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A Rare Case of CYP2D6 and CYP2C19 Poor Metabolizer: A Pain Management Dilemma.

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Introduction

- Cytochrome P450 enzymes are essential for the metabolism of many medications
- Genetic variability in these enzymes may influence a patient's response to commonly prescribed drug classes. **CYP2D6 and CYP2C19** enzymes are part of the CYP450 enzyme
- CYP2D6: responsible for the metabolism of most of the commonly prescribed opiate medications
- CYP2C19: affects the metabolism of diazepam and carisoprodol, as well as clopidogrel, proton pump inhibitors, and several antidepressants
- Poor metabolizers of these enzymes are extremely rare and when deficiency present can cause severe and fatal side effects and overdose of drugs
- We herein report an unusual case of a poor metabolizer of medications metabolized by CYP2D6 and CYP2C19 enzymes due to genetic deficiency diagnosed on genetic testing

Clinical Vignette

- **56 year old female patient – PMHx of Ehlers-Danlos Syndrome (EDS) and known deficiency of CYP2D6 and CYP2C19**
- Patient presented for an elective Occipital to T3 fusion
- The patient had a known deficiency of CYP2D6 and CYP2C19 diagnosed through genetic testing, the presenting deficiencies caused several instances of anaphylaxis, life threatening allergic reactions, serotonin syndrome and side effects including delirium to medications including morphine, hydromorphone, tramadol, codeine, diazepam, metoclopramide, ondansetron, amitriptyline, just to name a few
- On pre-operative visit patient did mention her concerns regarding post-operative pain management because of extensive allergy list to several pain medications. Since patient also had history of difficult airway and failed intubation in past due to cervical surgeries, focus was done on airway and the presence of genetic deficiency somehow got ignored.
- A pre-operative planning for post-operative pain control was not formulated and pain team was not involved prior to surgery
- She underwent spinal surgery leading to a pain management dilemma starting in the recovery room

Images

Table 1: Opioid Dosage and CYP Enzyme Deficiencies

Enzyme Variation	Opioid Dosage	Laboratory Terminology
Normal	Normal	Extensive metabolizer
Overactive	High or ultra-high dosage required because the enzyme continuously deactivates the opioid, which lowers serum levels	Rapid or ultrarapid metabolizer
Underactive	CYP enzymes are slow or "lazy" needing extra opioid to "force" metabolism	Intermediate metabolizer (about 50% less function)
Minimally active or inactive	Won't efficiently process an opioid, so opioid dosages may have to increase. An inactive enzyme may cause serum levels to rise and produce toxicity	Poor metabolizer (about 90% to 100% less function)

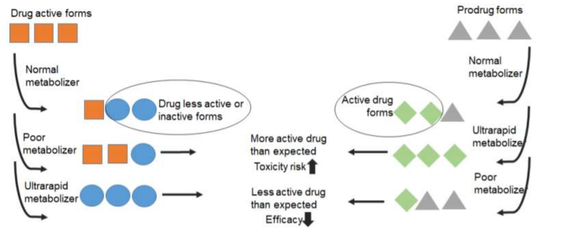

Figure 1. Drug metabolizing enzymes regulate the PK of drug molecules by inactivating active drugs or by activating prodrugs. Active drug forms (left side of Figure) are generally dosed at a level that anticipates they become inactivated at the rate of an extensive metabolizer's enzymes. This normal metabolism leaves fewer biologically active molecules and more less-active or inactive metabolites before the next dosing interval. Poor metabolizers inactivate at a slower rate leaving more active drug than anticipated, while ultrarapid metabolizers inactive at a faster rate leaving less active drug than anticipated in a general dosing scheme. Prodrugs (right side of Figure) are dosed in anticipation that some molecules will be metabolized into the active form(s) at a normal rate. Ultrarapid metabolizers produce more active drug than anticipated, while poor metabolizers produce less active drug than anticipated. In both scenarios, when more active drug than expected is present, the risk of toxicity increases (active drug and poor metabolizer or prodrug and ultrarapid metabolizer). When less active drug than expected is present, the risk of therapeutic efficacy decreases (active drug and ultrarapid metabolizer or prodrug and poor metabolizer).

