Oxycodone may not be a safe alternative to codeine for postoperative pain management at home setting in children: A Pharmacokinetic-Pharmacogenetic study

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Background

Use of opioid analgesics in children has been a great concern due to incidences of respiratory depression and death. Following 2013 FDA's warning against the use of codeine in children undergoing tonsillectomy, oxycodone is being prescribed as an alternative to codeine. In the last year alone, there are 3 reports of post-tonsillectomy deaths or significant respiratory depression requiring hospitalization with oxycodone at home setting in children. This study aimed to study whether oxycodone is a safer alternative to codeine in children by analyzing CYP2D6 genotype and oxycodone pharmacokinetic associations as oxycodone is partly metabolized to the active metabolite oxymorphone by hepatic CYP2D6 (Figure 1).

Methods

In a prospective observational study, 30 children ranging from 2-17 years were administered oral oxycodone postoperatively, eight serial blood samples were collected for 24 h after dosing and plasma level were measured by LC-MS/MS. CYP2D6 genotype and oxycodone metabolism phenotype were determined based on allelic information such as CYP2D6 total activity score (TAS) and metabolism phenotype; poor (PM), intermediate (IM), extensive (EM) or ultrarapid (UM) metabolizer.

Figure 1. CYP2D6 metabolic pathway of codeine and oxycodone. Depending on CYP2D6 metabolic activity (poor, intermediate, extensive or ultrarapid metabolizing status) varying levels of morphine from codeine, and oxymorphone from oxycodone are formed resulting in clinically unpredictable inter-individual variations in responses. Oxymorphone is 14 fold more potent than morphine, EMs and UMs form more oxymorphone than PMs and IMs potentially increasing risks of serious adverse effects including respiratory depression.

Results

Significantly greater oxymorphone exposure was seen in EM subjects (P = 0.02 for Cmax, P = 0.007 for AUC0-6 and P = 0.008 for AUC0-24) compared to PM/IM subjects (Figure 2). Similarly a higher TAS value was associated with greater oxymorphone exposure. Upon further analysis, higher oxymorphone / oxycodone exposure ratio were observed in EM subjects compared with PM/IM subjects (P = 0.0007 for Cmax, P = 0.0034 for AUC0-6 and P = 0.0004 for AUC0-24).

Conclusion

The greater extent of conversion to oxymorphone was associated with higher TAS values. These findings suggest that higher oxymorphone generation in extensive metabolizers than poor CYP2D6 metabolizers. Further studies are needed to predict the occurrence of adverse event and tailor personalized dosing of oxycodone based on underlying CYP2D6 genotypes and comorbidities such as sleep apnea. Without appropriate precautions, oxycodone may not be safe alternative to codeine to manage pain at home setting especially in children with ultrarapid metabolizing status and respiratory comorbidities.