Life-threatening adverse events following therapeutic opioid administration in adults: Is pharmacogenetic analysis useful?

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BACKGROUND: Systemic approaches are needed to understand how variations in the genes associated with opioid pharmacokinetics and response can be used to predict patient outcome. The application of pharmacogenetic analysis to two cases of life-threatening opioid-induced respiratory depression is presented. The usefulness of genotyping in the context of these cases is discussed.

METHODS: A panel of 20 functional candidate polymorphisms in genes involved in the opioid biotransformation pathway (*CYP2D6, UGT2B7, ABCB1, OPRM1, COMT*) were genotyped in these two patients using commercially available genotyping assays.

RESULTS: In case 1, the patient experienced adverse outcomes when administered codeine and morphine, but not hydromorphone. Genetic test results suggested that this differential response may be due to an inherent propensity to generate active metabolites from both codeine and morphine. These active metabolites are not generated with hydromorphone. In case 2, the patient experienced severe respiratory depression during postoperative recovery following standard doses of morphine. The patient was found to carry genetic variations that result in decreased morphine efflux transporter activity at the blood-brain barrier and increased sensitivity to opioids.

CONCLUSIONS: Knowledge of the relative contribution of pharmacogenetic biomarkers and their influence on opioid response are continually evolving. Pharmacogenetic analysis, together with clinical history, has the potential to provide mechanistic insight into severe respiratory depressive events in patients who receive opioids at therapeutic doses.

Key Words: *Adverse drug reactions; Opioids; Pharmacogenetics*

Les effets indésirables mettant en jeu le pronostic vital après l'administration thérapeutique d'opioïdes chez des adultes : l'analyse pharmacogénétique est-elle utile?

HISTORIQUE : Des démarches systémiques s'imposent pour comprendre comment utiliser les variations des gènes associés à la pharmacocinétique et à la réponse des opioïdes pour prédire l'issue des patients. L'analyse pharmacogénétique de deux cas de dépression respiratoire induite par les opioïdes et mettant en jeu le pronostic vital est présentée. L'utilité du génotypage est exposée à l'égard de ces cas.

MÉTHODOLOGIE : Les chercheurs ont procédé au génotypage d'un groupe de 20 polymorphismes candidats fonctionnels des gènes participant à la voie de biotransformation des opioïdes (*CYP2D6, UGT2B7, ABCB1, OPRM1, COMT*) chez ces deux patients, au moyen de titrages de génotypage offerts sur le marché.

RÉSULTATS : Dans le cas 1, le patient a ressenti des effets indésirables lorsqu'on lui a administré de la codéine et de la morphine, mais pas quand on lui a administré de l'hydromorphone. D'après les résultats génétiques, cette réponse différentielle pourrait être attribuable à une propension inhérente à générer des métabolites actifs, à partir de la codéine tout autant que de la morphine. Ces métabolites actifs ne sont pas produits par l'hydromorphone. Dans le cas 2, le patient présentait une grave dépression respiratoire pendant le rétablissement postopératoire après l'administration de doses standards de morphine. On a découvert que le patient était porteur de variations génétiques qui réduisaient l'activité de transporteur d'efflux de la morphine à la barrière hématoencéphalique et accroissaient la sensibilité aux opioïdes.

CONCLUSIONS : Les connaissances sur l'apport relatif des biomarqueurs pharmacogénétiques et sur leur influence sur la réponse des opioïdes sont en constante évolution. L'analyse pharmacogénétique, conjointement avec les antécédents cliniques, a le potentiel de donner un aperçu mécaniste sur les événements de grave dépression respiratoire chez les patients qui reçoivent des opioïdes à des doses thérapeutiques.

