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Case Report

Application of pharmacogenomics for trauma and critical care patients: A case report

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ABSTRACT

Background: Pharmacogenomics is increasingly becoming a valuable tool for improving health outcomes, reducing health care costs and avoiding adverse drug reactions. While application of pharmacogenomics is quite common in oncology and cardiology, routine use of this technology is rare in certain other fields including Trauma and Critical Care Surgery. We are testing feasibility of applying pharmacogenomic testing to improve therapeutic outcomes of trauma and acute care patients at MercyOne Medical Center in Des Moines, IA.

Methods: Trauma patients admitted to the hospital with projected stay of > 5 days, or with admission extended due to failed multiple trials of medication volunteered to participate in this IRB-approved study. Effectiveness of medical therapy was evaluated using standard pain scores recorded prior to admission of any pain medication to conscious and competent patients. Pharmacogenomic results were obtained from commercial providers within 3–5 days and used to alter medical therapy as needed.

Results: An 18-year-old African American male, admitted for gunshot wounds to the neck, exhibited an ASIA A spinal cord injury, with no sensation or movement of his extremities, persistent nausea with emesis and a history of depression. He also developed gastritis with hematemesis. In addition to all standard trauma procedures, he received standard doses of tramadol, oxycodone or hydrocodone, ondansetron, citalopram, and intravenous protonix daily. He reported no pain relief. The patient's pharmacogenomic analysis revealed his ultrarapid and rapid genotype for CYP2D6 and CYP2C19 respectively, allowing us to choose dilaudid resulting in immediate improvement of his pain scores. Additionally, using metoclopramide, duloxetine and famotidine led to immediate improvement or complete resolution of symptoms.

Conclusion: Pharmacogenomics testing is a useful tool for selecting appropriate pain management of trauma patients with expected hospital stay ≥5 days. Additionally, standard pharmacogenomic panels allow tailoring medical therapy to common conditions associated with traumatic injury.

Introduction

Pharmacogenomics (PGx) allows health care professionals to utilize genomic information of individual patients to make important decisions about drug choice and/or drug dose suitable to those patients [1]. This tool has been utilized quite effectively for

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long-term, inpatient [2] as well as outpatient care [3,4]. However, there is paucity of examples in applying PGx for patients in emergency and trauma cases [5,6]. We are investigating feasibility of employing PGx to improve health outcomes of trauma patients at MercyOne Medical Center, a tertiary health care facility in a metropolitan area. Toward this goal, we have undertaken an IRB-approved study to perform PGx testing on patients with spinal cord injuries with expected length of stay based on pauly trauma or on patients screened as having difficulty with pain management. Here we report successful application of PGx tests of a trauma patient for improved health outcomes.

Case report

We present a case of an 18-year-old African American male (hereafter referred as Patient 003) who was placed in a wheelchair and left at the entrance of the emergency department by an unknown person. Patient 003 appeared to be awake but was unresponsive. His body appeared flaccid as he sat in the wheelchair but without any obvious injury. He was taken to the trauma bay and the trauma team was activated.

On primary survey, his airway was patent, respiratory rate was 31 breaths per minute with an oxygen saturation of 99% on 15 l of oxygen via non-rebreather mask. Respirations were shallow and decreased breath sounds were auscultated bilaterally. Heart rate was 74 per minute with a blood pressure of 174/90 mm Hg. Neurologically, Patient 003 suffered from flaccid paralysis below the level of the neck. Sensation appeared intact approximately from the C4 dermatome and above. On examination, an apparent gunshot wound was discovered on the patient's lateral neck, with both entrance and exit wounds. Clinically, Patient 003 appeared anxious and was becoming increasingly diaphoretic. The patient's breathing was quickly declining with barely visible chest rises. We elected to intubate Patient 003 at that time due to impending respiratory failure.

