublingual doses than oral ones.

The coroner found that there was no evidence to suggest the patient was suicidal and therefore determined that ingestion of a toxic quantity of atropine was accidental.

Hypersalivation is not an approved indication for atropine eye-drops in Australia.

Extreme caution is recommended if you are considering off-label prescribing of atropine eye-drops for hypersalivation. You should discuss the risks and benefits of the proposed treatment with the patient and/or their carers, so that they are capable of providing informed consent, and patients should be closely monitored during treatment.

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

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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 (see [Black Triangle Scheme](#))
- 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:

- **online** at www.tga.gov.au
- **by email** to ADR.Reports@tga.gov.au
- **by fax** to 02 6232 8392
- **using the 'blue card'** available from the TGA website

For more information about reporting, visit www.tga.gov.au or contact the TGA's Pharmacovigilance and Special Access Branch at ADR.Reports@tga.gov.au

DISCLAIMER

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