The influence of pharmacogenetic variation on analgesia and anesthesia has long been known (1). Genetic polymorphisms have been described in drug-metabolizing enzymes (2-8), transporters (9,10) and receptors (11-16) involved in the opioid response. However, there is controversy related to the clinical utility of pharmacogenetic testing in the context of anesthesiology (17,18). This issue has been exacerbated by the complexity of pain as an outcome measure, the limited characterization of the opioid analgesic pathway and the inherent heterogeneity in study designs and patient cohorts. Moreover, the majority of pharmacogenetic studies in this area have investigated a single gene in a cause-and-effect approach. Aside from the notable exception of cytochrome P450 2D6 (*CYP2D6*), the clinical impact of these single pharmacogenetic markers has remained elusive in the context of pain management.

Given our current understanding of the multiple markers that may influence opioid action and response, a polygenic analytical approach may be useful to determine how genetic determinants interact to influence pain response and the occurrence of adverse outcomes. Therefore, we developed a panel of 20 functional candidate polymorphisms in five genes (*CYP2D6, UGT2B7, ABCB1, OPRM1* and *COMT*) that

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TABLE 1
Timeline of clinical events and opioid administration

Timeline	Doses administered and events
Case 1: Caesarean section	
Perioperative	Hyperbaric bupivacaine 0.75% spinal
	Morphine 0.1 mg intrathecal
	Fentanyl 0.01 mg intrathecal
Postoperative	Morphine 1 mg intravenous
In ward	
12 h after surgery	Morphine 2 mg subcutaneous
15 h after surgery	Morphine 2 mg subcutaneous
15.5 h after surgery	Respiratory rate 4 breaths/min; pupils 2+ reactive
	Naloxone 0.28 mg
	Patient recovered consciousness immediately
Postoperative	Prescribed hydromorphone 0.5 mg to 1 mg orally every 6 h as required
	Patient used hydromorphone 2 mg over 10 h
	Discharged
Case 2: Surgical resection of a complex intra-abdominal tumour	
Perioperative	Desflurane at MAC 0.6 to 0.7
	Bupivacaine 0.2% 10 mL and morphine 2 mg: epidural load
Intraoperative	Bupivacaine 0.2% and morphine 0.025 mg/mL morphine: epidural infusion rate of 5 mL/h for 4 h
Recovery room	
5 h after surgery	Extubated, stable condition
	Respiratory rate 16 breaths/min but unresponsive
5.5 h after surgery	Blood pressure 75/40 mmHg
	Phenylephrine 0.5 mg intravenous over 15 min
	Normal saline bolus 500 mL
	Ephedrine 25 mg intramuscular
	Epidural infusion discontinued
8 h after surgery	Level of consciousness did not improve; respiratory rate 4 breaths/min to 8 breaths/min (pH 6.64, PCO_2 286 mmHg, PO_2 121 mmHg)
8.5 h after surgery	Reintubated, hyperventilated (pH 7.18, PCO_2 52 mmHg, PO_2 537 mmHg)
Postoperative	Maximum pain: 1 of 10
	Total hydromorphone 0.6 mg intravenous over five days
	Discharged

MAC Minimum alveolar concentration; PCO_2 Partial pressure of carbon dioxide; PO_2 Partial pressure of oxygen

have been characterized in the opioid pharmacokinetic and pharmacodynamic pathways (9). This panel was tested in two patients who experienced rare and serious opioid-induced respiratory depression during or following surgical procedures in Toronto, Ontario. Together with a multidisciplinary team comprising the fields of anesthesiology, pharmacology, genetics, toxicology and surgery, we explored the value of post hoc pharmacogenetic analysis in the context of these two patients. The clinical utility of a pharmacogenetic analytical approach in predicting and preventing future opioid-related adverse outcomes from occurring is also discussed.

