Surgery 166 (2019) 476–482

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Use of pharmacogenetic data to guide individualized opioid prescribing after surgery

Raffaele Rocco, MD[a,*], Cornelius A. Thiels, DO, MBA[a,b], Daniel S. Ubl, MPH[b], Ann M. Moyer, MD, PhD[c], Elizabeth B. Habermann, MPH, PhD[b], Stephen D. Cassivi, MD, MS[a]

[a] Department of Surgery, Surgical Outcomes Program, Mayo Clinic, Rochester, MN
[b] The Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN
[c] Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

ARTICLE INFO

Article history:
Accepted 7 April 2019
Available online 15 July 2019

ABSTRACT

Background: Despite the current strategies aimed at avoiding opioid overprescription by implementing institutional guidelines, the use of opioids after surgical procedures remains highly variable. It is well known that opioids are activated by the cytochrome p450 CYP2D6 enzyme to exert pharmacologic effect. Individual variation in CYP2D6 activity affects drug metabolism, and genotyping can be performed to predict an individual's ability to metabolize CYP2D6 substrates. We postulate that the pharmacogenomic identification of patients with different opioid metabolism capacity may allow for the individualization of postsurgical opioid prescription.

Methods: This study was generated by the unison of data from 2 prior initiatives taking place at our Institution. In the first study, patients undergoing 1 of 25 elective surgical procedures were prospectively identified as part of a quality initiative and surveyed by phone 21 to 35 days after hospital discharge to complete a 29-question survey regarding opioid utilization and pain experience. Additional chart abstraction was conducted to obtain prescribing data and pain scores during the hospitalization. The second study was the Mayo Clinic Right Drug, Right Dose, Right Time study protocol, in which 5 pharmacogenes, including CYP2D6, were genotyped for 1,000 Mayo Clinic Biobank participants. The goal of this study was to implement preemptive pharmacogenomics in an academic health care setting and to generate data for further pharmacogenomic research. Patients were classified by their predicted CYP2D6 activity based on their CYP2D6 genotype.

Results: Of the 2,486 patients with prospective opioid utilization data, 21 had pharmacogenetic data available and were included in the analysis. These patients were classified according to their activity as opioid metabolizers, with 10 patients (48%) classified as intermediate, 4 patients (19%) as intermediate to normal, and 7 patients (33%) as normal or extensive. Compared with the intermediate to normal and intermediate phenotypes, normal or extensive patients had the highest percentages of preoperative opioid naivety and recorded pain scores throughout the surgical experience. The percentage of unused opioids for intermediate, intermediate to normal, and normal or extensive categories was 79%, 63%, and 46%, respectively. Moreover, of the 14 patients declaring the highest level of satisfaction for their pain control after discharge, 60% belonged to intermediate, 100% to intermediate to normal, and 57% to the normal or extensive group.

Conclusion: This study outlines a possible correlation between genetically controlled metabolism and opioid requirements after surgery. In this setting, an increased CYP2D6 enzymatic activity was associated to a greater opioid consumption, lesser amount of unused opioids, and a lower satisfaction level from opioid prescription.

Accepted for oral presentation at the 2019 Central Surgical Association Congress.

* Reprint requests: Raffaele Rocco, MD, Mayo Clinic, 200 First St SW, Rochester, MN 55905.

E-mail address: rocco.raffaele@mayo.edu (R. Rocco).

https://doi.org/10.1016/j.surg.2019.04.033
0039-6060/

Introduction

Despite significant efforts to reduce and standardize opioid prescribing,[1–3] opioids remain a cornerstone of postoperative pain management for many general surgical procedures. Various procedure-specific guidelines for postoperative prescribing exist[1–3]; however, these broad guidelines may not meet the individual needs of patients who require significantly more or less opioids, and additional patient-centered work is needed in this area.