Table 2: CYP2D6 is responsible for metabolism of most Opioids

Opioid	Phase 1 metabolism	Phase 2 metabolism
Morphine[12]	None	Glucuronidation via UGT2B7
Codeine[13]	CYP2D6 ←	None
Hydrocodone[14]	CYP2D6 ←	None
Oxycodone[11]	CYP3A4 CYP2D6 ←	None
Methadone[15]	CYP3A4 CYP2B6 CYP2C8 CYP2C19 CYP2D6 ← CYP2C9	None
Tramadol[16]	CYP3A4 CYP2D6 ←	None
Fentanyl[10]	CYP3A4	None
Hydromorphone[17]	None	Glucuronidation via UGT2B7
Oxymorphone[18]	None	Glucuronidation via UGT2B7

Source: Mayo Clin Proc. 2009 Jul; 84(7): 613–624. Note that CYP2D6 is responsible for the metabolism of most opioids.

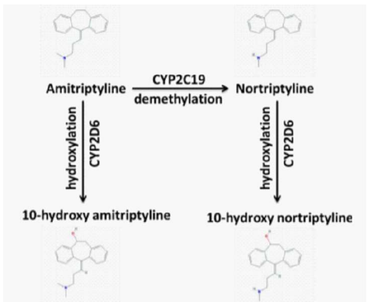

Figure 3: Metabolism of Amitriptyline in liver.

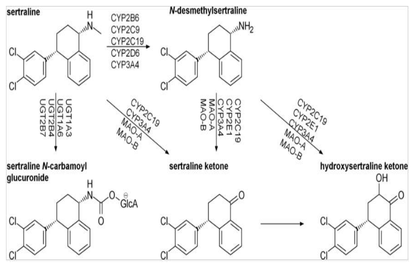

Figure 4: Metabolism of Sertraline in liver.

Post-operative Course

- Patient started complaining of intractable pain and due to lack of options in her case for pain control, Anesthesiology staff was called, who considering her known genetic deficiencies started her on intravenous (IV) ketamine infusion. Due to the complexity of her postoperative pain management and the risk of deleterious side effects, patient was admitted to the neurology intensive care unit (ICU).
- On POD (post op day) 1: Pain team was consulted who continued her on IV ketamine infusion. Her home medications for chronic pain and muscle spasms which included pregabalin and clonazepam were restarted.
- On POD 2: Methocarbamol was started which was then increased from 750 mg TID to 1 gm q6hr on POD 2. IV ketamine infusion was decreased to 0.5mg/kg/hr on POD 2.
- On POD 3: Ketamine infusion was decreased to 0.25mg/kg/hr and IV acetaminophen 1G q 8 hrs. scheduled was started.
- On POD 4: Memantine 5 mg bid was started and ketamine infusion was later discontinued. IV acetaminophen was continued.
- On POD 5: Patient reported improvement in pain as ketamine was transitioned to memantine.
- On POD 6: Transferred to General Practice Unit (GPU) and was discharged home on POD 7. The whole process required a six day close management in ICU with pain service onboard to manage her intractable pain causing an unpleasant experience for the patient.

Conclusion

- This case represents an unusual presentation where a patient with Ehlers-Danlos syndrome (EDS) has rare serious drug intolerance due to genetic deficiency of CYP2D6 and CYP2C19 enzymes
- When such patients are undergoing surgery, involving pain service early in the care can lead to a well formulated plan for postoperative pain management
- As seen in this case IV Ketamine is an excellent alternative medication for acute pain control when opioids can not be used due to the above mentioned genetic deficiencies as Ketamine's major pathway is CYP3A4 and CYP2B6 enzymes

References

1. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014;95(4):376–382. doi:10.1038/clpt.2013.254
2. Veldic M, Ahmed AT, Blacker CJ, et al. Cytochrome P450 2C19 Poor Metabolizer Phenotype in Treatment Resistant Depression: Treatment and Diagnostic Implications. Front Pharmacol. 2019;10:83. Published 2019 Feb 19. doi:10.3389/fphar.2019.00083
3. Obach RS, Cox LM, Tremaine LM (February 2005). "Sertraline is metabolized by multiple cytochrome P450 enzymes, monoamine oxidases, and glucuronyl transferases in human: an in vitro study". Drug Metabolism and Disposition. 33 (2): 262–70. doi:10.1124/dmd.104.002428. PMID 15547048.
4. Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37–44. doi:10.1002/cpt.597
5. Young EE, Lariviere WR, Belfer I. Genetic basis of pain variability: recent advances. J Med Genet. 2012;49(1):1-9.