Urine Drug Testing for Oxycodone and Its Metabolites as a Tool for Drug–Drug Interactions?

A recent article by Elder et al. (1) used urinary concentrations of oxycodone, oxymorphone, and noroxycodone from a large patient sample collected for routine drug monitoring purposes. The two aims were the identification of factors contributing to the known drug testing variability and the potential monitoring of clinically significant drug–drug interactions. Unfortunately, in only 49% of the urine specimens, noroxycodone was detected which was already addressed by DePriest et al. (2) showing the discrepancy to the current literature data where urinary noroxycodone prevalence was always above 90% questioning the validity of the study results. In reply to this letter, Elder et al. (3) admitted an ‘error’ at the start of the analysis and they present three updated tables with different results of the mole fractions.

This leaves a number of open questions for the original publication. This large discrepancy between the current knowledge of high prevalence of urinary noroxycodone published (4–6), and the study findings should have triggered a discussion about the reasons as well as a re-evaluation of the data. This was done only as a reaction to the letter by DePriest et al. (2). With the new data provided (3), the prevalence is now in the previously known range. The second aim of the investigation was the monitoring of clinically significant drug–drug interactions. With the new data analysis, there are numerous changes (listed in their Table III) in the alterations of the mole fractions based on the physician-reported CYP2D6 and CYP3A4 substrate and/or inhibitor use, which is not even discussed.

The authors acknowledge in their reply (3) the limitation of physician-reported medication. However, in the exclusion criteria of the dataset it is mentioned that 35 subjects have been excluded due to the use of CYP2D6 inducers (1). So far, no drug has been identified to be able to induce the polymorphic CYP2D6 enzyme in vitro and in vivo (7). This supports even more the uncertainty in the method of obtaining the physician-reported medication and hence the validity of the results.

Understanding the metabolism of a drug and the enzymes mediating this is a key point when interpreting urinary concentrations and mole fractions especially for the assessment of drug–drug interactions. For the assessment of CYP-mediated metabolic interactions, three metabolites are important; noroxycodone, oxymorphone, and noroxymorphone, the latter one is formed as a secondary metabolite (Figure 1). The metabolic pattern after oxycodone administration to humans has been studied thoroughly by Lalovic et al. (8). They showed that 72 ± 19% of a given oxycodone dose is excreted in urine over 48 h with oxycodone accounting for 8.9% only (8). Noroxycodone is the major urinary metabolite with 23.1% of the dose followed by the secondary metabolite noroxymorphone with 14.2%, and oxymorphone (mainly conjugated) with 10.7% (8). The two-step formation of noroxymorphone always involves CYP2D6 and CYP3A4 either in the first or the second step. Therefore, inhibition of CYP3A4 results in decreased formation of noroxycodone from oxycodone and also decreased formation of noroxymorphone from oxymorphone. Inhibition of CYP2D6 will reduce the formation of oxymorphone from oxycodone as well as noroxymorphone from noroxycodone (Figure 1). Unfortunately, Elder et al. quantified the primary metabolites only (1, 3). This is a very complex situation, which has also been reported for dextromethorphan that has very similar metabolic pathways and enzymes involved (9). It is therefore not possible to use urinary mole

Figure 1. CYP-mediated metabolic pathways of oxycodone and the proposed effects of single and dual enzyme inhibition on urinary excretion.

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fractions from drugs like oxycodone or dextromethorphan with its complex metabolism (several enzymes and primary and secondary metabolic steps involved) to monitor clinically significant drug–drug interactions.

References


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