Is it Noroxymorphone or Nornaloxone, and why should you care?

Stephanie J. Marin[1], Gwendolyn A. McMillin[2,3], Frederick G. Strathmann[2,3]

[1]ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, UT
[2]ARUP Laboratories, Salt Lake City, UT
[3]Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT

Introduction:

Noroxymorphone and nornaloxone are the same chemical compound that can result from two different metabolic pathways involving three different prescription drugs: oxycodone (OxyContin, PercoCet) via metabolism of either noroxycodone or oxymorphone, oxymorphone (Opana, Numorphan), or naloxone. Naloxone may not be observed in urine, but in a clinical (non-emergency) setting, the most common source of naloxone is through use of a drug co-formulated with buprenorphine (Suboxone, Zumbsolv). As such, buprenorphine is a good biomarker for naloxone exposure. Correct identification of the source of the norxoymorphone/nornaloxone metabolite is important for interpretation of urine drug testing results, a common compliance monitoring tool used in chronic pain management and drug addiction therapy.

This study was designed to evaluate concentrations of noroxymorphone/nornaloxone in urine specimens that contained parent drugs (naloxone, oxycodone and/or oxymorphone) with or without evidence of buprenorphine exposure (inferring naloxone), to establish concentrations of metabolite expected for the two pathways, and propose concentration ranges that could guide interpretation of results when noroxymorphone/nornaloxone is the only analyte detected.

Methods:

There were two data sources included in this study: targeted testing, and retrospective data retrieval. For the targeted testing, a total of 170 residual patient urine specimens were selected based on the hypothesis that the parent drug was naloxone. The samples were known to contain noroxymorphone/nornaloxone and buprenorphine, but no oxycodone, noroxycodone, or oxymorphone. Initial testing performed to identify these samples was conducted by either liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS, ABSciex) or time of flight high resolution mass spectrometry (LC-MS/TOF, Agilent). Quantitative testing by LC-MS/MS (ABSciex) was performed for all samples to determine concentrations of noroxymorphone/nornaloxone, naloxone (LLOQ 10 ng/mL), buprenorphine, norbuprenorphine (LLOQ 2 ng/mL), and glucuronide metabolites of buprenorphine and norbuprenorphine (LLOQ 5 ng/mL). Analytes were detected and quantitated as free drug (no hydrolysis).

Retrospective data were obtained from clinical testing based on the presence of noroxymorphone/nornaloxone, with or without oxycodone, noroxycodone, or oxymorphone. Buprenorphine and metabolites, and naloxone data were not available for this dataset.

Results:

From the retrospective data analysis there were 16,273 results positive for noroxymorphone/nornaloxone. Of these, 14,587 were also positive for oxycodone, oxymorphone, and/or noroxycodone. It is presumed that one or more of these were a precursor for metabolism, and that the true identity was noroxymorphone. The median concentration of noroxymorphone that was observed when the precursor drug was oxycodone or oxymorphone was 183 ng/mL, and 75% of results exceeded 75 ng/mL. When there was no evidence of oxycodone or oxymorphone use, the median concentration of noroxymorphone/nornaloxone was 40 ng/mL, and approximately 75% or results were less than 75 ng/mL.

The 170 specimens where the presumed source of metabolite was naloxone all contained analytes indicative of buprenorphine exposure. 56 of the specimens were positive for naloxone and the median concentration was 23 ng/mL. The median concentration of nornaloxone in this sample set was 35 ng/mL.

Discussion and Conclusions:

Detection of noroxymorphone/nornaloxone without any precursor drug is difficult to interpret. The best scenario is to include precursor drugs in the urine drug test, and compare results with patient prescriptions (pre-test expectation), keeping in mind that the presence of noroxymorphone/nornaloxone alone could be explained if the urine sample was collected late in the elimination process of any precursor drug, wherein noroxymorphone/nornaloxone may be the only residual metabolite detected.

Our review of 16,273 results suggests that noroxymorphone is associated with oxycodone, noroxycodone, and/or oxymorphone in 90% of samples. Thus, parent drug is useful for determining the source of noroxymorphone. Among buprenorphine-positive samples known to contain noroxymorphone/nornaloxone but no oxycodone, noroxycodone, or oxymorphone, naloxone was present in only 33% (56 of 170), suggesting that naloxone metabolites are more prevalent in the urine than parent drug. As such, evidence of buprenorphine exposure may suggest that the source of noroxymorphone/nornaloxone is naloxone. When detection of noroxymorphone/nornaloxone is unexpected and no precursor drug is detected, the concentration may help predict the precursor drug. In general the dose of oxycodone or oxymorphone that could contribute noroxymorphone to the urine is typically higher than the dose of naloxone administered in combination with buprenorphine. It is not surprising that the concentrations of noroxymorphone/nornaloxone are generally lower when the precursor drug is naloxone than when the precursor drug is oxycodone or oxymorphone.

Our data suggest that in the absence of parent drug, the concentrations of noroxymorphone/nornaloxone less than 75 ng/mL are most likely to be associated with metabolism of naloxone rather than an oxycodone or oxymorphone containing drug.