Pharmacogenomics is the study of the role of genetic variation in drug response phenotype. Owing to genetic variation, some individuals may not respond as expected to a medication, which could lead to life-threatening adverse effects at one end of the spectrum or to a lack of therapeutic efficacy at the other end of the spectrum.[4–7] CYP2D6 belongs to the cytochrome P450 gene superfamily, which includes many important phase I drug metabolizing enzymes, and participates to the metabolism of $\leq$25% of clinically used drugs, including codeine. The CYP2D6 gene is highly polymorphic, leading to marked interindividual variation in enzyme activity and corresponding CYP2D6-mediated drug metabolism. An individual's enzyme activity can be predicted based on his or her genotype. Opioids such as codeine require activation by CYP2D6 before for pharmacologic efficacy.[8] An individual with higher than typical ability to metabolize CYP2D6 substrates can be described as an ultrarapid metabolizer and would be expected to metabolize codeine to morphine more rapidly than average, which may lead to adverse events, such as respiratory depression. On the other hand, individuals with reduced or markedly reduced enzyme activity can be described as intermediate or poor metabolizers, respectively, and when prescribed standard doses, may not metabolize sufficient codeine to morphine and may experience lack of therapeutic efficacy. Individuals may also have activity that spans these categories (ie, poor to intermediate metabolizer; Table I).The frequency of CYP2D6 variant alleles and distribution of metabolizer status vary significantly across world populations; it has been reported that CYP2D6 poor metabolizers comprise 0.4% to 5.4% of individuals across populations, approximately 0.4% to 11% of individuals are intermediate metabolizers, 67% to 90% are normal metabolizers, and 1% to 21% of individuals across populations are predicted to be ultrarapid metabolizers.[9] At standard doses, a patient who is a CYP2D6 ultrarapid metabolizer would be expected to be at greater risk of rapidly converting codeine to morphine and experiencing overdose symptoms.[8,10,11] On the other hand, a patient with an intermediate or a poor metabolizer phenotype would be predicted to be at greater risk of experiencing lack of efficacy because they may not efficiently activate a prodrug like codeine or they may experience adverse events when treated with active drugs owing to reduced deactivation of the medication. Although codeine has been the subject of pharmacogenomic dosing guidelines,[12] current prescribing guidelines for other opioids would however result in each of these phenotype patients receiving the same number of opioids (Table I).

We postulate that pharmacogenetic data may help facilitate an improved approach to the prescription of opioids by identifying an individualized, preemptive, genotype-guided therapy. This study represented an opportunity to inform the postsurgical opioid prescription practice by integrating genomic data with opioid consumption, hypothesizing that different genetically predetermined metabolizers use a different number of opioids after surgery.

Methods

This study was generated by the unison of data from 2 prior initiatives taking place at our institution. The first was an initiative conducted from March 2017 to January 2018, which involved prospectively surveying 2,486 patients undergoing 1 of 25 elective surgical procedures at three affiliated academic institutions.[1] Eligible patients were selected from hospital procedure lists using stratified simple random selection without replacement. Patients were excluded if the procedure was combined with other major operations or if the patient had a second operation before the survey. As part of a quality initiative patients were surveyed by phone 21 to 35 days after hospital discharge and asked to complete a 28-question survey regarding opioid utilization and pain experience. Both of the aforementioned were undertaken so as to reduce social desirability and recall bias.[1,13] Patients were asked to report how many opioids were remaining (unused) for each of their opioid prescriptions and if they had obtained a refill. Patients were also asked to report their experience with their pain control after discharge. Complete study methodology is available in the manuscript and supplemental materials; in brief, the 2,486 patients that completed the survey corresponded to a response rate of 75.2%. Of the non-responders, the majority did not answer the call, and the rest (3.1% of all sampled) refused to participate.[1]

After obtaining institutional review board approval, the patients who participated in the quality initiative were matched with patients who had submitted blood samples to the Mayo Clinic Biobank and had additional pharmacogenetic testing done as part of the Right Drug, Right Dose, Right Time (RIGHT) study.[10,14]

Participants in the RIGHT study at Mayo Clinic underwent next-generation sequencing using the PGRN-Seq capture reagent. In addition, CYP2D6 was genotyped separately using a combination of the Luminex Tag-It Mutation Detection Kit (Luminex Corporation, Austin, TX) for Cytochrome P450 2D6, a laboratory-developed copy number variation assay, or sequencing assays.[15] Pharmacogenomic results including genotype and phenotype for CYP2C19, CYP2C9, VKORC1, SLCO1B1, and CYP2D6 were deposited in the electronic health record. Each of the 1,013 participants were selected based on enrollment in the Mayo Clinic Biobank and high risk for initiating a statin drug within 3 years.

CYP2D6 genotype data were used to predict the phenotype based on known functionality of the alleles identified for each participant as previously described.[10,15,16] The Activity score for each diplotype was calculated based on data from the Pharmacogene Variation (PharmVar) Consortium and review of functional studies available in the literature as per standard clinical practice in the Mayo Clinic Personalized Genomics Laboratory.[15] The activity score was used to assign a CYP2D6 phenotype for each patient, and both the activity score and predicted phenotype were used in the analyses.[5,15] The median of the activity score range was used for plotting.

Once the patients who had both survey data and pharmacogenetic data available were identified, additional chart abstraction was conducted to obtain patient demographic and surgical information and opioid prescribing data. Opioid prescriptions at discharge and consumption data were converted into morphine milligram equivalents (MME). In addition, routinely collected pain scores were obtained during the hospitalization. These were recorded using the 10-point patient-reported Numeric Pain Rating Scale as median (interquartile range [IQR]) values. Numeric Pain Rating Scale were collected during 3 different perioperative phases to generate the following: (1) preoperative pain score, (2) maximum pain score, and (3) discharge pain score.

