

Factors that may affect carisoprodol metabolism by cytochrome P450 (CYP) 2C19 in pain patients using urinary excretion data

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Purpose

Carisoprodol is a skeletal muscle relaxant that is used to treat mild to moderate pain. Carisoprodol is metabolized to meprobamate, an active metabolite with anxiolytic effects, by the genetically polymorphic CYP2C19 enzyme. Concomitant use of drugs that are substrates or inhibitors of CYP2C19 may alter carisoprodol metabolism, which may have therapeutic and/or toxic implications for treating patients with chronic pain. The primary objective of this study was to assess whether factors such as age, sex, and urinary pH and CYP2C19-mediated drug-drug interactions affect carisoprodol metabolism among the pain patient population as observed in excreted urine specimens.

Method

Urinary data from Millennium Laboratories collected from patients with chronic pain throughout the United States between March 2008 and May 2011 was analyzed. Parent drug and metabolite urine concentrations were measured by LC-MS/MS. The inclusion criteria for this retrospective analysis were: (1) creatinine concentration ≥ 20 mg/dL; (2) prescribed use of the parent drug and not the metabolite; and (3) measured metabolite and parent drug concentrations greater than or equal to the specified lower limit of quantitation (LLOQ). Only subjects' first visits were considered. Subjects concomitantly taking known CYP2C19 substrates or inhibitors as mentioned on the medication list were recorded per the physician's office records. The metabolic ratio (MR) is calculated as a ratio of meprobamate: carisoprodol concentrations and was used to assess metabolic capacity. Concentrations were creatinine-corrected and log-transformed to approximate a Gaussian distribution. Graphical and descriptive statistical analyses were employed using OriginPro v8.5 and Microsoft Excel.

Results

Urine specimens from 14,965 unique subjects were included out of a possible 1,025,138 specimens. Mean age was 50.5 year and included specimens from 8841 females and 6124 males. No relationship was observed between age and log carisoprodol and meprobamate concentrations (R^2 -values were .00197 and .0166, respectively). Significant differences in mean analyte concentrations were observed for sex. The geometric mean meprobamate concentration in females and males were 41.8 [95% CI: 40.9 to 42.7] and 30.2 [95% CI: 29.4 to 31.1] mg analyte per gram creatinine, respectively ($P < .01$); the geometric mean carisoprodol concentration in females and males were .514 [95% CI: .501 to .515] and .470 [95% CI: .454 to .486] mg analyte per gram creatinine, respectively ($P < .01$). Urinary pH and log analyte concentrations demonstrated a weak positive relationship with slope and R^2 -values of .0732 and .0175 for carisoprodol, and slope and R^2 -values of .0460 and .0100 for meprobamate, respectively.

Subjects were further stratified into one of 3 groups based on the comedication's effect on CYP2C19 enzyme: inhibitors, substrates, or noninterfering medications. Subjects taking noninterfering comedications served as the control group. Significant differences (at $P < .05$) in geometric mean meprobamate concentrations among the 3 groups were

observed: 32.8 [95% CI: 30.8 to 34.9] mg for the inhibitor group, 39.0 [95% CI: 37.3 to 40.9] for the substrate group, and 36.5 [95% CI: 35.8 to 37.3] mg for the control group.

Graphical analyses revealed a subpopulation of subjects (n=125) with reduced metabolic capacity; that is, these subjects had low meprobamate and high carisoprodol concentrations detected in the urine. Comedications did not seem to influence this subpopulation.

Conclusions

The study suggests that gender and comedication significantly influence carisoprodol metabolite formation. Comedication with CYP2C19 inhibitors did not significantly affect carisoprodol concentrations, but demonstrated decreased mean meprobamate concentrations compared to the control. This may be explained by the short half-life of the parent drug (approximately 2 hours) compared to the metabolite (approximately 10 hours). Graphical analyses of the log metabolic ratio (MR) showed a distinct subpopulation of subjects with high carisoprodol and low meprobamate concentrations not influenced by comedication. This result may suggest that the genetic component may have a larger role with regard to carisoprodol metabolism.