

## Variability of meperidine metabolism and excretion in patients with chronic pain

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### Purpose

Meperidine (Demerol<sup>®</sup>) is a mu opiate receptor agonist used for moderate-to-severe pain. As a Schedule II controlled substance it has high abuse potential. Overdose can result in respiratory depression and hypotension, while accumulation of its toxic metabolite, normeperidine, can cause delirium and seizures. Meperidine is demethylated primarily by cytochrome P450 2B6, 3A4, and 2C19 to normeperidine. Little data exist examining the intersubject and intrasubject variability of the urinary normeperidine to meperidine metabolic ratio (MR). A better understanding of this variability in meperidine metabolism can guide clinicians in monitoring medication therapy to improve safety and efficacy.

### Method

This retrospective study analyzed urine specimens collected from populations of those with chronic pain in accordance with routine patient care procedures. These de-identified specimens were analyzed at Millennium Laboratories using LC-MS/MS to quantitate meperidine and normeperidine concentrations. Specimens with a creatinine concentration less than 20 mg/dL or a meperidine or normeperidine concentration below the lower limit of quantitation (50 ng/mL) were excluded from the study. Intrasubject variability of the MR of normeperidine to meperidine in subjects with two or more specimens collected at separate office visits was determined. Intersubject variability was calculated from specimens collected from a subject's first visit only. Statistical analyses were carried out with Microsoft Excel 2010 and OriginPro 8.5.1.

### Results

Intrasubject variability was calculated from 98 subjects, resulting in a geometric mean MR=6.12 and a mean percent coefficient of variation (%CV) = 68% (range, 2%-159%). Intersubject variability was calculated from a single specimen obtained from 799 subjects, resulting in a geometric mean MR=6.20 and a %CV=212%. No significant relationship was found between subject age and MR. A weak, positive relationship was found between specimen urine pH and MR ( $P < .001$ ,  $r^2 = 0.08$ ,  $y = .20x - .44$ ). A significant difference was found between distribution of male and female MR (two-sample t-test, male geometric mean MR=5.1, female geometric mean MR=7.0,  $P = .02$ ).

### Conclusions

The high normeperidine to meperidine MR suggests rapid metabolism and/or substantial metabolite accumulation. Intersubject variability in meperidine metabolism was 3-fold greater than intrasubject variability. A significant difference in MR was found between males and females. This characterization of meperidine metabolism may impact a prescriber's approach to meperidine. The substantial variability in meperidine metabolism and the serious side effects of its metabolite normeperidine require greater vigilance in patient medication monitoring.