CASE PRESENTATIONS

Case 1

A 37-year-old woman (height 1.5 m, weight 58 kg) of French Canadian descent, with a history of six previous pregnancies resulting in two live births and three miscarriages, underwent elective caesarean section (Table 1). The patient experienced a previous episode of respiratory depression with codeine (single 60 mg dose), but tolerated hydromorphone based on self-report. Before surgery, she was given 0.75% hyperbaric bupivacaine, morphine 0.1 mg and fentanyl 0.01 mg intrathecally. In the operating room the patient received ketorolac 30 mg intravenously and acetaminophen 1300 mg parenterally. In the postanesthesia care unit, the patient received morphine 1 mg intravenously and tolerated it well. Twelve hours later, the patient complained of pain in the ward and received morphine 2 mg subcutaneously. Three hours later, a second dose of morphine 2 mg was administered subcutaneously. Thirty minutes after the second dose of morphine, the patient was not rousable to voice and painful stimulus and had a respiratory rate of 4 breaths/min. Heart rate and oxygen saturation were normal but blood pressure was elevated (152/90 mmHg). Pupils were equal and 2+ reactive. The resuscitation team arrived at the scene and intravenous naloxone was administered (0.16 mg plus 0.12 mg, for a total of 0.28 mg). The patient recovered consciousness immediately (Table 1).

The patient was subsequently continued on diclofenac 50 mg orally every 8 h and acetaminophen 1000 mg orally every 6 h. She was prescribed hydromorphone 0.5 mg to 1 mg orally every 6 h as needed and 0.2 mg to 0.4 mg orally every 3 h as needed, and administered 0.5 mg at 14:35 and 16:30, and 1 mg at 24:00. After that, no additional opioids were administered and pain was managed solely with diclofenac and acetaminophen.

The patient was retrospectively genotyped for polymorphisms associated with codeine/morphine metabolism and response (Table 2). The patient carried a *CYP2D6**2/*2 genotype associated with extensive/'normal' CYP2D6 enzymatic activity; however, she had a homozygous mutation in *UGT2B7* (802T/T), which has been previously associated with increased formation of the pharmacologically potent morphine 6-glucuronide metabolite from morphine in some (19,20) but not all (21) studies. Additionally, the patient was a homozygous carrier of a *COMT* haplotype 'TCA' at positions 389, 611 and 675, respectively. This haplotype has been associated with slightly decreased catechol-o-methyltransferase activity and potentially higher opioid sensitivity (22-26).

TABLE 2
Summary of genetic variants and genotype results

Gene	Variant(s)	dbSNP ID	Case 1	Case 2
CYP2D6	*2, *3, *4, *5, *6, *9, *10, *17, *29, *41, and gene duplication ×n		*2/*2	n/a
UGT2B7	802C→T	rs7439366	T/T	C/T
ABCB1	1236C→T	rs1128503	C/C	T/T
ABCB1	2677G→T/A	rs2032582	G/A	T/T
ABCB1	3435C→T	rs1045642	C/T	T/T
OPRM1	118A→G	rs1799971	A/A	G/G
COMT	389C→T	rs4633	T/T	C/C
COMT	611C→G	rs4818	C/C	C/C
COMT	675G→A	rs4680	A/A	G/G

dbSNP ID Single nucleotide polymorphism database identification; n/a Not applicable

Case 2

A 64-year-old woman of Filipino descent undergoing surgical resection of a complex intra-abdominal tumour received an epidural for perioperative pain control (Table 1). She was administered desflurane as a general anesthetic at a minimum alveolar concentration of 0.6 to 0.7 and the epidural was loaded with 0.2% bupivacaine and morphine 2 mg; an epidural infusion of 0.2% bupivacaine and 0.025 mg/mL morphine was maintained intraoperatively at a rate of 5 mL/h for 4 h. With the exception of 0.1 mg intravenous fentanyl at the time of induction, no additional opioids were administered and the patient was extubated at a minimum alveolar concentration of 0.7 and brought to the recovery room in stable condition, breathing spontaneously at a rate of 16 breaths/min but unresponsive. Her blood pressure declined to 75/40 mmHg within the first 30 min in the recovery room, which responded to phenylephrine 0.5 mg intravenously over 15 min, a bolus of 500 mL normal saline and ephedrine 25 mg intramuscularly; the epidural infusion was discontinued at this point after 5 h. The patient

