Case report

Response to hydrocodone, codeine and oxycodone in a CYP2D6 poor metabolizer

Margaret T. Susce, Elaina Murray-Carmichael, Jose de Leon *

University of Kentucky, Mental Health Research Center at Eastern State Hospital, Lexington, KY, USA

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Abstract

Codeine is metabolized by the cytochrome P450 2D6 (CYP2D6) to morphine. Codeine is a much weaker agonist at μ opioid receptors than morphine. Therefore, codeine analgesia is highly dependent on CYP2D6 activity. Large prospective studies in the clinical environment do not exist, but it appears reasonable to avoid codeine use in CYP2D6 poor metabolizers (PMs). CYP2D6 metabolizes other opioid analgesics, including tramadol, dihydrocodeine, oxycodone and hydrocodone, although they have been less systematically studied. It is unclear whether these other pro-drugs may be as completely dependent on CYP2D6 for their analgesia as codeine. We describe a patient identified as a CYP2D6 PM with a history of problems with opioid analgesics.

The patient was an 85-year-old female Caucasian who had hip surgery. She had a long-standing intolerance to codeine. In her first admission, she couldn’t tolerate the regimen of oxycodone combined with tramadol prns (as needed). She was genotyped as a CYP2D6 PM and after the information was provided to the treating physician in her second admission, she seemed to have a better response to hydrocodone. Large case-control naturalistic studies followed by randomized trials in patients taking opioid analgesics may be needed to definitively establish that CYP2D6 genotyping has clinical relevance in the use of several opioid analgesics.

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1. Introduction

Codeine is metabolized by the cytochrome P450 2D6 (CYP2D6) to morphine. Codeine is a much weaker agonist at μ opioid receptors than morphine. Therefore, codeine analgesia is highly dependent on CYP2D6 activity. CYP2D6 poor metabolizers (PMs), who lack CYP2D6, account for 7% of Caucasians and 1–3% of other races. Powerful CYP2D6 inhibitors (such as quinidine, paroxetine, fluoxetine and bupropion) can change the phenotype of normal subjects (called extensive metabolizers, EMs) to the PM phenotype as long as they are taking these medications. The review of Lotsch et al. (2004) found six studies focused on codeine analgesic response, including 45 CYP2D6 PMs identified by pheno or/and genotyping (Desmeules et al., 1991; Eckhardt et al., 1998; Persson et al., 1995; Poulsen et al., 1996; 1998; Sindrup et al., 1990). Five of those studies reported lack of analgesic effects for codeine treatment, and one reported decreased analgesia in postoperative pain (Poulsen et al., 1998). Large prospective studies in the clinical environment do not exist, but it appears reasonable to avoid codeine use in CYP2D6 PMs or in those taking these powerful CYP2D6 inhibitors.

CYP2D6 metabolizes other opioid analgesics, including tramadol, dihydrocodeine, oxycodone and hydrocodone, although they have been less systematically studied (Lotsch et al., 2004). It is unclear whether these other pro-drugs may be as completely dependent as codeine on CYP2D6 for their analgesia.

We describe a patient identified as a CYP2D6 PM with a history of problems with opioid analgesics.

2. Methods

The patient was an 85-year-old female Caucasian who had hip surgery. She had a long history of codeine intolerance resulting in nausea and vomiting. Codeine was even noted as an allergy on her chart. After the problems she had during her first
admission, she agreed to sign a consent form for one of our studies and be genotyped for CYP2D6. Her genotype in our laboratory (de Leon et al., 2005) was CYP2D6 PM (*4/*6).

3. Results

3.1. First admission

The patient fractured her right hip, and was transferred to a rehabilitation hospital after stabilization pins were placed. The rehabilitation process was complicated by multiple episodes of nausea and vomiting during oxycodone treatment. She was threatened with discharge due to noncompliance at one point; the family had to intervene. The experience was very negative to the patient, who lost 20 lb during her 17-day admission to the rehabilitation hospital. Her medications included nifedipine sustained release (240 mg/day), doxazosin (4 mg/day), enteric-coated aspirin (81 mg/day), hydrochlorothiazide (25 mg/day) and loratadine (10 mg/day). Loratadine is metabolized by the cytochrome P450 3A (CYP3A) and has a minor CYP2D6 component. None of the other drugs appeared to have substantial CYP2D6 involvement in their metabolism. Combined oxycodone and acetaminophen was used as an analgesic. Initially prescribed at 5 mg of oxycodone and 500 mg of acetaminophen (5/500) every 12 h, it was increased to 10/1000 every 12 h and then 7.5/750 every 6 h. Finally the dose was slowly reduced until she was discharged on 5/500 every 12 h. Analgesia was not achieved; she received several doses of tramadol 100 mg prn every 6 h during the admission. She also received several treatments for nausea/vomiting including prns of aluminum hydroxide and magnesium hydroxide, promethazine, and three days of unsuccessful treatment with ranitidine. Finally, she was discharged on famotidine 80 mg/day to try to control her nausea associated with oxycodone treatment.

