

Pharmacogenetics of Oxycodone in Post-Cesarean Section Mothers and Breastfed Infants

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INTRODUCTION

- Opioids are prescribed to >80% of women post-cesarean delivery (CD)
- Codeine and tramadol are contraindicated in breastfeeding women due to sleepiness and breathing problems in breastfed infants
- Oxycodone and hydrocodone are metabolized by CYP2D6, as are codeine and tramadol, carrying the same risk for life-threatening respiratory depression (RD) in an infant breastfeeding from a UM mother

OBJECTIVES

- To assess oxycodone safety in nursing mothers after CD and in breastfed infants
- To investigate the role of genetic variation in maternal and infant clinical outcomes with opioids after CD

METHODS

- **Setting:** Prospective collection of clinical and laboratory data assessing opioid-adverse effects (PONV and RD) in nursing mothers and sedation and breathing difficulty in infants
- **Observation:** CYP2D6 genetic association of Oxycodone 5 mg orally administered every 4-6 hours as needed post-CD
- **Maternal Primary Outcomes:** opioid-adverse effects (PONV, RD & sedation) and dependence, and Numerical Rating Scale (NRS) Pain scores and total opioid use, length of hospital stay, chronic post-surgical pain, and persistent opioid use at 3 months
- **Neonatal Outcomes:** Increased sleepiness, difficulty breastfeeding/latching, breathing difficulties/cyanosis, limpness, and hypothermia

RESULTS

- The incidence of maternal RD was 0% and PONV was 13%
- The mean overall in-hospital opioid use was 44.4 morphine milligram equivalents (MME)
- The incidence of neonatal RD was 4%, sedation 9%, limpness 19%
- There were significant differences between CYP2D6 poor and ultrarapid metabolizers in post-CD maternal pain scores and total in-hospital MME with poor metabolizers receiving 80.4 MME vs. ultrarapid metabolizers receiving 50 MME.
- There was no statistically significant differences in neonatal outcomes, though there was a clinical difference in neonatal limpness between maternal PM (n=1, 50%), UM (n=0, 0%) and NM/IM (n=11, 22%)
- No other significant associations between CYPD6 genotypes and other maternal and neonatal clinical outcomes.

Table 1. Maternal clinical outcomes by CYP2D6 phenotype among mothers receiving opioids in hospital (n=155)

Maternal CYP2D6 Phenotype	n	PONV	Prolonged hospitalization (>3 days)	Averaged Pain Score	Peak Pain Score	Total in-hospital MME*
		n (%)	n (%)	mean (SD)	mean (SD)	mean (SD)
		p=0.33	p=0.64	p=0.043	p=0.031	p=0.65
Normal or Intermediate	138	17 (12%)	9 (7%)	3.5 (1.5)	5.3 (1.8)	56.6 (44.6)
Ultra-rapid	6	2 (33%)	0 (0%)	5.2 (1.5)	7.3 (2.0)	50.0 (44.7)
Poor	7	1 (14%)	0 (0%)	3.4 (2.2)	4.7 (2.2)	80.4 (76.9)

RESULTS

Table 3.2. Neonatal Outcomes by maternal CYP2D6 phenotype among infants whose mother receiving opioids (n=151)

Maternal CYP2D6 Phenotype	n	Opioid Side Effect Composite Outcome	Monitoring of Infant Respiratory Depression by PPD3	Neonatal Sedation (Any nap >4 hr)	Neonatal Limpness (Any limpness >0)	Infant Extended Length of Stay (>72 hrs)
		p=0.99	p=0.31	p=0.82	p=0.55	p=0.30
Normal or Intermediate	138	21/138 (15%)	6/138 (4%)	6/52 (12%)	11/51 (22%)	50/136 (37%)
Ultra-rapid	6	1/6 (17%)	1/6 (17%)	0/1 (0%)	0/1 (0%)	1/6 (17%)
Poor	7	1/7 (14%)	0/7 (0%)	0/2 (0%)	1/2 (50%)	1/7 (14%)

DISCUSSION

- No incidence of maternal opioid-induced RD to manage post-CD pain with oxycodone
- Though breastfed infants had 4% incidence of RD, there was no significant association with maternal CYP2D6 genotypes.
- Use of the lowest effective doses of oxycodone as post-CD was not associated with serious opioid-related RD in nursing mothers.
- CYP2D6 poor metabolizers (80.4 MME) needed 60% more opioids compared to ultrarapid metabolizers (50 MME), possibly contributing to higher dose-related limpness in breastfed neonates of maternal poor metabolizers.
- Preoperative genotyping could potentially identify mothers and breastfed neonates at risk for higher post-CD pain, opioid use and opioid-related adverse outcomes.
- We conclude CYP2D6 phenotypes influence postoperative pain, in-hospital opioid requirement in mothers and possibly neonatal limpness following cesarean delivery.