remained in the recovery room for an additional 3 h and her level of consciousness did not improve; her blood pressure and oxygen saturation were well maintained but her respiratory rate was between 4 breaths/min and 8 breaths/min during this period. At 3 h, her blood pressure again declined to 70/40 mmHg and she was unresponsive to repeated doses of intravenous ephedrine and phenylephrine. An arterial blood gas was drawn on 3 L fraction of inspired oxygen and revealed a pH of 6.64, a partial pressure of carbon dioxide of 286 mmHg and a partial pressure of oxygen of 121 mmHg. The patient was reintubated and hyperventilated; a repeat arterial blood gas drawn 30 min later showed a pH of 7.18, partial pressure of carbon dioxide of 52 mmHg and partial pressure of oxygen of 537 mmHg. The patient was drowsy but rousable 5 h to 6 h after admission to postoperative recovery and was extubated successfully the next morning. During her five-day postoperative recovery period, the patient's self-rated maximal pain was very low (1 of 10) and she was administered a total of 0.6 mg intravenous hydromorphone (equivalent to approximately 3 mg of morphine) for pain management during this time. She was well controlled on acetaminophen 1000 mg orally every 6 h as the sole analgesic and discharged in stable condition five days postoperatively.

The patient was subsequently genotyped for polymorphisms associated with morphine biotransformation and response (Table 2). The most remarkable finding was that the patient carried homozygous mutations in both *ABCB1* and *COMT* that may have predisposed her to morphine-induced respiratory depression. The haplotype 'TTT' in *ABCB1* (at 1236, 2677, 3435), which leads to substantially decreased P-glycoprotein expression and activity, has been associated with increased systemic morphine exposure (27) and morphine accumulation in the brain (28). Similarly, the *COMT* haplotype 'CCG' (at 389, 611, 675) has been associated with markedly reduced enzyme activity and increased sensitivity to opioids (22,25,26). However, the interpretation of this case was complicated by the presence of a polymorphism in the μ opioid receptor (*OPRM1* 118G/G) that has previously been associated with increased morphine dose requirements in some studies (10,23,29).

DISCUSSION

These two cases illustrate the potential utility of pharmacogenetic analysis in elucidating the mechanism of respiratory depression in otherwise unexplained cases. In the context of case 1, the incidence of anesthesia-related complications related to childbirth is 0.5% (30), which amounts to 1700 deliveries per year in Canada, assuming a birth rate of 340,000. Of these complications, only a small number (2%) are related specifically to drug-induced central nervous system depression (30). This low incidence of respiratory depression in pregnant patients is due to several factors: they have high levels of endorphins; the progesterone stimulates the respiratory centre; they are young and healthy; and their extracellular space is increased (31). Pharmacogenetic analysis revealed that this patient had the propensity to generate active metabolites from both codeine (extensive CYP2D6 activity) and morphine (increased UGT2B7 activity). Both the CYP2D6 extensive metabolizer phenotype and the *UGT2B7**2/*2 genotype occur commonly in the Caucasian population (approximately 80% and 30%, respectively), but are less prevalent in other ancestral populations (32,33). Moreover, the tolerance to hydromorphone did not suggest that the sensitivity demonstrated in this case was inherent to the μ opioid receptor itself. This is further corroborated by the genetic findings. Furthermore, the timing of respiratory depression in this case is typical of intrathecal opioids (13 h after intrathecal injection). Thus, it is believed that the overall mechanism of opioid toxicity was an interaction of intrathecal and systemic opioid exposure in a patient sensitive to morphine.

The patient in case 2 carried genotypes corresponding to increased exposure and overall sensitivity to morphine and hydromorphone. Substantially decreased P-glycoprotein efflux transporter activity at the blood-brain barrier, in combination with low catechol-o-methyltransferase activity associated with increased sensitivity of the μ opioid receptor system, may have predisposed the patient to the adverse outcome reported here. However, her μ opioid receptor genotype (118G/G) has been associated in the literature with an increased morphine dose requirement. It is likely a balance of scales: more opioids are crossing the blood-brain barrier; there is high opioid receptor density; but the binding affinity of opioids to the receptor is weaker and/or the receptor activity is lower compared with the wild-type μ receptor genotype.

