Suspected Opioid Overdose Case Resolved by CYP2D6 Genotyping

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Abstract: A 14-year-old female with suspected narcotic overdose had CYP2D6 genotyping performed to verify opiate intoxication. The role of pharmacogenetics in pain management and individualization of opiate pharmacotherapy is discussed.

Key Words: CYP2D6, pharmacogenetics, opioids

(Ther Drug Monit 2012;34:121–123)

CLINICIAN

A 14-year-old female patient with Angelman syndrome arrived at the emergency department (ED) with possible opiate intoxication after Tylenol #3 (Ortho-McNeil-Janssen Pharmaceuticals, Inc., Titusville, NJ) administration for hip pain.

The previous evening, the patient was given 1 tablet (containing 300 mg of acetaminophen, 15 mg of caffeine, and 30 mg of codeine phosphate) before bed for hip pain manifesting as decreased movement at rest and irritability with passive movement and palpation. Subsequently, the patient became increasingly irritable and restless, which her mother attributed to continued hip pain. Due to the behavioral phenotype of the Angelman syndrome, the patient was unable to clearly express her reason for distress through speech or body movement. The next morning, she was given a second tablet of Tylenol #3 presumably due to a continuation of pain symptoms. Within 30 minutes of the morning dose, the mother reports that the child seemed to have jerking hand movements and trouble breathing, while gasping and opening her mouth widely. She was taken to the local community hospital ED. The admitting physician reported signs of irritability, 10- to 15-second episodes of drowsiness, and potentially gasping—The latter was not confirmed upon admission. Naloxone (0.4 mg) was administered intramuscularly 107 minutes after ED admission, which seemed to relieve symptoms. The patient was discharged home when stable.

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Codeine biotransformation by the genetically polymorphic enzyme, cytochrome P450 2D6 (CYP2D6), has been well characterized in the literature.1,2 Codeine predominately exerts its analgesic effect via the active metabolite morphine, which relies on CYP2D6 for conversion. CYP2D6 enzyme activity can be predicted based on the CYP2D6 alleles present using an activity score, which classifies patients as poor metabolizers (PMs), intermediate metabolizers, extensive metabolizers (EMs), or ultrarapid metabolizers.3 It is estimated that EMs convert 10% of codeine into morphine, whereas in PMs, the conversion is reduced approximately 20-fold (0.5% of morphine).4 Additionally, the CYP2D6 gene is subject to copy number variation, which can also enhance or limit codeine metabolism into active morphine depending on how many copies of the gene are present.5 The clinical consequence is interpatient variability in drug response (pain relief) and adverse drug reactions occurring from opiate intoxication when codeine is used.6–8

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Due to the apparent effectiveness of naloxone in relieving symptoms, I hypothesize that the patient may be a carrier of a functional CYP2D6 gene duplication, leading to increased concentrations of codeine’s active metabolite, morphine, and subsequent opioid overdose.

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CYP2D6 genotyping results in this patient revealed a CYP2D6 *4/*5 genotype. The *4 variant is a common polymorphism in the white population resulting in an mRNA splicing defect and the production of a nonfunctional CYP2D6 enzyme.9 The *5 allele is a deletion of the CYP2D6 gene and a complete loss of enzyme activity.10 Combined, these alleles result in a loss of CYP2D6 enzyme activity and a PM phenotype. The clinical implication of this genotype is a lack of therapeutic response when given codeine for pain relief due to an inability to convert codeine into morphine.

It is most likely that the irritability and apparent respiratory distress displayed by the child were due to a lack of narcotic analgesia rather than a narcotic overdose. This clinical interpretation is supported by CYP2D6 genotyping results and...
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Due to the lack of sufficient evidence to support this effect, the standard dose of naloxone administered and the patient’s CYP2D6 genotype, it is unlikely that such an effect would have contributed to pain relief in this scenario. However, the Angelman syndrome involves the deletion or inactivation of genes in chromosome 15, particularly those that code for ubiquitin ligase and gamma-aminobutyric acid (GABA) receptor complex. GABA system impairment partially explains some of the neurologic signs and symptoms of these patients, such as sleep disturbances and seizures, and paradoxical effects of drugs interacting with the GABA receptor, including vigabatrin and tiagabine, have been reported in Angelman syndrome patients. Naloxone has also been shown to interact with the GABA receptor complex by causing a weak antagonist effect. Therefore, given the existing GABA receptor impairment in this patient and the interaction of naloxone with the GABA system, it is possible that the positive response to naloxone observed by the clinician in this patient was a true effect. The observed response may therefore have been the relief of pain. The 300 mg of acetaminophen in Tylenol #3 may also have contributed to pain relief, but this explanation is unlikely as any analgesic effect would have worn off by the time of naloxone administration. Alternatively, it is also possible that the observed symptomatic relief from naloxone administration was serendipitous and related primarily to the exhaustion of the child and not a therapeutic response from naloxone or acetaminophen.

CONCLUDING REMARKS

CYP2D6 genotyping before codeine administration is not currently performed in routine clinical practice at all centers. The highly polymorphic nature of the enzyme and the possibility of drug metabolism through alternative cytochrome P450 enzymes complicates genotype–phenotype and gene–dose relationships, leading to uncertainty when interpreting results. In this case, the absence of any functional CYP2D6 alleles prevented codeine from providing naloxone and suggests that a different analgesic should be used in this patient for narcotic analgesia in the future. Oxycodone is another analgesic that is metabolized by CYP2D6 to an active metabolite and has been shown to have different analgesic effects between CYP2D6 poor and EMs. Opioids that do not rely on CYP2D6 for phase 1 metabolism, such as morphine or hydromorphone, may therefore be a better alternative but are also associated with their own set of adverse drug reactions. This is also a unique case in that the patient was unable to express the pain she continued to feel after codeine administration, leading to a misdiagnosis of narcotic overdose and a highly uncomfortable experience for the patient. An accurate assessment of pain control is critical in these situations but often complicated by the lack of verbal response capability. In circumstances in which patients are unable to report pain or opioid adverse effects CYP2D6 testing before codeine administration could therefore help to better anticipate therapeutic response.

REFERENCES