3.2. Second admission (genotype was known)

A year later, the patient had a second surgery to replace her right hip secondary to avascular necrosis from the previous hip pinning. After four days, she was sent to the same rehabilitation hospital for 16 days. This time a family member informed about CYP2D6 genotyping explained the possible pharmacological reason for her previous lack of appropriate response to opioid analgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist. He prescribed tegaserod, a serotonin 5-HT4 receptor agonist, ahead of time and hydroanalgesics to the anesthesiologist.

4. Discussion

The patient had a long-standing intolerance to codeine, which was noted as an allergy on her chart. Codeine appears clearly dependent on CYP2D6 for its analgesic effects. However, codeine appears to be able to directly cause some of its side effects. In a randomized double-blind placebo-controlled study using morphine and codeine in 9 CYP2D6 PMs and 9 CYP2D6 EMs, Eckhardt et al. (1998) demonstrated that CYP2D6 PMs can show codeine side effects but lack analgesic response.

The patient couldn’t tolerate the regimen of oxycodone combined with tramadol prns during her first admission, having significant side effects. She obtained no pain relief and was considered a difficult patient for not collaborating with her treatment. We are aware of no studies on oxycodone’s analgesic effects on CYP2D6 PMs, but Otton et al. (1993) described loss of oxycodone analgesic effects after adding CYP2D6 inhibitors. Conversely, adding quinidine did not appear to change oxycodone psychomotor or subjective effects (Heiskanen et al., 1998) but quinidine may not be an ideal drug to block CYP2D6 in the brain. This case report appears to suggest that, like codeine, oxycodone may need CYP2D6 to provide analgesic effects. The patient was taking some other medications, which arguably could have contributed to the lack of response to oxycodone. However, none of her medications (nifedipine, doxazosin, enteric coated aspirin, hydrochlorothiazide and loratadine) appear likely to inhibit CYP2D6 in a significant way.

Hydrocodone is metabolized by CYP2D6 to hydromorphone (Hutchinson et al., 2004). We are aware of no studies on hydrocodone’s analgesic effects on CYP2D6 PMs, but hydrocodone by itself appears to have some agonist effects on μ opioid receptors (Chen et al., 1991). Some animal studies supported this, suggesting that inhibiting the CYP analog to CYP2D6 does not decrease hydrocodone analgesia (Lelas et al., 1999; Tomkins et al., 1997). Also, human studies propose that CYP2D6 inhibition does not affect hydrocodeone abuse liability (Kaplan et al., 1997).

Per the literature and our case, the very limited data suggest that hydrocodone may be a better option for CYP2D6 PMs than codeine, and perhaps oxycodone. More importantly, a study needs to explore whether patients with unusual responses to hydrocodone, oxycodone, tramadol and dihydrocodeine overrepresent subjects with unusual CYP2D6 genetic variations, such as CYP2D6 PMs or even CYP2D6 ultrarapid metabolizers (UMs) (de Leon et al., 2003; Gasche et al., 2004). Next, a large case-control study in patents taking these analgesics may be needed, controlling for confounders (de Leon et al., 2005) associated with lack of response. It may be even better to conduct a double-blind randomized study using CYP2D6 genotyping; unfortunately there is limited experience in the practical aspects of combining well-controlled designs in the real world with CYP2D6 genotyping.

5. Conclusions

This CYP2D6 PM had problems with several opioid analgesics and knowing her CYP2D6 genotype helped to treat her. The patient had a long-standing intolerance to codeine. She
couldn’t tolerate the regimen of oxycodone combined with tramadol prns during her first admission, having significant side effects. She seemed to have a better response to hydrocodone in her second admission. Large case-control naturalistic studies followed by randomized trials in patents taking opioid analgesics may be needed to definitively establish that CYP2D6 genotyping has clinical relevance in the use of several opioid analgesics.

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