Secondary survey was grossly unremarkable. Chest X-ray and FAST examination were normal. Patient 003 was taken to CT where a noncontrast CT of the head was negative. The CTA neck revealed C4–5 level injury with bullet fragments traversing the cervical canal, involving the right C4 & 5 pedicles, C4–5 facet joint and comminuted fractures of the left C4 lamina. No carotid injury was detected; however, a Grade 1 right vertebral artery injury was obvious (Fig. 1). Patient 003 was classified as an ASIA A spinal cord injury, with no sensation or motor function below the level of C4. Pain was localized to his neck, at and above the level of injury. Urine Drug Screen performed as a routine part of trauma care at this institution was positive for tetrahydrocannabinol but negative for other drugs including alcohol and cocaine. Neurosurgery was consulted and no surgical intervention was deemed appropriate for the patient's clinical scenario. Following the IRB guidelines, patient's written consent was obtained and he was swabbed using the sample collection kit provided by a commercial company and was sent to them for pharmacogenomic analysis. The PGx service providers directly bill the patient's private insurance company. Charges are waved by the service provides in the event the insurance company does not cover the costs.

Patient 003 was cared for in the Neurotrauma ICU for 5 weeks. He underwent tracheostomy and gastrostomy on hospital day 2. He was able to be quickly weaned down on his sedation to begin ventilator weaning trials and to participate in his routine assessments and therapies. His course was complicated by several medication-related issues involving management of pain, nausea, depression and gastritis. Patient 003 was started on routine medication at standard doses including oxycodone 5–10 mg q4h for pain, ondansetron (Zofran®) 4 mg q4 for nausea and citalopram (Celexa®) 10 mg daily for depression without any relief. The patient's intractable nausea required multiple changes in dosing and frequency as well as several drug changes. His nausea caused multiple episodes of emesis resulted in aspiration pneumonia and an extended ventilator dependence. The patient's pain management was very difficult. Patient 003 constantly complained that the pain medication was only helpful for negligible periods of time. His pain was rated 7–10, despite oxycodone 10 mg every 3–4 h. Hydrocodone made him feel anxious and did not reduce his pain. Tramadol worsened his nausea and GI upset. Patient 003 had a previous diagnosis of depression which was exacerbated by his life altering injury. Patient 003 was previously prescribed citalopram (Celexa®) which, according to Patient 003, he took as prescribed for several months without any relief of his depressive symptoms. He had also trialed escitalopram, paroxetine and sertraline. He subsequently stopped the medications without approval of his physician and began self-medicating with marijuana. Upon admission to the ICU Patient 003 was started on citalopram (Celexa®) again and complained that the medication was not effective. He expressed suicidal ideation with a plan during his admission while on medication.

Pharmacogenomic data was received on day 7 of the patient's ICU admission (Table 1). The data revealed Patient 003 was a rapid metabolizer for CYP2C19 and CYP2B6, ultra-rapid metabolizer of CYP2D6 and a CYP3A5 intermediate metabolizer [7]. This explained why Patient 003 was having issues with oxycodone, hydrocodone (Vicodin®), tramadol (Ultram®), ondansetron (Zofran®), pantoprazole (Protonix®) and citalopram (Celexa®.) The data revealed that Patient 003 had variant forms of genes for the enzymes responsible for the metabolism of these medications. As a result, phenotypically, Patient 003 is a poor metabolizer for CYP2B6, rapid metabolizer for CYP2C19 and an ultra-rapid metabolizer for CYP2D6. Guided by these pharmacogenomic results, we selected an alternative for each medication including switching metoclopramide (Reglan®) for ondansetron (Zofran®), hydromorphone (Dilaudid®) for oxycodone and fluoxetine (Prozac®) and duloxetine (Cymbalta®) for citalopram (Celexa®). Patient 003 experienced acceptable pain relief following the medication changes, maintaining a pain scale of 3–7 with 2–4 mg of hydromorphone via gastrostomy tube 2–3 times per day. Within 10 days of altering his antidepressants, he had improvements in his depressive symptoms. His GI symptoms resolved within 48 h.

