Does *CYP2D6* genotype-predicted-phenotype based EMR guidance influence oral opioid prescription after surgery?

Soroush Merchant,[1] Cynthia A. Prows,[2] Xue Zhang,[2] Senthilkumar Sadhasivam,[3] Victor Garcia,[4] Peter Sturm,[5] Vidya Chidambaran[1]
1 Department of anesthesia, Cincinnati children's hospital medical center (CCHMC); 2 Division of human genetics, CCHMC;
3 Department of anesthesia, Riley Hospital for Children, Indiana University; 4 Division of Pediatric General and Thoracic Surgery, CCHMC; 5 Division of orthopedic surgery, CCHMC

Objectives

1. Determine whether electronic medical record (EMR) directed use based on *CYP2D6* predicted phenotypes would significantly influence oral opioid prescription pattern after inpatient surgery.
2. Determine if risks of poor analgesia and opioid side effects are dependent on *CYP2D6* predicted phenotype/total activity score (TAS).

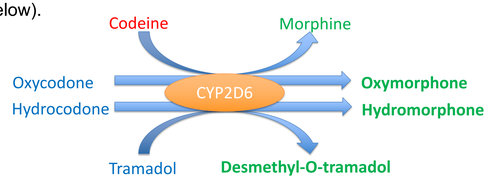
Hypotheses

1. EMR directed group (clinicians) will prescribe non-CYP2D6 opioid (hydromorphone) for poor metabolizers (PM) and ultra-rapid metabolizers (UM) more often compared to control group.
2. Any decrease in CYP2D6 function (intrinsic: poor metabolizers; extrinsic: inhibitors) will favor the CYP3A4 pathway resulting in lower oxymorphone/oxycodone ratio. This may lead to poor pain control in the affected individuals. Conversely, ultra-rapid metabolizers (UM) will have higher oxymorphone/oxycodone ratio leading to possible overdose. Since hydromorphone is not metabolized by CYP2D6, it is equally effective in individuals with different CYP2D6 activity.

Introduction

Safe and effective postoperative analgesia is critical to successful recovery after invasive surgery in children. Genetic variants associated with altered opioid metabolism could lead to variability in opioid response, including poor analgesia and side effects. Hence, incorporating pharmacogenomics in clinical decision making may assist individualized opioid prescription and improve their risk-benefit profile.

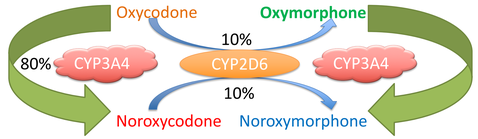
Cytochrome P450 family 2 subfamily D type 6 (CYP2D6) enzyme is responsible for converting prodrug codeine to its biologically active metabolite morphine; and oxycodone, hydrocodone and tramadol to their more active metabolites oxymorphone, hydromorphone and desmethyl-O-tramadol, respectively (figure below).



Alterations in its activity (intrinsic or extrinsic) will result in clinically unpredictable interindividual opioid level and response.

Introduction

Order of highest to lowest potency of oxycodone metabolites: **Oxymorphone**>Noroxymorphone>Oxycodone>Noroxycodone



CYP2D6 phenotypes are classified as poor metabolizers (PM), intermediate metabolizers (IM), normal metabolizers (NM) or ultra-rapid metabolizers (UM), based on diplotypes and activity scores proposed by the Clinical Pharmacogenetics Implementation Consortium (CPIC) (table below).

CYPD6 genotypes to phenotypes (CPIC guidelines)		
Likely Phenotype	CPIC activity score	Examples of CYP2D6 diplotypes
UM	>2	*1/*1xN, *1/*2xN,*2/*2xN
NM	1.5-2	*1/*1, *1/*2, *1/*9, *1/*41, *2/*2, *1/*10
IM	0.5-1	*4/*10,*4/*41, *1/*5, *10/*10, *41/*41
PM	0	*3/*4, *4/*4, *5/*5, *5/*6

These activity scores are further modified by presence of concomitant CYP2D6 inhibitors: for example: TAS activity multiplied by 0 for strong CYP2D6 inhibitors (e.g. fluoxetine, bupropion) and by 0.5 for moderate inhibitors (e.g. duloxetine).

Methods

Under IRB approved protocol, a prospectively recruited control group (2012-2015; no EMR directed use, N=87) and clinically genotyped group (2016-2018; EMR directed use at the time of oxycodone order, N=127) were included for data review. Inclusion criteria: ASA 1-3 subjects undergoing major surgery.

