THERAPEUTIC DRUG MANAGEMENT AND TOXICOLOGY DIVISION NEWS
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Therapeutics & Toxins News

Newsletter for the TDM and Toxicology Division of AACC

In This Issue:

Tapentadol cross-reacts with the DRI Methadone immunoassay

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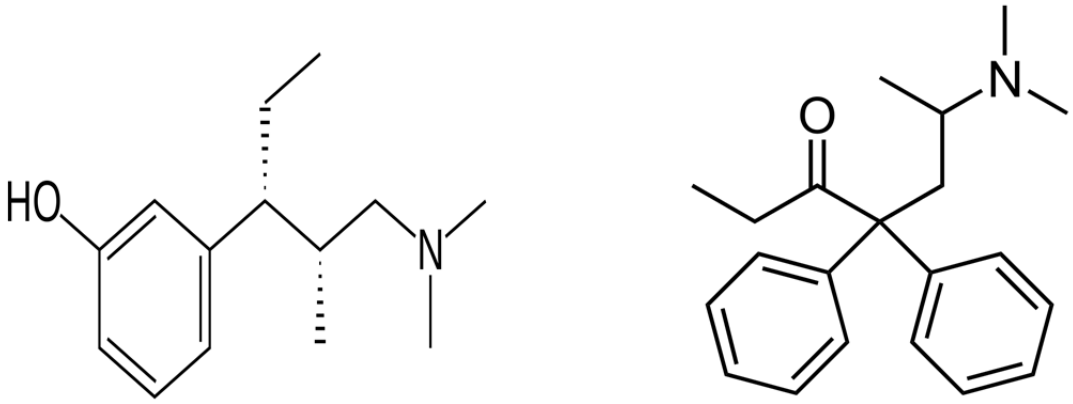
Introduction. Tapentadol (Nucynta) is a centrally acting analgesic approved by the Food and Drug Administration in 2008 for the treatment of moderate to severe acute and chronic pain. It entered the commercial market in 2009 and is listed as a schedule II drug by the U.S. Drug Enforcement Agency. It is sold as the hydrochloride salt in 50, 75, and 100 mg tablets to be consumed every 4-6 hours with a maximum of 600 mg/day (1). An extended release formulation was marketed in 2011 with an additional indication to treat pain associated with diabetic peripheral neuropathy. Tapentadol's potency is between that of tramadol and morphine, with an analgesic efficacy similar to that of oxycodone but with more tolerable side effects. It acts as both a mu-opioid receptor agonist and a norepinephrine reuptake inhibitor. Unlike tramadol, it is a very weak inhibitor of serotonin reuptake and has been shown to be extensively metabolized to multiple pharmacologically-inactivate glucuronidated and sulfated products. In humans, a 24 hour urine contained only 3% of the parent drug and ~ 99% was eliminated in the urine over a five day interval (2). In 2012, Collins et al. (3) reported a substantial number of false positive urine methadone screens when using the DRI Methadone enzyme immunoassay among patients taking therapeutic levels of tapentadol. Since then, the manufacturer has either not appropriately updated their methadone package insert to include this cross-reactive prescribed drug or they have changed

their formulation (4). We sought to determine whether the DRI Methadone immunoassay still exhibits this pronounced cross-reactivity with tapentadol and if so, whether it could be utilized as an effective presumptive screen for this drug.

Figure 1. Chemical Structures of Tapentadol and Methadone.



Tapentadol **Methadone**

Methods. Initially, we performed a retrospective analysis of urine drug results from patients who were participating in a pain management program. We then analyzed negative drug-free urine spiked with a broad range of tapentadol (Cerilliant, Round Rock, TX) concentrations. The DRI Methadone immunoassay was performed on an Indiko Plus analyzer (Thermo Scientific, Fremont, CA) at a standard methadone cut off at 300 ng/mL following the procedures stated in the Thermo Scientific package insert (4). Quantitation was performed by liquid chromatography tandem mass spectrometry (LC-MS/MS) using a Shimadzu 20AD LC coupled with a SCIEX 3200MD tandem MS (Foster City, CA). Chromatographic separation of the pain panel occurred on a Phenomenex Kinetex Phenyl-Hexyl analytical column (Torrance, CA). Sodium acetate buffer and beta-glucuronidase (Campbell Science, Rockford, IL) were added to samples and allowed to incubate at 55 ^{0}C for 60 minutes to liberate glucuronidated metabolites. Samples then underwent LC-MS/MS analysis using the method set up by the manufacturer. Mass spectral data was acquired in positive electrospray

ionization mode with two selected transition ions for each analyte and one for internal standards. The limit of linearity (LOL) for tapentadol was 2 – 500 ng/mL.