Based on an increasing extent of metabolizing activity, 3 CYP2D6 metabolizer phenotypes were identified, namely, the intermediate metabolizers (IM), the intermediate to normal metabolizers (INM), and the normal (extensive, NM) metabolizers. Opioid consumption, pain scores, and patient experience with pain control were compared across CYP2D6 metabolizer phenotypes. Genotype to phenotype translation was performed using the same process as used for clinical CYP2D6 testing in our laboratory. Briefly, an activity score was used where each allele was assigned a value from 0 (no activity) to 1

Table I
Explanation of cytochrome phenotypes and examples

Cytochrome phenotype	Metabolism rate	Example
Ultra-rapid metabolizer	Highest	A patient is expected to metabolize opioids more rapidly than average. Greater risk of overdose symptoms with prodrugs; greater risk of lack of efficacy with active drugs.
NM		A patient is expected to metabolize opioids at an average rate. This rate is faster than INM, IM, and poor metabolizer rate.
INM		A patient is expected to metabolize opioids less quickly than average but at a higher rate than IM and poor metabolizers.
IM		A patient is expected to metabolize opioids less quickly than average but at a higher rate than poor metabolizers.
Poor metabolizer	Lowest	A patient is expected to metabolize opioids less quickly than average. Greater risk of lack of efficacy with prodrugs; greater risk of overdose symptoms with active drugs.

Table II
Surgical procedures performed correlated to MME prescribed or consumed, patient satisfaction, and CYP2D6 metabolizer phenotype

Procedure	MME prescribed	MME consumed	Percent used of MME	Satisfaction level	Current phenotype	Activity score
Breast lumpectomy ± sentinel node	80	56	70.00%	Somewhat satisfied	Normal (extensive) metabolizer	1.8–2
Carotid endarterectomy	0	0	0.00%	Very satisfied	Intermediate metabolizer	0.8–1
Carpal tunnel release	75	37.5	50.00%	Very satisfied	Intermediate to normal (extensive) metabolizer	1.3–1.5
Carpal tunnel release	75	0	0.00%	Very satisfied	Intermediate metabolizer	1
Knee arthroscopic meniscectomy	225	75	33.33%	Very satisfied	Intermediate to normal (extensive) metabolizer	1.3–1.5
Knee arthroscopic meniscectomy	0	0	0.00%	Somewhat satisfied	Intermediate metabolizer	1
Lumbar fusion	200	10	5.00%	Very satisfied	Intermediate metabolizer	1
MIS inguinal hernia repair	75	0	0.00%	Very satisfied	Intermediate to normal (extensive) metabolizer	1.6–2
MIS inguinal hernia repair	150	0	0.00%	Very satisfied	Intermediate metabolizer	0.8–1
MIS lung wedge resection	600	150	25.00%	Very dissatisfied	Intermediate metabolizer	1
MIS prostatectomy	150	37.5	25.00%	Very satisfied	Normal (extensive) metabolizer	2
Parathyroidectomy	75	0	0.00%	Very satisfied	Normal (extensive) metabolizer	2
Parathyroidectomy	100	5	5.00%	Very satisfied	Intermediate metabolizer	0.8–1
Rotator cuff surgery	1025	140	13.66%	Somewhat satisfied	Intermediate metabolizer	1
Simple mastectomy ± sentinel node	212.5	45	21.18%	Very satisfied	Intermediate metabolizer	1.2
Total hip	587.5	115	19.57%	Very satisfied	Intermediate metabolizer	1
Total knee	900	600	66.67%	Very satisfied	Intermediate to normal (extensive) metabolizer	1.3–1.5
Total knee	600	600	100.00%	Somewhat dissatisfied	Normal (extensive) metabolizer	2
Total knee	475	0	0.00%	Somewhat satisfied	Normal (extensive) metabolizer	1.8–2
Total knee	550	475	86.36%	Very satisfied	Normal (extensive) metabolizer	1.8–2
Total knee	1000	977.5	97.75%	Very satisfied	Normal (extensive) metabolizer	1.8–2

(normal activity), and then the scores for each allele detected were added. The activity score was then translated into the corresponding phenotype based on predefined ranges depicted in Table I.

These 2 categories were compared by univariate analysis using Wilcoxon rank-sum tests for continuous variables, and χ^2 and Fisher exact tests were used for categorical variables. Statistical analysis was performed using version 9.4 of SAS (SAS Institute Inc., Cary NC).

Results

Of the 2,486 surgical patients with prospective survey data on opioid utilization, 21 also had pharmacogenomic information available and were included in analysis. In this cohort of patients the median age was 63 years (IQR 59–68) and 14 (67%) were females. Patients underwent a variety of operations that ranged from breast lumpectomy to total knee replacements (Table II).