DNA was collected from blood/saliva for *CYP2D6* genotyping before surgery in all subjects. Based on *CYP2D6* alleles, TAS and predicted phenotypes were determined. Data collected included demographics, opioid doses, other CYP2D6 substrate medications prescribed, pain scores and opioid related adverse reactions (respiratory depression and emesis).

Method 1: Groups were compared for opioid prescribing practices. Specifically, first opioid medication prescribed (CYP2D6 vs non-CYP2D6 substrate) and need for change in first choice opioid to last opioid prescribed on discharge among PM/UM vs IM/NM were analyzed.

Method 2: Postoperative pain scores on POD 2-3 and occurrence of emesis and respiratory depression (SpO2<92% or RR<10 bpm or need for O_2 beyond POD 0) after start of PO opioids were compared between *CYP2D6* predicted phenotype groups.

Results

Demographics, TAS and *CYP2D6* phenotypes of subjects in the two groups are described in Table 1.

Table 1:	Non-genotype guided N= 87	Genotype guided N= 127
Age Mean ± SD years	13.6 ± 3.9	16.2 ± 3.8
Sex (F/M) %F	(46/41) 53% F	(21/106) 17% F
Race (%) White	91%	94%
Phenotype distribution	PM: 2.3%; IM: 35.6%; NM: 57.5%; UM: 4.6%	PM: 5.5%; IM: 41.7% NM: 52.0%; UM: 0.8%
TAS Mean (SD)	1.54 ± 0.61	1.38 ± 0.59

Comparing PM/UM to IM/NM, the odds ratio of being prescribed a non-*CYP2D6* alternative opioid was 115 and 13 in the genotype and non-genotype directed groups; Breslow-Day test suggested a higher odds ratio in the genotype-guided group (*P*=0.24), Table 2.

	Control group			EMR directed use group			
Table 2:	**IM/NM**	**PM/UM**	**[a]p**	**IM/NM**	**PM/UM**	**[a]p**	**[b]p**
HM	2 (4%)	1 (33%)	0.15	1 (1%)	4 (50%)	<0.001	0.24
Oxy	53 (96%)	2 (67%)		115 (99%)	4 (50%)		

Note: data were shown as frequency (proportion) and tested using (*a*) Fisher's exact test, and (*b*) Breslow-Day test; HM: Hydromorphone (Non-CYP2D6 opioid); Oxy: Oxycodone (CYP2D6 opioid).

A higher proportion of subjects needed change from 1st prescribed oxycodone in non-genotype guided (19% vs 11%; *P*=0.17, Fisher's exact test) compared to genotype-guided group, Table 3.

Table 3: Variable	Control group	EMR directed	*P* value
No change	47 (81%)	110 (89%)	0.17
Change	11 (19%)	14 (11%)	

Note: Variable: change in oral opioid from 1st choice to discharge; Change: oxycodone to hydromorphone; *P* value: Fisher's exact.

A higher proportion of subjects needed change from 1st prescribed oxycodone in PM/UM compared to NM/IM phenotypes (50% vs 13%; *P*=0.039, Fisher's exact test), Table 4.

Table 4: Variable	IM/NM	PM/UM	*P* value
No change	146 (87%)	3 (50%)	0.039
Change	22 (13%)	3 (50%)	

Note: Variable: change in oral opioid from 1st choice to discharge; Change: oxycodone to hydromorphone; *P* value: Fisher's exact.

Objective 2 data analysis is ongoing, and results will be presented at the oral presentation.

Results

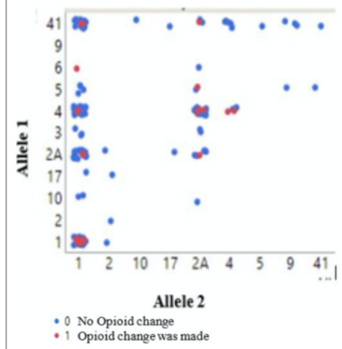


Figure 1: Opioid change from first prescribed to home discharge opioid in individuals with different *CYP2D6* allele combinations. *alleles forming the individual *CYP2D6* genotype are represented on X and Y axes and affect CYP2D6 function differently. For example, alleles known to have normal function: *1, *2, *2A; decreased function: *10, *17, *41; no function: *3, *4, *5, *6.

Conclusion

1. Our results demonstrate a trend towards more appropriate opioid prescription in presence of EMR guided *CYP2D6* genotype data. PM/UM phenotypes may benefit more from *CYP2D6* guidance.
2. Effects of alleles on opioid prescription (Figure 1) and opioid outcomes per *CYP2D6* predicted phenotype are being evaluated.
3. Larger studies are required to evaluate cost-effectiveness of CYP2D6 (and other genotype) guided opioid prescription for post-surgical subjects, especially for oxycodone.

Reference

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