

## Assessing concomitant use of oxycodone formulations with known strong cytochrome P450 (CYP) 2D6 inhibitors in patients with chronic pain

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### Purpose

Oxycodone is an opioid analgesic used for moderate to severe pain and comes in many formulations including immediate release (IR) and controlled release (CR). Oxycodone is metabolized to noroxycodone and oxymorphone by cytochrome P450 (CYP) 3A and CYP2D6, respectively. Oxymorphone provides more analgesia compared to noroxycodone. Thus, oxycodone taken with CYP2D6 inhibitors may be a clinically relevant drug-drug interaction as active metabolite production may be altered. The potential of CYP2D6 inhibitors to alter oxymorphone and noroxycodone in urine is unknown. Our study purpose was to examine the effect of CYP2D6 inhibitors on the oxycodone metabolism pathway in patients with chronic pain.

### Method

In this retrospective study, urine specimens from routine clinical testing of patients with chronic pain were analyzed at Millennium Laboratories using liquid chromatography tandem mass spectrometry (LC-MS/MS) to quantify oxycodone as well as its metabolites oxymorphone and noroxycodone in urine. Specimens included were those that had a concentration of either the parent drug or its metabolites greater than 50 ng/mL and a creatinine concentration greater than 20 mg/dL. Out of 64,403 urine specimens from patients that have reported use of oxycodone IR or CR along with other medications excluding oxymorphone, a total of 1892 unique subjects were selected for analysis due to concurrent use of strong CYP2D6 inhibitors: 796 oxycodone IR specimens, 271 oxycodone CR specimens, and 825 oxycodone in combination with acetaminophen (APAP) specimens. Data were converted to mole units for comparisons. Statistical analyses were conducted using OriginPro 8.5.1.

### Results

Mean oxymorphone mole fraction for oxycodone IR, with and without the presence of strong CYP 2D6 inhibitors, was .110 and .241, respectively. The mean difference between mole fractions was -.132 [95%CI: -.145, -.119;  $P < .001$ ]. Similar statistically significant decreases in the mean oxymorphone mole fractions were also seen with oxycodone CR and oxycodone/APAP formulations. The mean noroxycodone mole fraction for oxycodone IR, with and without the presence of strong CYP 2D6 inhibitors was .646 and .512, respectively. The mean difference between mole fractions was .134 [95%CI: .121, .148;  $P < .001$ ]. Similar statistically significant increases in the mean noroxycodone mole fraction were also seen with oxycodone CR and oxycodone/APAP formulations.

### Conclusions

The oxymorphone mole fraction significantly decreased, while the noroxycodone mole fraction significantly increased, during concomitant administration of strong CYP2D6 inhibitors. This indicates that the metabolic pathway shifted to produce less oxymorphone. The CYP2D6-mediated drug-drug interaction may be of clinical significance since oxymorphone contributes to the analgesic effect of oxycodone. Precaution and careful urine monitoring of the

concentration of oxycodone and its metabolites is recommended when prescribing oxycodone with concomitant medications known to inhibit CYP2D6.