

Observations on the urinary metabolic profile of codeine in patients with chronic pain

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Purpose

Codeine is a prodrug that is metabolized by cytochrome (CYP) P450 2D6 to its major metabolite morphine and to a lesser extent to hydrocodone. Morphine and hydrocodone possess analgesic properties and both are further metabolized to hydromorphone. Numerous reports suggest that variable metabolic rates affect codeine pharmacokinetics and pharmacodynamics. This study explored the relationship between codeine and its metabolites morphine, hydrocodone, and hydromorphone. The objective was to examine the observed ranges of urinary drug concentrations. The fractions of each metabolite were assessed to determine if the proportions of each metabolite change with total exposure.

Method

This was a retrospective analysis of de-identified urine specimens collected between March 2008 and May 2011 and analyzed at Millennium Laboratories by LC/MS-MS to determine concentrations of codeine, morphine, hydrocodone and hydromorphone. Specimens were excluded for physician-reported prescriptions for any of the metabolites of codeine, specimens with creatinine concentrations <20 mg/dL, and for nonadherence defined by specimens with concentrations of codeine and its metabolites below the lower limit of quantitation. The final population consisted of single urine specimens from 2170 subjects with physician-reported use of codeine. Statistical analyses and linear regression were conducted using OriginPro 8.5.1 to determine associations between fractions of each metabolite and total exposure. Total exposure was estimated using the molar sum of codeine and its active metabolites, morphine, hydrocodone, and hydromorphone. Urine concentrations of codeine and its metabolites were normalized to correct for differences in hydration status using creatinine values. Final concentrations are presented in milligrams per gram (mg/g) of creatinine.

Results

The geometric mean of codeine urine concentrations was 2.46 mg/g. The geometric mean for morphine, hydrocodone, and hydromorphone urine concentrations were .73 mg/g, .11 mg/g, and .06 mg/g, respectively. The geometric means of parent and metabolite fractions were .62, .27, .03, and .02 for codeine, morphine, hydrocodone, and hydromorphone, respectively. 11.1% of the specimens contained codeine, morphine, hydrocodone, and hydromorphone. Of subjects with reported use of codeine, the percent that were positive for codeine, morphine, hydrocodone, and hydromorphone were 80.1%, 82.7%, 46.9% and 24.4%, respectively. A weak correlation existed between the amount of codeine and the amount of hydrocodone (log-scale, slope = $.23 \pm .02$, $R^2 = .14$, $P < .0001$). A correlation existed between the total moles per gram of creatinine and the fraction of the total for each metabolite. The fraction of codeine increased as the total moles increased (log-scale, slope = $.07 \pm .01$, $R^2 = .03$, $P < .0001$). Morphine fractions decreased as total moles increased (log-scale, slope = $-.26 \pm .01$, $R^2 = .16$, $P < .0001$). A similar relationship was observed for hydrocodone (log-scale, slope = $-.77 \pm .02$, $R^2 = .48$, $P < .0001$), and hydromorphone (log-scale, slope = $-.84 \pm .02$, $R^2 = .57$, $P < .0001$).

Conclusions

Codeine and morphine were observed in greater than 80% of specimens while hydrocodone and hydromorphone were found in 46.9% and 24.4% of the specimens, respectively. A relationship between codeine and hydrocodone concentrations suggests that increasing amounts of codeine leads to increasing amounts of hydrocodone. The fraction of excreted codeine in the urine increased with total moles while the fraction of each metabolite (morphine, hydrocodone, hydromorphone) decreased. This may indicate codeine metabolism saturation. This saturation effect may explain the lack of additional analgesia and/or low abuse potential at high doses of codeine in some patients.