Codeine is commonly prescribed to children to manage postoperative pain at home. This inactive pro-drug is bio-transformed to the active metabolite morphine by cytochrome P450 2D6 (CYP2D6). Genetic variants of CYP2D6 are very common with 10-15% of the American population being poor metabolizers leading to inadequate pain relief; and 2-5% being ultra-rapid or extensive metabolizers with a high risk of morphine toxicity. Following recent case reports of multiple deaths in young children following codeine, the Federal Drug Administration (FDA) issued a safety warning that children undergoing tonsillectomy and being administered codeine are at risk of breathing problems and death. Despite this, codeine is still commonly used following surgery in children. The aim of this large prospective study is to determine the risk factors associated with codeine’s adverse effects (including over sedation) at home following outpatient tonsillectomy in children.

**BACKGROUND**

Codeine is commonly prescribed to children to manage postoperative pain at home. This inactive pro-drug is bio-transformed to the active metabolite morphine by cytochrome P450 2D6 (CYP2D6). Genetic variants of CYP2D6 are very common with 10-15% of the American population being poor metabolizers leading to inadequate pain relief; and 2-5% being ultra-rapid or extensive metabolizers with a high risk of morphine toxicity. Following recent case reports of multiple deaths in young children following codeine, the Federal Drug Administration (FDA) issued a safety warning that children undergoing tonsillectomy and being administered codeine are at risk of breathing problems and death. Despite this, codeine is still commonly used following surgery in children. The aim of this large prospective study is to determine the risk factors associated with codeine’s adverse effects (including over sedation) at home following outpatient tonsillectomy in children.

**RESULTS**

High CYP2D6 activity score was associated with increased ADRs (p = 0.004) during POD 0–2. Sedation after codeine was more common in girls (p = 0.05). High pain intensity (p = 0.003) and an interaction between CYP2D6 activity and time of the day after surgery (p = 0.003) contributed to sedation risk.

**CONCLUSION**

- Codeine’s use at home in children after surgery is associated with higher incidences of ADRs especially in patients with higher CYP2D6 activity, high pain scores and in the evening after surgery.
- Over sedation was noted more in girls.
- The Clinical Pharmacogenetics Implementation Consortium recently recommended avoiding codeine use in ultra-rapid and extensive metabolizers. Yet, CYP2D6 testing is rarely done in current clinical settings. The associations of high CYP2D6 activity with codeine ADRs and sedation should serve as caution for stronger opioids that are also metabolized through the CYP2D6 pathway: hydrocodone, oxycodone, tramadol. These should not be considered safe alternatives without CYP2D6 testing.
- An alternative approach is use of non-opioid analgesics such as acetaminophen and non-steroidal anti-inflammatory drugs on a scheduled basis and/or use of lowest effective doses of opioids that are not significantly metabolized by CYP2D6 such as oral morphine on an as needed basis with appropriate administration and monitoring instructions to parents.