Discussion

Application of PGx testing is well established and used in other fields of medicine [1–4]. There is a paucity of information on the

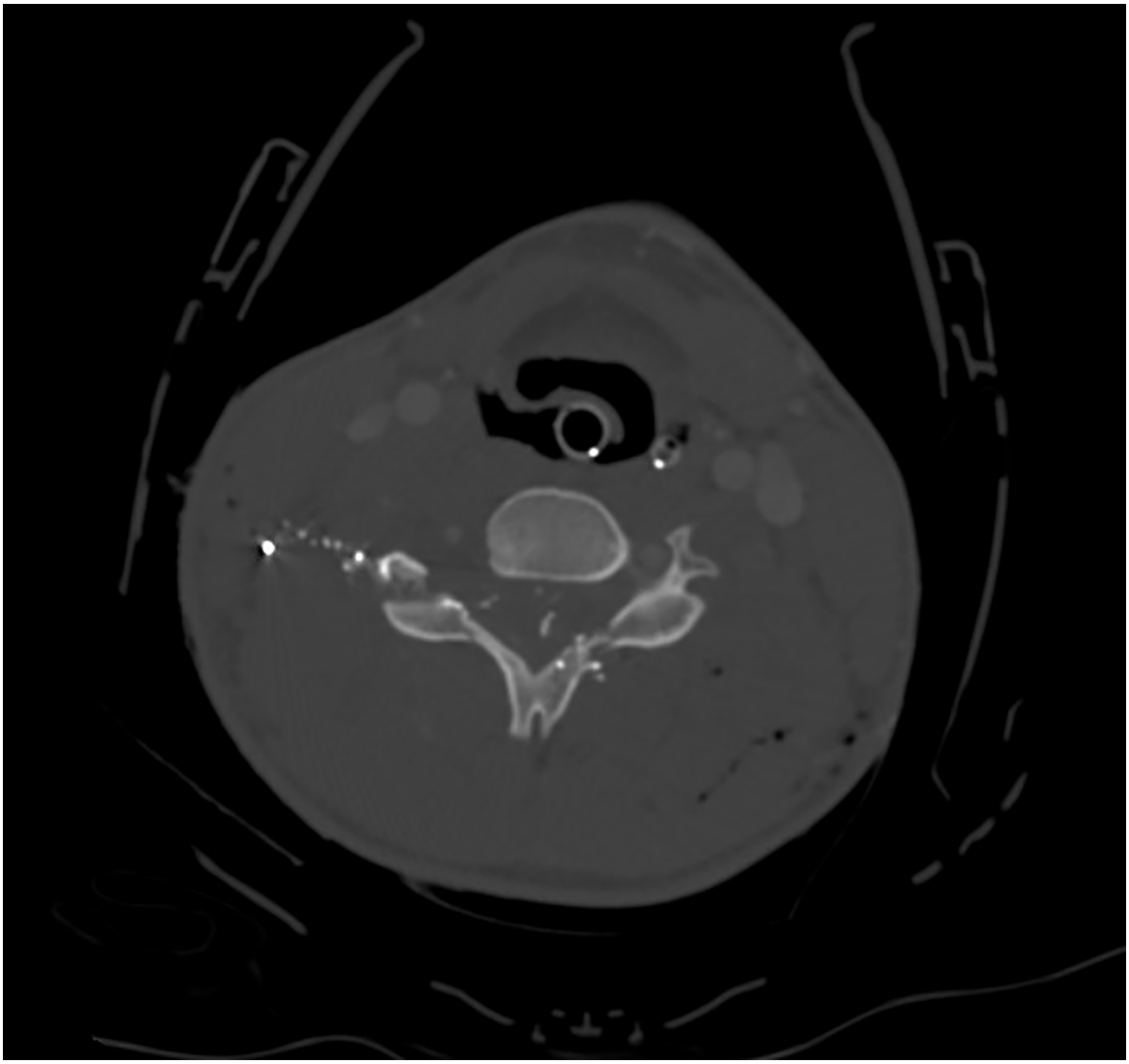

Fig. 1. Cervical spinal cord computed tomography image of Patient 003.

