

What's New in the Patient Safety World

November 2015

FDA Safety Communication on Tramadol in Children

The use of opioids in children, particularly use of codeine after tonsillectomy, has been associated with dangerous outcomes (see our What's New in the Patient Safety World columns for September 2012 "[FDA Warning on Codeine Use in Children Following Tonsillectomy](#)", March 2013 "[Further Warning on Codeine in Children Following Tonsillectomy](#)" and May 2014 "[Pediatric Codeine Prescriptions in the ER](#)"). These described cases of death and serious adverse effects in children treated with codeine following adenotonsillectomy for obstructive sleep apnea. Those cases led to the FDA issuing a safety alert ([FDA 2012](#)) and additional cases led to a subsequent black box warning for products containing codeine ([FDA 2013](#)).

Now the FDA has issued a "safety communication" on the use of tramadol in children ([FDA 2015](#)). Tramadol is available under the brand names Ultram, Ultram ER, Conzip, and also as generics. Tramadol is also available in combination with the pain reliever acetaminophen under the brand name Ultracet and as generics. The FDA announced it is investigating the use of tramadol in children aged 17 years and younger, because of the rare but serious risk of slowed or difficult breathing and that this risk may be increased in children treated with tramadol for pain after surgery to remove their tonsils and/or adenoids. The announcement notes the FDA is evaluating all available information and will communicate its final conclusions and recommendations to the public when that review is complete. The FDA notes that tramadol is not FDA-approved for use in children but that data show it is being used "off-label" in the pediatric population.

The problem originally noted for codeine was that there are genetic variations that cause some people to be "ultra-rapid metabolizers" of codeine, which leads to higher concentrations of morphine earlier. The new FDA safety communication suggests there may be a similar issue for tramadol. The FDA notes some people have genetic variations that cause tramadol to be converted to the active form of the opioid faster and more completely than usual. These people, called ultra-rapid metabolizers, are more likely to have higher-than-normal amounts of the active form of the opioid in their blood after taking tramadol, which can result in breathing difficulty that may lead to death. They cite a case of a 5-year-old child in France who experienced severely slowed breathing requiring emergency intervention and hospitalization after taking a single prescribed dose of tramadol oral solution for pain relief following surgery to remove his tonsils and adenoids. The child was later found to be an ultra-rapid metabolizer and had high levels of the the active form of the opioid, O-desmethyltramadol, in his body.

The FDA notes that health care professionals need to be aware of this and consider prescribing alternative FDA-approved pain medicines for children.

A recent meta-analysis of complications of adenotonsillectomy in children ([De Luca Canto 2015](#)) showed that the most frequent complication was respiratory compromise (9.4%), followed by secondary hemorrhage (2.6%). Moreover, it revealed that children with OSA (obstructive sleep apnea) have nearly 5 times more respiratory complications after adenotonsillectomy than children without OSA. So all healthcare workers, as well as parents, need to be aware of the dangers of opioid use in children after adenotonsillectomy, and particularly with codeine or tramadol.

Our May 2014 What's New in the Patient Safety World column "[Pediatric Codeine Prescriptions in the ER](#)" showed that codeine continues to be prescribed to children in significant numbers, at least in children seen in the emergency room.

Not only are opioids risky in some children but even when prescribed for appropriate indications they may be overprescribed. A recent study ([Yaster 2015](#)) presented in abstract form at the Anesthesiology 2015 annual meeting showed that 60% of opioids prescribed for children after surgery go unused and are not properly disposed of. They found that a 10-14 day supply was typically prescribed and filled but that the average use was only 5 days, resulting in substantial accumulation of unused opioids. Almost half of those households also had adolescent siblings who might be at risk of abusing these prescription opioids.

It's pretty clear that guidelines and provider education have been inadequate in stopping use of codeine in children. If you do educational interventions, remember that **stories are better than statistics**. Be sure to include descriptions of cases in the original literature of 3 deaths and one near-miss case of respiratory depression related to codeine ([Ciszkowski 2009](#), [Kelly 2012](#)). But remember that **education and training are what we consider to be weak actions**. In our March 27, 2012 Patient Safety Tip of the Week "[Action Plan Strength in RCA's](#)" we included some [slides](#) to help you remember which actions are strong and which are weak. **Forcing functions** and **constraints** that make it difficult to order or prescribe codeine for children are much more likely to be successful.

So when it comes to opioid use in children you need to consider use of other tools to limit the risks. If you are using CPOE or electronic prescribing systems, alerts could be triggered by the age of the patient and/or the procedure (adenotonsillectomy) to warn the prescriber of the risks of codeine or tramadol. Rather than a "soft" stop you might consider a "**hard**" stop in such cases, requiring the prescriber to make a phone call to the pharmacist if he/she wishes to prescribe codeine or tramadol despite the warning. And, in view of the findings in the Yaster study, you might also consider limits to the amounts of opioids prescribed for children. These are evolving issues that pit tradeoffs in convenience vs. safety and undoubtedly we'll hear more in the future.

Some of our previous columns on opioid safety issues in children:

- September 2012 “[FDA Warning on Codeine Use in Children Following Tonsillectomy](#)”
- March 2013 “[Further Warning on Codeine in Children Following Tonsillectomy](#)”
- May 2014 “[Pediatric Codeine Prescriptions in the ER](#)”

References:

FDA (Food and Drug Administration). FDA Drug Safety Communication: FDA evaluating the risks of using the pain medicine tramadol in children aged 17 and younger. FDA Safety Warning. September 21, 2015

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