Identifying Levorphanol Ingestion using Urine Markers in Chronic Pain Patients

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Background / Purpose:
Levorphanol is a long-acting opioid analgesic that binds mu, delta, and kappa opioid receptors in the brain; additionally, it decreases activity at the N-methyl-D-aspartate (NMDA) receptor and blocks uptake of serotonin and norepinephrine.[1] It is a chemical isomer of dextrorphan, which is a metabolite of dextromethorphan.[2,3] However, while dextromethorphan metabolizes to dextrorphan,3-methoxymorphinan, and (+)-3-hydroxymorphinan, levorphanol only metabolizes to norlevorphanol, or (-)-3-hydroxymorphinan. This study investigates urinary concentrations of levorphanol/dextrorphan and 3-hydroxymorphinan in chronic pain patients, and characterizes cases of potential levorphanol ingestion based on detection of relevant urinary markers.

Methodology:
Urine drug test results from chronic pain patients submitted to Aegis® Sciences between July 2014 and July 2015 were evaluated for the presence of levorphanol/dextrorphan and 3-hydroxymorphinan by liquid chromatography / tandem mass spectrometry (LC-MS/MS) above the limit of quantitation (LOQ) of 10 ng/mL (*N* = 279). An isomeric analysis was not performed; therefore, dextrorphan and levorphanol could not be differentiated. Results for patients with detectable concentrations of dextromethorphan or 3-methoxymorphinan were eliminated, as these are specific to dextromethorphan ingestion (*N* = 211).

Results:

Prescription Information (per laboratory requisition form)	*N*	Mean Urinary Concentrations (ng/mL) [SEM (range)]	
		Levorphanol/Dextrorphan	3-hydroxymorphinan
Dextromethorphan	16	430.27 [213.14 (14.54-2663.01)]	358.65 [178.5 (27.71-2702.96)]
Levorphanol	4	5032.84 [2360.16 (1997.43-12070.9)]	514.5 [244.79 (173.96-1241.18)]
No Prescription Indicated	48	525.02 [124.48 (18.99-4789.87)]	306.71 [96.84 (19.56-4298.53)]
Total	**68**	**767.89** [204.28 (14.54-12070.9)]	**331.16** [80.75 (19.56-4298.53)]

The average parent to metabolite ratio for levorphanol/dextrorphan to 3-hydroxymorphinan for all patients was 2.56.

Conclusions:
To our knowledge, this is the first report identifying urinary concentrations of levorphanol/dextrorphan and 3-hydroxymorphinan in chronic pain patients. Mean concentrations of levorphanol and 3-hydroxymorphinan were elevated in patients prescribed levorphanol in comparison with those prescribed dextromethorphan; however, many patients prescribed dextromethorphan did not have any detectable urinary concentrations of dextromethorphan or 3-methyoxymorphinan at the time of urine collection. Therefore, it may

be impossible to distinguish between levorphanol or dextromethorphan ingestion unless dextromethorphan or 3-methoxymorphinan are present or an isomeric analysis is performed.

References:

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