Table 1
Pharmacogenomic panel test results of Patient 003.[a]

Gene	Genotype	Phenotype
CYP1A2	*1A/*1A	Efficient metabolizer
CYP2B6	***6/*6**	**Poor metabolizer**
CYP2C19	***1/*17**	**Rapid metabolizer**
CYP2C9	*1/*1	Normal metabolizer
CYP2D6	***1/*2 X N**	**Ultrarapid metabolizer**
CYP3A4	*1/*1B	Normal metabolizer
CYP3A5	***3/*3**	**Poor metabolizer**
FACTOT II	20210 G > A, GG	No increased risk of thrombosis
FACTOR V	1691 G > A, GG	
MTHFR	1298 A > C, AA 677 C > T, CT	No increased risk of hyper-homocysteinomia
VKORC1	1639 G > A GG	Low warfarin sensitivity

Results of select genes critical for this case are shown in boldface.
[a] Pharmacogenomic tests were carried out by a commercial provider.

Table 2
Pharmacogenomics guided therapeutic actions for Patient 003.

Gene	Patient genotype	Patient phenotype	Diagnosis	Original prescription	Expected response	PGx guided action
CYP2C19	*1/*17	Rapid metabolizer	Depression	Cetalopram [Celexa®]	No or low response due to increased drug clearance or metabolism	Changed to fluoxetine [Prozac®] and duloxetine [Cymbalta®]
			G1 prophylaxis	Pantoprazole [Protonix®]	Insufficient response	Increase dose 150%, monitor response or change to H2 blocker
CYP2C9	*1/*1	Normal metabolizer	Depression	Fluoxetine [Prozac®]	Normal	No change
CYP2D6	*1/*2XN	Ultrarapid metabolizer	Pain	Tramadol [Ultram®] Hydrocodone [Hysingla®] Oxycodone [Roxicodone®]	Increased toxicity, respiratory depression; decreased length of response	Changed to hydromorphone (Dilaudid®)
			Nausea	Ondansetron [Zofran®]	No response	Changed to metoclopramide (Reglan®)
CYP3A4	*1/*1B	Normal metabolizer	Anxiety	Ranitidine [Zantac®]	Normal	No change
			Depression	Fluoxetine [Prozac®]	Normal	No change

application of this data for management of trauma patients [5,6,8]. This case report, one of the first in trauma care, is part of our broader study to incorporate PGx data to select the best pharmacotherapy for trauma patients, a group, we submit, is particularly well suited to benefit from use of this tool. For example, post-traumatic depression occurs frequently and has traditionally been treated with a trial-and-error approach to medication selection. Adams et al. [8] recently reviewed of role of PGx for predicting therapies in severe traumatic brain injuries, including sedation, analgesia, seizure prevention, intracranial pressure-directed therapy and neurobehavioral/psychiatric symptoms. Genotype variant identification aids in medication selection and gives prognostication of patients at increased risk of complications, such as decreased clearance of ketamine increasing the risk of hepatic and/or renal dysfunction [8]. It must be noted that ketamine was not part of our institution's acute pain regimen strategy in October 2017, when this patient was under our care. We used ketamine only during induction/intubation of this patient.

Lack of education and training, additional costs incurred in PGx testing and extra time needed to get actionable test results are often cited as three major factors limiting utilization of PGx for treating trauma (and other) patients [9,10]. However, with availability of innovative formal and continuing medical education programs, rapidly declining costs and significant reduction in the turnaround time for test results, we foresee a robust rise in application of PGx testing in all therapeutic areas including trauma and critical care.

Conclusion

Pharmacogenomics testing is a useful tool for selecting appropriate pain management of trauma patients with expected hospital stays > 5 days (Table 2). Standard panels also assist with tailoring medical therapy to common conditions associated with traumatic injury, including ulcer prophylaxis, VTE prevention and treatment, gastrointestinal and psychiatric illnesses. There is a need for continued research in clinical applications of PGx for enhanced precision in pharmacotherapy leading to improved patient outcomes.

Declaration of competing interest

None.

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