At discharge patients were prescribed a median of 200 MME (IQR 475; 75,550). The median amount of MME consumed after discharge was 37.5 MME (IQR 150; 0, 150). This resulted in 75 MME (IQR 143.5; 24,167.5) or 63% of the prescribed opioids that remained unused. Aforementioned MME values do not sum owing to the fact that they were not normalized. Based on our findings, 10 patients (48%) were found to be in the IM group, 4 patients (19%) were in the INM group, and 7 patients (33%) were in the NM group.[9] None of the participants were found to be ultrarapid or poor metabolizers.

If the opioid use per each metabolizer phenotype is analyzed, the NM phenotypes showed the highest utilization (57%) compared with IM (40%) and INM (25%) without reaching statistical significance ($P = .57$).

In this series, IM phenotype patients were significantly older (in the 60–79 years group range) than the other patients ($P = .02$). However, the INM phenotype patients showed a trend toward lower preoperative (75% vs 100% of IM and NM, respectively; $P = .58$) and lower maximal pain scores (50% vs 90% and 100% of IM and NM, respectively; $P = .094$) and an overall MME consumption more than the 75th percentile (75% vs 85.7% and 80% of IM and NM, respectively; $P = .062$). Conversely, compared to the INM and IM phenotypes, NM had highest percentages of opioid naivety and pain scores throughout the surgical experience, but the difference did not reach statistical significance. Of the 21 patients, 14 declared the highest level of satisfaction for their pain control after discharge. In this subgroup, the NM phenotype demonstrated the least level of satisfaction (57% vs 60% and 100% of the IM and INM, respectively; $P = .83$). The need for opioid refill from the time of discharge to time of survey was not statistically different among the different metabolizer phenotypes ($P = 1.00$; Table III).

Activity score based on phenotypic categories of opioid metabolizers was plotted against amount of opioids consumed (MME) for each patient and suggested a trend toward increasing opioid consumption correlating with increasing activity score (Fig 1).

Table III
Patient characteristics and pain scores correlated to CYP2D6 metabolizer phenotype

	All (n = 21)	CYP2D6 metabolizer status: intermediate (n = 10)	CYP2D6 metabolizer status: intermediate to normal (extensive) (n = 4)	CYP2D6 metabolizer status: normal (extensive) (n = 7)	*P* value
Age					.03
No. (%) used	21 (100.0%)	10 (100.0%)	4 (100.0%)	7 (100.0%)	
Median (IQR)	63 (59–68)	68 (63–73)	59.5 (54.5–61.5)	58 (55–65)	
Range	49–79	60–79	50–63	49–76	
Age group, no.					.02
80+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
60–79	15 (71.4)	10 (100.0)	2 (50.0)	3 (42.9)	
40–59	6 (28.6)	0 (0.0)	2 (50.0)	4 (57.1)	
18–39	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Sex, no.					.70
Female	14 (66.7)	7 (70.0)	2 (50.0)	5 (71.4)	
Male	7 (33.3)	3 (30.0)	2 (50.0)	2 (28.6)	
Preoperative opioid user (self-defined)					1.00
Opioid naive	17 (81.0)	8 (80.0)	3 (75.0)	6 (85.7)	
Opioid tolerant	4 (19.0)	2 (20.0)	1 (25.0)	1 (14.3)	
Preoperative pain score					.58
No. (%) used	20 (95.2%)	10 (100.0%)	3 (75.0%)	7 (100.0%)	
Median (IQR)	2 (0–3)	1 (0–3)	1 (0–4)	2 (0–6)	
Range	0 to 8	0 to 5	0 to 4	0 to 8	
Max pain score					.09
No. (%) used	18 (85.7%)	9 (90.0%)	2 (50.0%)	7 (100.0%)	
Median (IQR)	6 (3–8)	3 (2–6)	3 (0–6)	6 (6–9)	
Range	0–10	0–9	0–6	5–10	
Prescribed opioids at discharge					.67
No	2 (9.5)	2 (20.0)	0 (0.0)	0 (0.0)	
Yes	19 (90.5)	8 (80.0)	4 (100.0)	7 (100.0)	
Discharge MME					.64
No. (%) used	21 (100.0%)	10 (100.0%)	4 (100.0%)	7 (100.0%)	
Median (IQR)	200 (75–550)	175 (75–450)	150 (75–562.5)	475 (80–600)	
Range	0–1025	0–1025	75–900	75–1000	
Consumed MME					.46
No. (%) used	21 (100.0%)	70 (100.0%)	4 (100.0%)	7 (100.0%)	
Median (IQR)	37.5 (0–150)	7.5 (0–140)	56.25 (18.75–337.5)	56 (0–600)	
Range	0–977.5	0–450	0–600	0–977.5	
MME consumed >75th percentile, no. (col %)					.06
No	17 (81.0)	10 (100.0)	3 (75.0)	4 (57.1)	
Yes	4 (19.0)	0 (0.0)	1 (25.0)	3 (42.9)	
Opioid refill from time of discharge to time of survey (self-defined)					1.00
No	20 (95.2)	9 (90.0)	4 (100.0)	7 (100.0)	
Yes	1 (4.8)	1 (10.0)	0 (0.0)	0 (0.0)	
Patient satisfaction with pain control after discharge, no. (col %)					.83
Very satisfied	14 (66.7)	6 (60.0)	4 (100.0)	4 (57.1)	
Somewhat satisfied	4 (19.0)	2 (20.0)	0 (0.0)	2 (28.6)	
Neither satisfied nor dissatisfied	1 (4.8)	1 (10.0)	0 (0.0)	0 (0.0)	
Somewhat dissatisfied	1 (4.8)	0 (0.0)	0 (0.0)	1 (14.3)	
Very dissatisfied	1 (4.8)	1 (10.0)	0 (0.0)	0 (0.0)	

