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Hydrocodone in postoperative personalized pain management: Pro-drug or drug?

M. Elaine Stauble [a], Andrew W. Moore [a], Loralie J. Langman [b], Mark V. Boswell [c], Richard Baumgartner [d], Suzanne McGee [a], Jonathan Metry [a], Saeed A. Jortani [e,*]

[a] Dept. of Obstetrics and Gynecology, University of Louisville School of Medicine, Louisville, USA
[b] Dept. of Lab Medicine and Pathology, Mayo Clinic, Rochester, USA
[c] Dept. of Anesthesiology and Perioperative Medicine, University of Louisville School of Medicine, Louisville, USA
[d] Dept. of Epidemiology and Population Health, University of Louisville, Louisville, USA
[e] Dept. of Pathology and Laboratory Medicine, University of Louisville School of Medicine, Louisville, USA

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ABSTRACT

Background: Genetic variations in enzymes that produce active metabolites from pro-drugs are well known. Such variability could account for some of the clinically observed differences in analgesia and side effects seen in postoperative patients. Using genotyping and quantitation of serum concentrations of hydrocodone and its metabolites, we sought to demonstrate the clinical effects of the metabolites of hydrocodone on pain relief. The objective of the current study was to determine whether CYP2D6 genotype and serum hydromorphone levels account for some of the variability in pain relief seen with hydrocodone in a cohort of women post-Cesarean section.

Methods: In 156 post-Cesarean section patients who received hydrocodone, we assessed serum opioid concentrations and CYP2D6 genotypes. Blood samples were collected at that time for genotyping and determination of concentrations of hydrocodone and metabolites by LC–MS/MS. Multivariate analysis was used to determine the relationship between CYP2D6 genotypes, pain relief, side effects, and serum concentrations of hydrocodone and hydromorphone.

Results: The CYP2D6 genotyping results indicated that 60% of subjects were extensive, 30% intermediate, 3% poor, and 7% ultra-rapid metabolizers. In the poor metabolizers, the mean plasma hydromorphone concentration was 8-fold lower when compared to that of ultra-rapid metabolizers. Hydromorphone, and not hydrocodone concentrations correlated with pain relief.

Conclusions: This study shows that hydromorphone is generated at substantially different rates, dependent on CYP2D6 genotype. Pain relief correlated with plasma concentrations of hydromorphone, and not with hydrocodone. This suggests that pain relief will vary with CYP2D6 genotype. Inability to metabolize hydrocodone to hydromorphone as seen in the poor metabolizers should alert the clinician to consider alternative medications for managing pain postoperatively.

1. Introduction

Hydrocodone is the most widely prescribed analgesic medication in the United States [1]. It is often prescribed to manage postoperative pain as well as for long-term management of chronic pain. The analgesic effectiveness of hydrocodone appears to be highly variable, and in some patients is devoid of therapeutic effect [2]. Some opioids such as codeine are known to be pro-drugs, and require metabolic conversion to an active metabolite (e.g. morphine) for pharmacodynamic benefit [3]. Genetic polymorphism of the enzyme CYP2D6 has been reported to lead to variable codeine metabolism [4]. Patients with deficient CYP2D6 activity produce very low concentrations of morphine leading to suboptimal pain relief with codeine. In contrast, patients with duplication of active CYP2D6 genes are ultra-rapid metabolizers of codeine and produce relatively high concentrations of morphine, which can lead to morphine poisoning [3]. Similarly, it has been postulated that hydrocodone must be converted to hydromorphone for analgesic effect through CYP2D6 activity (Fig. 1) [5]. The active metabolite, hydromorphone, has 7–10 times more analgesic potency than morphine [6]. The affinity of hydromorphone for the opioid Mu-receptor has been reported to be over 100 times greater than that of hydrocodone, with the Ki values being 0.36 for hydromorphone versus 41.58 for hydrocodone [7]. Therefore, hydrocodone would not be expected to have potent analgesic effects at usual therapeutic doses.

In this study, we sought to demonstrate the importance of hydrocodone to hydromorphone conversion by assessing CYP2D6

* Corresponding author at: 511 South Floyd Street, Louisville, KY 40245, USA. Tel.: +1 502 852 8835; fax: +1 502 852 1177.
E-mail address: sjortani@louisville.edu (S.A. Jortani).

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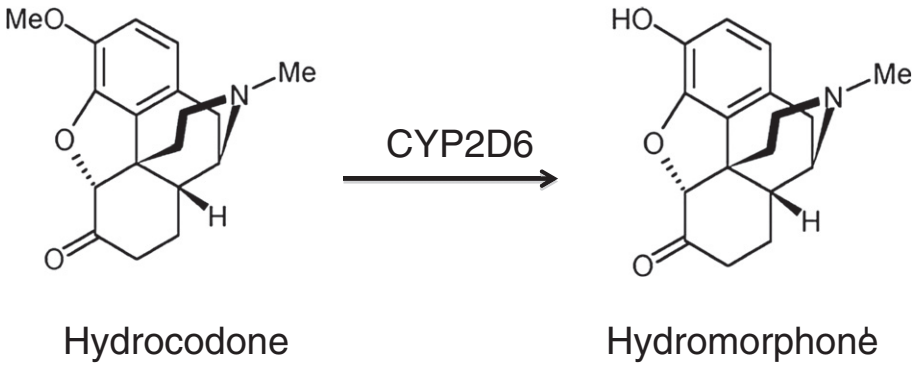

Fig. 1. Conversion of hydrocodone to its active metabolite hydromorphone catalyzed by the CYP2D6 enzyme.

activity in post-Cesarean section patients. In addition to CYP2D6 genotyping, we measured serum hydrocodone and metabolite concentrations by LC–MS/MS, pain scores and side effects. This study is the first to demonstrate the role of CYP2D6 genotype and conversion of hydrocodone to hydromorphone in the analgesic effect of hydrocodone in postoperative pain relief.

