Effects of CYP 2C19 Inhibitors on the Distribution of Urinary Diazepam Metabolites in Patients with Chronic Pain

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BACKGROUND
- Diazepam is used as an adjuvant to spastic therapy to reduce pain-related anxiety and serve as a rescue analgesic in pain patients.1,2
- Metabolites include: Nor-diazepam by cytochrome P450 2C19,
  - Tazepam by CYP 3A4,
  - Nor-diazepam and nor-tazepam are further metabolized to desmethyldiazepam in the liver.
- All the metabolites are pharmacologically active.
- Diazepam and its metabolites bind to the alpha-adrenergic receptors in the brain.
- Clinical effects are not well characterized, although it has been shown to have significant inhibitory effects on diazepam.
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OBJECTIVES
The aim of this study was to examine the effects of CYP 2C19 substrates and inhibitors on the urinary distribution of metabolites.

METHODS
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RESULTS
- Figure 1. Histogram and descriptive table of the fraction of nor-diazepam for those concurrently on CYP 2C19 substrates as compared to those not on any CYP 2C19 substrates or inhibitors.
- Figure 2. Histogram and descriptive table of the fraction of nor-diazepam for those concurrently on CYP 2C19 substrates as compared to those not on any CYP 2C19 substrates or inhibitors.
- Figure 3. Histograms and descriptive table of the fraction of nor-diazepam and tazepam for those concurrently on CYP 2C19 substrates as compared to those not on any CYP 2C19 substrates or inhibitors.
- Figure 4. Histograms and descriptive table of the fraction of nor-diazepam and tazepam for those concurrently on CYP 2C19 substrates as compared to those not on any CYP 2C19 substrates or inhibitors.

DISCUSSION
- With a CYP 2C19 substrate, there is a trend, but significant decrease in the fraction of nor-diazepam.
- With a CYP 2C19 inhibitor, there is no trend in the fraction of nor-diazepam.
- Fraction of nor-diazepam decreases, perhaps due to inhibition of the nor-diazepam formation pathway.
- Fraction of nor-diazepam increases, perhaps due to inhibition of the nor-diazepam formation pathway.

CONCLUSIONS
- In a large population of pain patients, it is possible to distinguish the effects of CYP 2C19 substrates and inhibitors on the urinary fraction of diazepam metabolites.
- CYP 2C19 substrates have a normal effect on the fraction of nor-diazepam.
- CYP 2C19 inhibitors have no effect on the fraction of nor-diazepam.
- The changes seen with esomeprazole and fluoxetine are greater than the effect seen when all inhibitors are grouped together.
- Esomeprazole appears to have a larger effect on the fraction of nor-diazepam.

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