Discussion

In recent years, many institutions have adopted procedure-specific guidelines to address the issue of opioid prescribing after discharge from surgery.[11,17,18] Although these guidelines represent a significant step forward from the prior era of opioid prescribing, they are not patient specific. Our preliminary data suggests that pharmacogenetics may provide an innovative, tailored approach to allow for patient-related predictor of opioid use.[5]

Opioids are among the top 30 drugs with high pharmacogenetic risk[7]; thus, there is room for development and integration of the concept of using genetic data to guide clinical management. In this setting, the genomic profile for opioid sensitivity and responsiveness could be used as a surrogate of the so-called individual pain threshold.[19–21] In our study, NM patients tend to show a higher preoperative and maximal pain score and an overall MME consumption of more than the 75th percentile. Nevertheless, NM patients were the least satisfied with their pain control after surgery. Without the information about their CYP2D6 status, these features would probably classify NM patients as having a low pain threshold.

Over-and underprescribing of outliers is a significant concern with the current procedure specific opioid prescribing guidelines after surgery.[21] Identifying those patients at risk of not receiving enough opioids may prevent poor patient experiences with pain control and refills.[22] For example, 48% of patients in our study (IM) exhibited a phenotype that suggested the opioids may be more potent, and would potentially require less opioids than other patients.

The era of standardized postsurgical prescriptions, facilitated by ERAS Protocols,[23] may soon be over in favor of modulated opioid prescription possibly based on a genomic-related addiction risk score.[21] Moreover, the genetic identification of a specific inclination towards the development of opioid-related side effects will contribute to a personalized dosing of the drug.[22] Figure 1 also suggested a possible association between increasing activity score being associated with increasing opioid consumption. This demonstrates a possible association between genetically controlled metabolism and

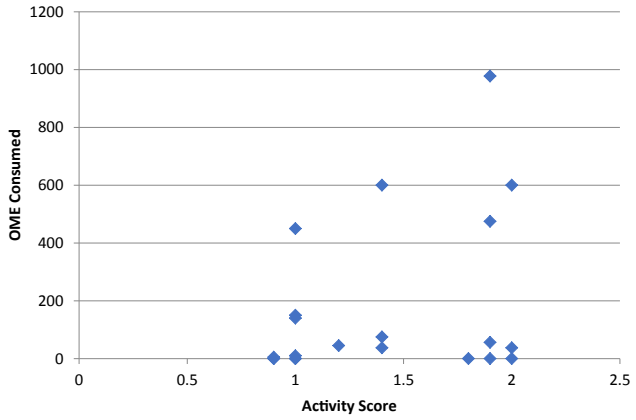

Fig 1. Oral morphine equivalents (OME) consumed by CYP2D6 activity score. Median of the activity score range used for plotting.

opioid requirements in the postoperative setting.[24] The low numerosity of our study does not allow for definite conclusions.

Our pilot study has significant limitations. The retrospective nature and limited patient population limit our ability to perform a statistical analysis. That being said, the aim of this preliminary study was to determine feasibility and potential value of genomic profiling in the context of perioperative opioid use. We did not identify any participants with ultrarapid (faster than typical) or poor (greatly reduced) CYP2D6 activity. In addition, we did not account for concurrent medication with strong CYP2D6 inhibitors that could impact the phenotype. Our study only evaluated genetic variation in CYP2D6. Variation in other genes likely contributes to interindividual variation in opioid response as well. The surgical procedures that our patients were subjected to were highly variable. Furthermore, opioid prescribing was not yet standardized during the course of this study. Our study also does not address how to resolve the disadvantages of incorporating pharmacogenetic data in clinical practice, such as the following: (1) legal, social, and financial concerns regarding genomic medicine by patients and their families; (2) lack of support for commercial electronic medical record systems to integrate large-scale genomic data linked to automated clinical decision support; or (3) delay in the initiation of therapy when traditional reactive ordering of pharmacogenetic testing at point-of-care is used. Lastly, our matching of 2 study cohorts has significant bias and our findings can therefore likely not be generalized to other institutions or the greater population. Despite the aforementioned significant limitations, the results of this exploratory pilot study do suggest a potential avenue for future research and possible practice change.