2. Materials and methods

2.1. Enrollment of subjects

We targeted a homogeneous cohort of patients for this study by choosing subjects who were pregnant and about to undergo Cesarean section. This group was chosen since they generally have similar endocrine status and the same type of surgery planned (i.e. Cesarean delivery). Following approval of the study by the University of Louisville's Institutional Review Board (IRB), we enrolled women within an age range of 18–45 years old who were to receive the same type of anesthesia and analgesia post operation, except for 5 patients who required general anesthesia. Inclusion criteria were: women about to undergo Cesarean delivery, body mass index (BMI) under 40, and patients who could speak English or Spanish. Exclusion criteria were those women with known drug abuse, allergy to hydrocodone, or major medical diseases. Among study subjects, we collected a blood sample on the 3rd day after delivery. Level of pain control was documented at that point in time using VAS scores [8]. The oral survey taken then recorded 13 possible side effects of the narcotic: confusion, constipation, dizziness, dry mouth, loss of appetite, nausea, pruritus, respiratory depression, sleep disturbance, somnolence, sweating, vomiting, and weakness (mild, moderate, or severe). All patients took ibuprofen 800 mg every 8 h after delivery, in addition to their hydrocodone as needed. Patient characteristics, including age, race, weight, height, and total analgesic usage, were likewise recorded.

2.2. Blood sample processing and testing

One 5-mL tube of blood was obtained from each subject on the morning of their release from the University of Louisville Hospital. Plasma was collected in a purple top tube containing the anticoagulant EDTA. The blood sample was processed to form a buffy coat sample (white blood cells/leukocytes) by centrifugation for 15 min at 2000 $\times g$ at room temperature, after which the leukocytes (middle layer) were aspirated from the tube and transferred into a 1.5 mL microcentrifuge tube. All samples were stored at −80 °C until analysis. Qiagen's (Valencia, CA) EZ-1 BioRobot and Blood kit were used to isolate DNA. At Pharmacogenetics Diagnostics Laboratory (Louisville, KY), CYP2D6 genotyping was performed using the xTAG Mutation Detection system for P450-2D6 on a Luminex 100 xMAP IS System (Luminex Molecular Diagnostics). This test detected 17 nucleotide variants and two gene rearrangements in a multiplex polymerase chain reaction and allele-specific primer extension. The plasma samples were sent to the Mayo Clinic (Rochester, MN) for LC–MS/MS analysis. The new method for the LC–MS/MS analysis of serum opioids which include hydrocodone and metabolites has been described elsewhere [9].

2.3. Statistical analyses

Means and SDs were calculated for all metabolites and relevant subject characteristics and covariates by 2D6 phenotype and tested for statistically significant differences among groups using analysis of variance. Because the pain index is technically an ordinal variable, the median score and range were also calculated and group differences tested using the K-sample equality of medians test. The sum of symptoms was calculated. The median duration of hydrocodone use after Cesarean section was 49 h, with a range of 4 to 79.5 h. Summation of the number of doses and of the total doses in milligrams of hydrocodone was recorded. BMI was calculated as weight (kg) / height $(m)^2$.

The association of the metabolites with pain score was quantified using multivariable ordered logistic regression analysis, adjusting for age, body mass index, total dose, treatment duration and other relevant covariates. However, because the pain score was approximately, normally distributed, ordinary multivariable least squares regression was also applied. Statistical computations were performed using the StataR statistical package (StataCorp LP, College Station, TX).

3. Results

The frequency of CYP2D6 polymorphisms in our study population is illustrated in Fig. 2. Extensive metabolizers comprised 60% of the group, with intermediate metabolizers comprising 30%, poor metabolizers 3%, and ultra-rapid metabolizers 7% of the study group.

Table 1 provides descriptive statistics (mean ± SD) for all serum metabolites and relevant subject characteristics and covariates by CYP2D6 phenotype. There were no statistically significant differences among phenotypes for any variables, with the exceptions of hydromorphone, norhydrocodone and dihydrocodeine (P for trend < 0.05). In contrast, norhydrocodone concentrations increased in PM versus UM or EM patients, suggesting that hydrocodone was shunted to the CYP3A4 route of metabolism in PM subjects, rather than to the CYP2D6 pathway, which is required for analgesia. Only hydromorphone is thought to be a clinically active metabolite of hydrocodone.

Table 2 shows the results for the regression of the pain index on serum hydromorphone, hydrocodone, norhydrocodone and dihydrocodeine concentrations, adjusting for age, BMI, total dose, and duration of treatment with hydrocodone. Only serum hydromorphone achieved statistical significance. In contrast, there was no association with serum hydrocodone, norhydrocodone or dihydrocodeine. Results for ordered logistic regression and ordinary least squares regression analysis were closely similar, with no differences in p-values for