Results and Discussion. We retrospectively identified eighteen samples that had recently screened positive for methadone but whose medical records indicated the patient's had been prescribed tapentadol and not methadone. All 18 had no detectable methadone present but each had tapentadol levels above the upper LOL. A review of their medical records did not indicate any other commonly prescribed opioid apart from tapentadol. We also identified two samples with tapentadol levels of 282 ng/mL and 74 ng/mL that screened negative for methadone. To augment these results, we spiked tapentadol at a wide range of concentrations into negative drug-free urine and found that the DRI Methadone immunoassay produced a false positive result between 10,000 ng/mL and 25,000 ng/mL. Collins et al. (3) illustrated that the urinary levels of tapentadol and its three major metabolites contributed an additive cross-reactivity to the methadone immunoassay. Further, they determined that the sulfated metabolite had a significantly greater cross-reactivity than the parent drug. Our results corroborate theirs and expand the methadone screening cut off where false positives can occur from 130 ng/mL to 300 ng/mL. These false positives occur at tapentadol levels achievable in patients therapeutically using the drug. Tapentadol and its key metabolites share a phenalkylamine structure with methadone which is believed to lead to this observed cross-reactivity (Figure 1). This observed cross-reactivity appears to be unique to the DRI Methadone immunoassay as a recent Washington University investigation with the Syva EMIT II Methadone enzyme immunoassay showed a lacked cross-reactivity at a tapentadol concentration above 50,000 ng/mL (5).

Based on our results it appears that the DRI Methadone immunoassay can be used as an effective screen in pain management laboratories to detect the presence of tapentadol in urine. Our results also serve as a reminder that false positive methadone screens can, in part, be attributed to the presence of tapentadol.

References

1. Nucynta IR product monograph. Janssen Inc., Toronto, Canada, March, 2014.

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3. Collins AA, Merritt AP, Bourland JA. Cross-reactivity of tapentadol specimens with DRI Methadone Enzyme Immunoassay. *Journal of Analytical Toxicology*. 2012; 36: 582-587.

4. Thermo Scientific, DRI Methadone immunoassay package insert, October 2015. https://tools.thermofisher.com/content/sfs/manuals/0666-DRI-Methadone-Assay-EN.pdf Accessed June 4, 2016.

5. Mullins ME, Hock K, Scott MG. Does therapeutic use of tapentadol cause false-positive urine screens for methadone or opiates. *Clinical Toxicology*. 2015; 53: 493-494.

Editor's Corner: Division News

1. Dr Li-Rong Wu of FDA won the Division's 2016 Best Abstract Award. Congratulations to Dr Wu! Furthermore, he donated the cash award back to the Division. Thank you, Dr Wu.
2. The Division is working with AACC Society for Young Clinical Laboratarians (SYCL) to arrange webinars in collaboration between Division and SYCL.
3. The Division is working with International Association of TDM & CT (IATDMCT) to arrange multiple activities between Division members and IATDMCT and their journal Therapeutic Drug Monitoring.

Announcement from Division Chair

Attention TDM/ TOX Division Members:

Dr. Michael Oellerich who spoke at our Division luncheon and Mr. Druanne Martin, publisher at Wolters Kluwer, have offered Division members a very nice gift. They propose to give away 10 one year online subscriptions to the journal Therapeutic Drug Monitoring (TDM). TDM is the journal of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT). They are doing this to try and stimulate more involvement of Division members in the international association.

AACC TDM TOX Web Resources:

Toxicology FAQ

Clinical Chemistry Articles Related to TDM and Toxicology

Presentations on LC/MS and LC-MS/MS in Clinical and Forensic Toxicology

Upcoming Conferences

Northeast Lab Conference
Oct 18-20
Portland, ME

AMP 2016
November 10-12
Charlotte, NC

MSACL 2017 US
January 22-26
Palm Springs, CA

SLAS 2017
February 4-8
Washington, DC

PITTCON 2017
March 5-9
Chicago, IL

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