The results of our pilot study suggests that pharmacogenomic data has the potential of reducing over and under prescription of opioids after surgery and eventually creating personalized opioid prescribing practices. Additional data and research on opioid pharmacogenomics is warranted to confirm the value of our findings and guide the transition from a one size fits all guideline approach to postoperative opioid prescribing to a patient centered approach.

Conflict of interest/Disclosure

The authors have no relevant financial disclosures.

Funding/Support

Support provided by the Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery (Ubl and Habermann). This work was supported by Mayo Clinic Center for Individualized Medicine, Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, National Institutes of Health grants U19 GM61388 (The Pharmacogenomics Research Network), R01 GM28157, U01 HG005137, R01 GM125633, R01 AG034676 (The Rochester Epidemiology Project), and U01 HG06379 and U01 HG06379 Supplement (The Electronic Medical Record and Genomics [eMERGE] Network).

References

1. Thiels CA, Anderson SS, Ubl DS, et al. Wide variation and overprescription of opioids after elective surgery. *Ann Surg*. 2017;266:564–573.
2. Hill MV, McMahon ML, Stucke RS, et al. Wide variation and excessive dosage of opioid prescriptions for common general surgical procedures. *Ann Surg*. 2017;265:709–714.
3. Hilliard PE, Waljee J, Moser S, et al. Prevalence of preoperative opioid use and characteristics associated with opioid use among patients presenting for surgery. *JAMA Surg*. 2018;153:929–937.
4. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med*. 2003;349:1943–1953.
5. Adams SM, Crisamore KR, Empey PE. Clinical pharmacogenomics: Applications in nephrology. *Clin J Am Soc Nephrol*. 2018;13:1561–1571.
6. Zambrano T, Salazar LA. MicroRNAs and response to statins in patients with hypercholesterolemia: From basic research to precision medicine. *Pharmacogenomics*. 2018;19:748–751.
7. Jiang F, Choi JY, Lee JH, et al. The influences of SLCO1B1 and ABCB1 genotypes on the pharmacokinetics of simvastatin, in relation to CYP3A4 inhibition. *Pharmacogenomics*. 2017;18:459–469.
8. Gaedigk A, Sangkuhl K, Whirl-Carrillo M, Klein T, Leeder JS. Prediction of CYP2D6 phenotype from genotype across world populations. *Genet Med*. 2017;19:69–76.
9. St Sauver JL, Olson JE, Roger VL, et al. CYP2D6 phenotypes are associated with adverse outcomes related to opioid medications. *Pharmagenomics Pers Med*. 2017;10:217–227.
10. Crews KR, et al. *Clin Pharmacol Ther*. 2014;95:376–382.
11. Olson JE, Rohrer Vitek CR, Bell EJ, et al. Participant-perceived understanding and perspectives on pharmacogenomics: The Mayo Clinic RIGHT protocol (Right Drug, Right Dose, Right Time). *Genet Med*. 2017;19:819–825.
12. Thiels CA, Ubl DS, Yost KJ, et al. Results of a prospective, multicenter initiative aimed at developing opioid-prescribing guidelines after surgery. *Ann Surg*. 2018;268:457–468.
13. Bowling A. Mode of questionnaire administration can have serious effects on data quality. *J Public Health (Oxf)*. 2005;27:281–291.
14. Ji Y, et al. *J Mol Diagn*. 2016;18.
15. Yang JJ, Whirl-Carrillo M, Scott SA, et al. Pharmacogene variation consortium gene introduction: NUDT15. *Clin Pharmacol Ther*. 2019;105:1091–1094.
16. Gaedigk A, Sangkuhl K, Whirl-Carrillo M, Twist GP, Klein TE, Miller NA; PharmVar Steering Committee. The Evolution of PharmVar. *Clin Pharmacol Ther*. 2019;105:29–32.
17. Hill MV, McMahon ML, Stucke RS, Barth Jr RJ. Wide variation and excessive dosage of opioid prescriptions for common general surgical procedures. *Ann Surg*. 2017;265:709–714.
18. Overton HN, Hanna MN, Bruhn WE, et al. Opioids after surgery workgroup. Opioid-prescribing guidelines for common surgical procedures: An expert panel consensus. *J Am Coll Surg*. 2018;227:411–418.
19. Zahari Z, Ismail R. Influence of cytochrome P450, family 2, subfamily D,Polypeptide 6 (CYP2D6) polymorphisms on pain sensitivity and clinical response to weak opioid analgesics. *Drug Metab Pharmacokinet*. 2014;29:29–43.
20. Yokoshima Y, Sumitani M, Nishizawa D, et al, Japanese TR-Cancer Pain Research Group. Gamma-aminobutyric acid transaminase genetic polymorphism is a candidate locus for responsiveness to opioid analgesics in patients with cancer pain: An exploratory study. *Neuropsychopharmacol Rep*. 2018;38:175–181.
21. Robishaw J, Caceres J, Hennekens CH. Genomics and precision medicine to combat opioid use disorder. *Am J Med*. 2019;132:395–396.
22. Muriel J, Margarit C, Barrachina J, et al. Pharmacogenetics and prediction of adverse events in prescription opioid use disorder patients. *Basic Clin Pharmacol Toxicol*. 2019;124:439–448.
23. Gerrish AW, Fogel S, Lockhart ER, et al. Opioid prescribing practices during implementation of an enhanced recovery program at a tertiary care hospital. *Surgery*. 2018;164:674–679.
24. Smith DM, Weitzel KW, Elsey AR, et al. CYP2D6-guided opioid therapy improves pain control in CYP2D6 intermediate and poor metabolizers: A pragmatic clinical trial. *Genet Med*. 2019. https://doi.org/10.1038/s41436-018-0431-8 [Epub ahead of print].