Evidently, the systemic picture and our pharmacogenetic interpretation is not clear based on our limited understanding of how these different markers interact with one another to protect against or exacerbate adverse outcomes. In addition, little is known about each of the individual markers, their mechanisms of action and their clinical usefulness in the context of complex and diverse patients. With additional cases, we may be better able to evaluate the predictive value of this panel of candidate genes and determine whether it may be useful in preventing adverse events or in identifying patients who may be at risk of complications due to opioids. In conjunction, functional studies may help shed light on how these polymorphisms may modulate treatment and response with opioid medications.

In the current context, the post hoc application of the opioid pharmacogenetic panel was useful in providing a mechanistic insight into the severe respiratory depressive events observed in these patients. However, because it was not clear how this information could prevent future adverse events from occurring, the patient's clinical history remains the most important piece of information by which to guide future analgesic decisionmaking.

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REFERENCES

1. Kalow W. Pharmacogenetics and anesthesia. Anesthesiology 1964;25:377-87.
2. Eckhardt K, Li S, Ammon S, Schanzle G, Mikus G, Eichelbaum M. Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. Pain 1998;76:27-33.
3. Susce MT, Murray-Carmichael E, de Leon J. Response to hydrocodone, codeine and oxycodone in a CYP2D6 poor metabolizer. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:1356-8.
4. Madadi P, Hildebrandt D, Gong IY, et al. Fatal hydrocodone overdose in a child: Pharmacogenetics and drug interactions. Pediatrics 2010;126:e986-9.
5. Stamer UM, Stuber F, Muders T, Musshoff F. Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication. Anesth Analg 2008;107:926-9.
6. Samer CF, Daali Y, Wagner M, et al. Genetic polymorphisms and drug interactions modulating CYP2D6 and CYP3A activities have a major effect on oxycodone analgesic efficacy and safety. Br J Pharmacol 2010;160:919-30.
7. Samer CF, Daali Y, Wagner M, et al. The effects of CYP2D6 and CYP3A activities on the pharmacokinetics of immediate release oxycodone. Br J Pharmacol 2010;160:907-18.
8. Kelly LE, Rieder M, van den Anker J, et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics 2012:129:e1343-7.
9. Sistonen J, Madadi P, Ross CJ, et al. Prediction of codeine toxicity in infants and their mothers using a novel combination of maternal genetic markers. Clin Pharmacol Ther 2012;91:692-9.
10. Campa D, Gioia A, Tomei A, Poli P, Barale R. Association of ABCB1/MDR1 and OPRM1 gene polymorphisms with morphine pain relief. Clin Pharmacol Ther 2008;83:559-66.
11. Klepstad P, Rakvag TT, Kaasa S, et al. The 118 A > G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. Acta Anaesthesiol Scand 2004;48:1232-9.
12. Lotsch J, Skarke C, Grosch S, Darimont J, Schmidt H, Geisslinger G. The polymorphism A118G of the human mu-opioid receptor gene

