

The conversion of hydrocodone to hydromorphone and norhydrocodone comparison in subjects with chronic pain

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Purpose

Hydrocodone in combination with acetaminophen is commonly used to control mild-to-moderate pain. Hydrocodone is metabolized by cytochrome P450 (CYP) 2D6 to form hydromorphone (active) and by CYP3A4 to form norhydrocodone (inactive). Understanding how patients on comedication can have an effect on the conversion from hydrocodone to norhydrocodone and hydromorphone may help establish a predictive model for physicians to better assess pain control. The primary goal of this study is to assess the prevalence of norhydrocodone, hydromorphone, and/or hydrocodone concentration in the urine in patients with chronic pain. The secondary goal of this study was to determine the concentrations of the metabolites in the presence of CYP2D6 inhibitors or CYP3A4 inhibitor and the correlation with age and gender.

Method

This retrospective study examined the data from 328,656 urine specimens from patients with chronic pain tested at Millennium Laboratories (San Diego, CA) between January 2011 and May 2011. The inclusion criteria were subjects with creatinine concentration above 20 ng/mL and had reported taking hydrocodone. From this population, the exclusion criteria were subjects who were taking hydrocodone but had concentrations (above the lower limit of quantitation) of morphine, codeine, 6-monacetylmorphine (6-MAM, heroine metabolite), oxycodone, or taking hydromorphone. In addition, subjects that had undetectable (below the lower limit of quantitation) of hydrocodone were excluded. LC-MS/MS was used to quantitate hydrocodone and hydromorphone concentrations in urine specimens. Statistical and graphical analyses were conducted using Microsoft Excel 2007 and OriginPro v8.1.

Results

A total of 43,951 specimens were positive for either hydromorphone alone, norhydrocodone alone, hydrocodone alone, or any combination of the 3. Eighty percent of the specimens were positive for all of the 3 compounds: hydrocodone, hydromorphone, and norhydrocodone. About 12% were positive for both norhydrocodone and hydrocodone, and 3.5% were positive for norhydrocodone alone. Only 1.7% were positive for both norhydrocodone and hydromorphone, and 1.2% were positive for hydrocodone alone. Less than 1% (0.82%) were positive for hydromorphone alone, and .13% of the specimens were positive for both hydrocodone and hydromorphone.

A mean difference of 0.75 mg/g cr [95% CI: .71, .79; $P < .0001$], representing a 25% decrease, in hydromorphone urine concentrations was seen in subjects with single specimens with CYP2D6 inhibitors compared to subjects without CYP2D6 inhibitors. These subjects also had a 20% increase in urine hydrocodone, with a mean difference of 1.24 mg/g cr [95% CI: 1.31, 1.17; $P < .0001$], and a 27% increase in norhydrocodone, with a mean difference of 1.36 mg/g cr [95%: 1.29, 1.44; $P < .0001$].

Subjects who were taking medications that inhibit CYP3A4 had a decrease in norhydrocodone by 23% with a mean difference of .77 mg/g cr [95% CI: .65, .91; $P < .001$] compared to subjects who were not taking medications that inhibit CYP3A4. The hydrocodone and hydromorphone concentrations in the presence of CYP3A4 inhibitors increased

by 17% with a mean difference of 1.21 mg/g cr [95% CI: 1.00, 1.45, $P < .0001$] and 67% with mean difference of 0.32 mg/g cr [95% CI: .26, .40; $P < .0001$], respectively.

No correlations were seen between age and metabolic ratios (metabolite to parent concentrations). A 17% increased metabolic ratio of norhydrocodone to hydrocodone urine concentrations was observed in women compared to men, with a mean difference of 0.89 mg/g cr [95% CI: .87, .91; $P < .0001$].

Conclusions

Subjects taking hydrocodone, most of the time, were in the middle of the dosing interval; however a few of the subjects, were positive for one of the metabolites or the parent drug. This was observed because; subjects were either at the end or the beginning of the dosing interval. Also, subjects taking CYP2D6 and CYP3A4 inhibitors have different concentrations compared to subjects who were not comedicated. In addition, there was a correlation between gender and metabolism.