Discussion

Dr John Mellinger (Springfield, IL): I want to thank Dr Rocco and his associates for providing a nicely written manuscript well before the meeting, allowing plenty of time to prepare some questions, so thank you.

As was very nicely presented, you have married 2 sets of data from prior studies at your institution, and identified a group of patients for whom you had both survey-based data on post-operative opioid utilization and pharmacogenetic data from a separate database, delineating this group of patients for analysis. The punch line is that individuals who have higher levels of opioid related enzymatic activity on pharmacogenetic analysis had increased opioid utilization rates and lower pain satisfaction scores after surgery, suggesting that there is a possible correlation worthy of further investigation.

This is a very relevant topic in the current opioid crisis in our country, so I commend you for this investigation, and for thinking of a novel way to look at this issue.

My first question relates to the fact that there is a difference in the number of patients analyzed, 22 in our abstract book versus 21 in what you presented and what was in the manuscript. Could you clarify that discrepancy?

Second, and this may have been in your prior published work in *Annals of Surgery*, but could you inform us a bit more about the survey you employed. Was it a validated instrument for studying this population, vs. a novel instrument you developed? If the latter, can you describe how it was developed? This would be helpful to know for the present analysis, given the effect that survey structure and design can have on the data generated.

In addition, there's a figure in your manuscript which you didn't show in the presentation, Fig 1, that talks about the correlation between activity scores and opioid utilization. There was one outlier in the data, and to my review it seemed that outlier datapoint made the figure look more meaningful than I thought it probably was. If you have eliminated that figure from your ultimate manuscript, fine. If that's still something you are going to use, I would like you to comment on that outlier datapoint and whether it skewed the results presented.

Finally, it strikes me that there are a couple of variables here that maybe we haven't talked about, and probably should with the small sample sizes of anywhere from 4 to 10 in your 3 comparison groups. Specifically, I suspect there was some variability in opioid utilization between the 25 or so operations included in your survey data. There's a big difference between a breast lumpectomy and a total knee replacement. Did you look at that vis-a-vis the 3 comparison groups, particularly given the small sample sizes? It would seem very possible that if one group contained a larger number of more complex operations, that could have skewed the survey data for that group of patients. Additionally, is there a plasticity to opioid metabolism, particularly because the enzyme you studied in the pharmacogenetic data doesn't just govern metabolism of opioids? Did you look at polypharmacy issues in these patients and how that might affect opioid utilization, and whether opioid metabolism can change with aging? It would be helpful to know if these issues were considered.

In summary, this was very nicely presented. In addition, this is an important and timely topic in an era where we are looking at treating cancer patients differently based on genetic analyses. Investigating this topic from a genetic perspective in an area that's of such public health interest has evident relevance and significance. Thank you.

Dr Raffaele Rocco: In regards to the initial question, the one patient that we excluded from our study retracted his consent to share his genetic information; thus, we had to exclude him from our study.

In regards to the second question, this was addressed in one of our prior initiatives in *Annals of Surgery*; in this, we prospectively identified patients that underwent procedures in 3 different institutions in 3 states. Telephone interviews rather than paper or E-mail interviews were undertaken in order to avoid social desirability bias stemming from the major social media attention of the opioid crisis. We also tried to decrease recall bias by calling the patients within 3 weeks of their discharge.

