SPANZA Advisory on Tramadol - May 2017

Recommendations Following FDA Warnings about Tramadol Use in Children

Introduction

Tramadol is a weak opioid that is structurally related to morphine and codeine.(1) It is widely used within NZ and Australia in children as a second-line analgesic or rescue medication when paracetamol and NSAIDs prove inadequate. Mortality from codeine use primarily occurred after tonsillectomy and this cohort may be the most concerning when tramadol is prescribed.

An important metabolic pathway for tramadol is that provided by CYP2D6 to form *O*-desmethyltramadol; the active M1 metabolite. This active M1 metabolite has a μ-receptor affinity approximately 200 times greater than tramadol.(2) There is concern that this metabolite can cause respiratory depression in those children who are ultra-rapid metabolizers.

FDA announcement

The FDA identified nine cases of serious breathing problems, including three deaths, with the use of tramadol in children younger than 18 years from January 1969 to March 2016. The FDA recently announced (20 April 2017) that it is restricting the use of codeine and tramadol medicines in children. Their recommendations include the following:

1. The FDA's strongest warning, called a *Contraindication*, to be added to the drug labels of codeine and tramadol alerting that codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children younger than 12 years.
2. A new *Contraindication* to the tramadol label, warning against its use in children younger than 18 years to treat postoperative pain following adenotonsillectomy.
3. A new *Warning* to the drug labels of codeine and tramadol to recommend against their use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems

4. A strengthened *Warning* to mothers that breastfeeding is not recommended when taking codeine or tramadol medicines due to the risk of serious adverse reactions in breastfed infants. These can include excess sleepiness, difficulty breastfeeding, or serious breathing problems that could result in death.

(https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery)

Such warnings as these issued by the FDA highlight potential dangers in order to protect patients. They can be considered part of the process of drug education. These warnings are "living documents" and will change with new evidence; they are not “coffins” for drugs. Both succinylcholine (3, 4) and droperidol (5, 6) have been part of this process in the past. The use of general anaesthesia in children under the age of 2 years is currently being reviewed.(7)

Tramadol is not codeine

Tramadol is not quite the same as codeine. Codeine has little analgesic activity and it is its metabolite, morphine that is active and provide analgesia. Morphine is produced through CYP2D6 activity. Both tramadol and its M1 metabolite are active. There is also more than one clearance pathway for the parent drug. Tramadol is extensively metabolized in the liver by O - and N-demethylation and by conjugation reactions to form glucuronides and sulfates. Elimination of tramadol and its metabolites is predominantly through the kidneys.

Tramadol toxicity

Respiratory depression attributable to tramadol overdose is described and is associated with doses in excess of 7-10 mg/kg in children younger than 6 years, although seizures have been reported after a minimal dose of 4.8 mg/kg.(8-10) However, evidence that polymorphism of CYP2D6 contributes to reported toxicity is lacking. There is a report of one 5 year old child prescribed a single tramadol dose (formulation comprised oral drops containing 100 mg/mL) after adenotonsillectomy. He presented the next morning with opioid intoxication and was resuscitated. Genotyping of CYP2D6 was conducted, and three functional alleles were found that were consistent with ultra-rapid metabolism. Although a single urine sample was taken for metabolite concentration, no plasma samples were available for assay and interpretation is difficult.(11)

The three fatalities reported by the FDA occurred outside the USA in children younger than 6 years. Elevated serum tramadol concentrations were noted in all three, suggesting overdose. The reasons for tramadol use in these children was postoperative pain following tonsillectomy and clubfoot surgery,

and to manage fever. All three children were administered tramadol oral drops (100 mg/mL). This formulation is no longer available in New Zealand and has been replaced with a more preferable tramadol 10 mg/mL elixir.

There is no question that ultra-metabolisers of tramadol could potentially get into trouble in the following circumstances:
1. Excessive dosing – due to iatrogenic, intentional or inadvertent parental overdose.
2. Children with known respiratory disease have increased opioid sensitivity - of particular concern are those with obstructive sleep apnea secondary to tonsillar hypertrophy or obesity.(12)

Tramadol, respiratory depression and other opioids

There are very limited data on respiratory depression from tramadol in children. Respiratory depression is minimal in children undergoing hernia repair after tramadol 1 mg/kg (13) and was less than after pethidine 1mg/kg. Data comparing tramadol 0.6 mg/kg IV revealed no respiratory depression when compared to pethidine 0.6 mg/kg IVor oxycodone 0.04 mg/kg IV in adults.(14, 15) Tramadol caused less respiratory depression at a dose of 1 mg/kg than 2 mg/kg in adults (13) and children.(14)

Recommendations

1. Tramadol can have a useful role as part of a multimodal analgesic regimen for managing acute pain in children.
2. Tramadol dose should be limited for acute pain after tonsillectomy (e.g., maximum dose 1 mg/kg 6-8 h, max 400 mg/day). We suggest starting with a lower dose of 2 mg/kg daily in divided doses (e.g., 0.5 mg/kg 6-8 h). Tramadol overdose is a greater danger than CYP variants.
3. Children with obstructive sleep apnoea who have undergone tonsillectomy should continue to be monitored in hospital overnight to assess both response and sensitivity to opioids before discharge. While evidence is lacking, it may be prudent to observe any child given opioids during a period of sleep before discharge.
4. The use of any opioid in children after day-stay surgery should be done so with caution.

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