decreases the pupil constrictory effect of morphine-6-glucuronide but not that of morphine. Pharmacogenetics 2002;12:3-9.
13. Lotsch J, Zimmermann M, Darimont J, et al. Does the A118G polymorphism at the mu-opioid receptor gene protect against morphine-6-glucuronide toxicity? Anesthesiology 2002;97:814-9.
14. Oertel BG, Schmidt R, Schneider A, Geisslinger G, Lotsch J. The mu-opioid receptor gene polymorphism 118A>G depletes alfentanil-induced analgesia and protects against respiratory depression in homozygous carriers. Pharmacogenet Genomics 2006;16:625-36.
15. Romberg RR, Olofsen E, Bijl H, et al. Polymorphism of mu-opioid receptor gene (*OPRM1*:c.118A>G) does not protect against opioid-induced respiratory depression despite reduced analgesic response. Anesthesiology 2005;102:522-30.
16. Zhang Y, Wang D, Johnson AD, Papp AC, Sadee W. Allelic expression imbalance of human mu opioid receptor (*OPRM1*) caused by variant A118G. J Biol Chem 2005;280:32618-24.
17. Landau R, Bollag LA, Kraft JC. Pharmacogenetics and anaesthesia: The value of genetic profiling. Anaesthesia 2012;67:165-79.
18. Candiotti K. Anesthesia and pharmacogenomics: Not ready for prime time. Anesth Analg 2009;109:1377-8.
19. Sawyer MB, Innocenti F, Das S, et al. A pharmacogenetic study of uridine diphosphate-glucuronosyltransferase 2B7 in patients receiving morphine. Clin Pharmacol Ther 2003;73:566-74.
20. Hirota T, Ieiri I, Takane H, et al. Sequence variability and candidate gene analysis in two cancer patients with complex clinical outcomes during morphine therapy. Drug Metab Dispos 2003;31:677-80.
21. Eissing T, Lippert J, Willmann S. Pharmacogenomics of codeine, morphine, and morphine-6-glucuronide: Model-based analysis of the influence of CYP2D6 activity, UGT2B7 activity, renal impairment, and CYP3A4 inhibition. Mol Diagn Ther 2012;16:43-53.
22. Rakvag TT, Klepstad P, Baar C, et al. The Val158Met polymorphism of the human catechol-O-methyltransferase (*COMT*) gene may influence morphine requirements in cancer pain patients. Pain 2005;116:73-8.
23. Reyes-Gibby CC, Shete S, Rakvag T, et al. Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: *OPRM1* and *COMT* gene. Pain 2007;130:25-30.
24. Zubieta JK, Heitzeg MM, Smith YR, et al. *COMT* val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science 2003;299:1240-3.
25. Nackley AG, Shabalina SA, Lambert JE, et al. Low enzymatic activity haplotypes of the human catechol-O-methyltransferase gene: Enrichment for marker SNPs. PLoS One 2009;4:e5237.
26. Andersen S, Skorpen F. Variation in the *COMT* gene: Implications for pain perception and pain treatment. Pharmacogenomics 2009;10:669-84.
27. Nawa A, Fujita-Hamabe W, Kishioka S, Tokuyama S. Decreased expression of intestinal P-glycoprotein increases the analgesic effects of oral morphine in a streptozotocin-induced diabetic mouse model. Drug Metab Pharmacokinet 2011;26:584-91.
28. Meineke I, Freudenthaler S, Hofmann U, et al. Pharmacokinetic modelling of morphine, morphine-3-glucuronide and morphine-6-glucuronide in plasma and cerebrospinal fluid of neurosurgical patients after short-term infusion of morphine. Br J Clin Pharmacol 2002;54:592-603.
29. Tan EC, Lim EC, Teo YY, Lim Y, Law HY, Sia AT. Ethnicity and *OPRM* variant independently predict pain perception and patient-controlled analgesia usage for post-operative pain. Mol Pain 2009;5:32.
30. Cheesman K, Brady JE, Flood P, Li G. Epidemiology of anesthesia-related complications in labor and delivery, New York State, 2002-2005. Anesth Analg 2009;109:1174-81.
31. Carvalho B. Respiratory depression after neuraxial opioids in the obstetric setting. Anesth Analg 2008;107:956-61.
32. Sistonen J, Sajantila A, Lao O, Corander J, Barbujani G, Fuselli S. *CYP2D6* worldwide genetic variation shows high frequency of altered activity variants and no continental structure. Pharmacogenet Genomics 2007;17:93-101.
33. Zimmermann A, Blaszkewicz M, Roth G, et al. UDP-glucuronosyltransferase 2B7 C802T (His268Tyr) polymorphism in bladder cancer cases. J Toxicol Environ Health A 2008;71:911-4.