Patients that were eligible were taken from hospital procedure lists and identified via a stratified simple random selection without replacement. Patients were excluded if they had had 2 procedures at the same time or prior to our survey. We identified around 3,400 surgical patients and, of these, around 2,500 completed our survey, resulting in a response rate of 75.2%. Of the 900 or so non-responders, around 700 did not answer the call, around 100 refused (3.1% of all sampled).

In regards to the third question about the figure, given that this is a pilot study and thus the information available at this time is limited, we cannot draw any definite conclusions. That being said, I agree in this context that the outlier mentioned does seem to generate a trend. This gives us something to work towards and I, as well as the team, believe that this pilot study is ground enough for possible further research in the future.

In regards to the final questions, no, we did not look into the concept of polypharmacy. Obviously, various other medications can induce or inhibit the enzyme itself, acetaminophen and haloperidol, for example. We also did not try to stratify the different procedures themselves but rather decided to include them all.

One of my objectives for the future, as I am looking into becoming a thoracic surgeon, is to use the information from this study among thoracic surgery patients specifically.

Dr L. Michael Brunt (St. Louis, MO): Congratulations on a very clear and crisp presentation. It was really beautifully presented, and this is really important and intriguing work. I think we have all had the experience of patients coming back to the office and saying, I never took a pain pill, or only took one pain pill, and then others that will sometimes call in for a refill.

I would like to get just a little back to Dr Mellinger's question again about the survey from the original study. You may have answered this. You said 2 to 3 weeks but I think the timing of your assessment on patient satisfaction with their pain and how much pain meds that they used is really critical. So if you did it within that 2- to 3-week interval consistently across all of the patients that you looked 3 in this study, then I think that's certainly a plus for your interpretation.

Also, in regard to other agents, does the metabolizer rate affect nonsteroidal metabolism at all in any way? Because that's the other agent that oftentimes patients will use for pain management as well.

Dr Raffaele Rocco: In regards to the first question: yes, we mainly looked into patients that were within 3 weeks of discharge.

In regards to the second question: I do not recall any literature in terms of NSAIDs, but various other studies were published for statins and antidepressants, with various institutions looking into the aforementioned. It's certainly a topic for the future.

Dr Christopher R. Mchenry (Cleveland, OH): I, too, enjoyed your presentation. I have 2 quick questions for you.

First, how do you define opioid naive? For instance, if a patient was on opioids 3 months prior to your surgery and not on opioids at the time of your surgery, would that patient be opioid naive?

Secondly, for opioid users at the time they underwent surgery, I wonder if the reason that they got more opioids was not the result of the enzyme effect but it may have been related to the fact that they were already on opioids. So wouldn't it be better to look at truly opioid-naive patients to determine enzyme effects?

Dr Raffaele Rocco: In regards to the first question, we defined opioid-naive patients as those with no prior opioid use.

In regards to the second question: we looked at the difference between opioid naives and opioid tolerant in the study without finding any statistical significance; however, it is certainly something to keep in mind for the future as the pain threshold could vary in patients that are already on opioids.

Dr Robert C.G. Martin (Louisville, KY): One quick question about patient expectation and education. Can you tell us what your institutional bias is preoperatively as an opioid-free expectation? Are you even talking about that? Are the patients aware of this, that they may not even need narcotics?

Then the education postoperatively; you and I both know prn means "as needed." I do not know why we even write "prn" on scrips anymore. Patients see Q4, Q6, and they take it as scheduled. What type of educational aspects have you instituted? Or do you have any?

Dr Raffaele Rocco: In terms of education, I can only speak for my experience on breast surgery. For example, when a patient is about to undergo a lumpectomy, we try to educate the patients on the fact, that per the literature, opioid necessity is minimal.

If we do prescribe opioids in an outpatient setting, we try to explain to them that in the next few days after their operation their mobility will increase and their pain can also increase concomitant to it. We try to reiterate that an increased amount of pain at the time is expected, especially because the anesthesia and analgesia from the previous surgery wears off.

Adding to the aforementioned context, if the case was adequately hemostatic, we try to encourage Toradol in the hospital and other NSAIDs out of the hospital. That is the only example I can think of. Again, it will be something I will analyze further in the setting of thoracic surgery.

Dr Margo Shoup (Dansbury, CT): Along the lines of Dr Martin's question, we have started telling patients both during their hospital stay and when they are ready to go home, the goal is not zero on the pain score; the goal is 3 or 4. Because you have had surgery, you are going to have pain. Just as long as it's something that you can bear, then that's okay, because opioid side effects are really pretty miserable if you stay on them for too long a time. Stating those expectations from the beginning will lower their opioid use.

Dr Raffaele Rocco: Yes, ma'am, we do that. Thank you.

Surgery is abstracted and/or indexed in *Index Medicus, Science Citation Index, Current Contents/ Clinical Medicine, Current Contents/Life Sciences,* and MEDLINE.