Society for
Paediatric Anaesthesia
in New Zealand and Australia

SPANZA Tramadol Advisory Update – February 2025

Recommendations Following FDA Warnings about Tramadol Use in Children

Recommendations

1. Tramadol has a role as part of a multimodal analgesic regimen for the management of acute pain in children.
2. For the treatment of acute postoperative tonsillectomy pain, the tramadol dose should be limited. It is safest to start with a total daily dose of 2 mg/kg given in divided doses, for example:

    2.1 0.5 mg/kg 6-8 hourly, with a maximum dose of 400mg/day.
    2.2 Some clinicians use up to 1mg/kg 6-8 hourly, with a maximum dose of 400mg/day.

3. Tramadol overdose poses a greater danger to children than ultra-rapid metabolism. Preparations appropriate for paediatric use should be used where available and highly concentrated preparations (eg: 100mg/mL oral drops) avoided in children under 12 where the risk of inadvertent overdose is greatest.
4. Children with obstructive sleep apnoea who have undergone tonsillectomy should have an extended post-operative stay in hospital and be monitored closely for signs of respiratory depression and sedation.
5. The use of any opioid in children after day-stay surgery should be done so with caution.

Background

Tramadol is a centrally acting analgesic that is structurally related to morphine and codeine. Its dual mechanism of action on mu-opioid receptors and inhibition of serotonin and norepinephrine reuptake enhance it's analgesic properties. (1) It is widely used in children in Aotearoa New Zealand and Australia when paracetamol and non-steroidal anti-inflammatories do not provide adequate analgesia. Tramadol use increased in children after codeine was contraindicated. (2) Contention surrounding the use of tramadol in the paediatric population arose in 2017 when the United States Food and Drug Administration (FDA) mandated new warning labels restricting the use of tramadol in children. (3) New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE) and the Therapeutic Goods Administration (TGA) issued similar type warnings. (4,5) SPANZA issued an advisory in 2017 in response to the FDA, recommending the continued use of tramadol in children in Aotearoa New Zealand and Australia with certain considerations. (6)

Risks of Tramadol

Respiratory depression attributable to tramadol is described in children younger than 6 years and is associated with doses more than 7 – 10 mg/kg over 24 hours in multiple doses. Seizures have been reported after a minimal dose of 4.8mg/kg. (7-9) Tramadol caused less respiratory depression at a dose of 1mkg/kg than 2mg/kg in adults (10) and children. (11) It has been found that respiratory depression was minimal in children undergoing hernia repair after tramadol 1mg/kg (10) and was less than after pethidine of 1mg/kg. In adults, no respiratory depression was observed after a dose of tramadol 0.6mg/kg IV when compared with pethidine 0.6mg/kg IV or oxycodone 0.04mg/kg IV. (11,12) The bioavailability of tramadol has not been established in children. (13,14)

Tramadol can cause significant side effects in children who are ultra-rapid metabolisers. CYP2D6 metabolises tramadol to *O*-desmethyl-tramadol, the active M1 metabolite, which has a μ-receptor affinity approximately 200 times greater than tramadol. (15) Ultra-rapid metabolisers could have significant side effects in the context of excessive dosing due to iatrogenic, intentional or inadvertent overdosing or if they have known respiratory disease with increased opioid sensitivity (eg obstructive sleep apnoea secondary to tonsillar hypertrophy or obesity). (16)

Children with obstructive sleep apnoea who have undergone tonsillectomy may require an extended post-operative stay in hospital and be monitored closely for signs of respiratory depression and sedation. The evidence for a specific period of time is poor and likely depends on a multitude of factors. Each instituition should rationalise this period of observation depending on local factors. (17)

2017 FDA warning

From 1968 – 2016, the FDA identified nine cases of serious breathing problems, including three deaths outside of the USA, with the use of tramadol in children. Elevated serum tramadol concentrations were noted in all three deaths, suggesting overdose. The children were taking tramadol for postoperative pain and/or to manage fever following tonsillectomy and clubfoot surgery. They were all administered tramadol oral drops (100mg/mL). This formula is no longer available in Aotearoa New Zealand and has been replaced with a more preferable tramadol 10mg/mL elixir. Dosing recommendations for tramadol oral drops are only valid for adults and adolescents over 12 years of age. The use of tramadol oral drops under 12 years of age is off-label.

The FDA made the following changes to the tramadol drug label:

- a contraindication was added stating tramadol should not be used to treat pain in children under 12 years and used in children younger than 18 years to treat post operative pain following adenotonsillectomy;
- a warning was added to recommend against the use of tramadol in children between the ages of 12 and 18 years who are obese or who have conditions such as obstructive sleep apnoea or severe lung disease, which may increase the risk of serious breathing problems;
- a warning to people who breastfeed was added advising that breastfeeding is not recommended when taking tramadol due to the risk of serious adverse reactions in breastfed infants, including excess sleepiness, difficulty breastfeeding or serious breathing problems that could result in death.

2020 MEDSAFE Updated Advice

MEDSAFE provided updated advice for the use of tramadol in children and updated data sheets in 2020:

- a contraindication for its use in children under 12 years;
- a contraindication for its use in children aged under 18 years for post-operative pain management following tonsillectomy and/or adenoidectomy.

2015 TGA Medicines Safety Update

TGA provided a medicines safety update for the use of tramadol drops in children under 12 years of age after the death of a 2 year old Australian child:

- tramadol oral drops are safe and appropriate in adults and adolescent patients;
- the concentration of the drops (100mg/mL) could result in a potential overdose in children;
- dosing recommendations in the Product Information for tramadol drops are only valid for adults and adolescents over 12 years of age;
- using tramadol oral drops in children under 12 years of age is off-label.

Conclusion

Tramadol is a useful analgesia as part of a multi-modal analgesic regime. In most instances this benefit may outweigh the risks of its use in the paediatric population where modalities to treat pain are limited. Special consideration should be given to children under the age of 18 years with respiratory disease or obstructive sleep apnoea. Whilst its use in children who are ultra-rapid metabolisers is an important consideration, the use of highly concentrated oral drops in children under 12 years of age should be avoided to prevent inadvertent overdose.

Document history

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