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:

Diphenhydramine cross reacts with DRI Fentanyl Immunoassay

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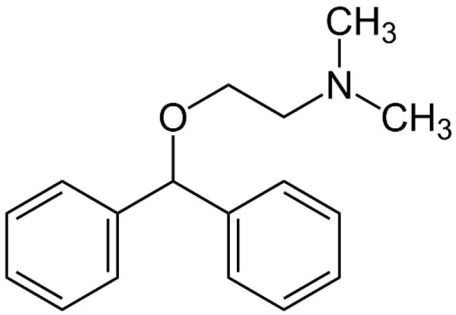
Introduction:

Diphenhydramine is a popular antihistamine that is used to relieve symptoms of allergy, hay fever, and the common cold. Diphenhydramine can be found in products such as Benadryl, Zzzquil, Tylenol PM, Unisom, and many other allergy medications. Diphenhydramine was discovered in 1946 by George Rieveschl and it became the first prescription antihistamine approved by the FDA. Diphenhydramine is available in many forms in tablet, liquid, and topical cream. The tablet form can contain 12.5 mg to 50 mg of diphenhydramine. For adults the dosage is 25-50 mg, three or four times daily without exceeding 300 mg.[1] A single oral dose of diphenhydramine is quickly absorbed with maximum activity occurring in approximately one hour. The duration of activity following an average dose of diphenhydramine is from four to six hours. [2]

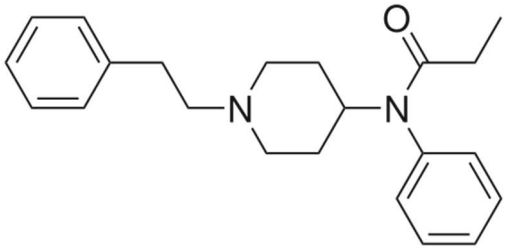
A substantial number of positive urine specimens submitted to our laboratory and analyzed with DRI Fentanyl Immunoassay (Thermo Fisher Scientific) tested negative by LC-MS/MS. The purpose of the study was to determine the cause of the false positive fentanyl urine

screen immunoassay results. We utilized patient reported medication lists and National Institute of Standard and Technology (NIST) mass spectral database to identify the reason for false positive Fentanyl screens. Since diphenhydramine containing medications were a common factor amongst the patients for whom the immunoassay screen was Fentanyl positive, but LC-MS/MS tests for fentanyl were negative, we sought to investigate its role in DRI fentanyl Immunoassays.

Figure 1: Chemical Structure Diphenhydramine and Fentanyl



Diphenhydramine



Fentanyl

Method:

A Clean screen® DAU extraction column (UCT) was conditioned with 3 mL of methanol, followed by 3 mL of distilled water, and 0.1 M potassium phosphate buffer (pH 6.0). 2 mL of urine sample was pretreated with 2 mL of 0.1 M potassium buffer (pH 6.0) and was added to the extraction column. The column was washed with 3 mL of distilled water, followed by 1.0 M acetic acid, followed by 3 mL of methanol, and eluted with 4 mL of methylene chloride/isopropanol/ammonium hydroxide (78/20/2). Specimens were analyzed by full-scan mass detection using Agilent GC-MS. Unknown compounds were identified based upon NIST mass spectral database.

Benadryl and Unisom pills were crushed and dissolved in methanol to prepare 2.5 mg/mL of working stock for each drug. Blank urine was spiked with varying levels of Benadryl and Unisom to determine if diphenhydramine cross reacts with the DRI fentanyl assay.

Results and Discussion:

The DRI Fentanyl Assay package insert shows that diphenhydramine had been tested for cross-reactivity for a concentration up to 10,000 ng/mL. At this concentration samples produced a negative fentanyl result and had less than 0.02% cross-reactivity.[3]

In our laboratory, in most cases, we do not reflex positive screen results to confirmations by LC-MS/MS. Confirmation requests come from the clinicians after reviewing initial screening results. We analyzed 37 specimens that screened falsely positive for fentanyl, by full scan analyses and determined 17 of those specimens contained diphenhydramine.

Next, we spiked blank urine with various concentration of diphenhydramine, ranging from 10,000 ng/mL to 1,000,000 ng/mL, and analyzed with fentanyl reagent. Consistent with the fentanyl package insert, diphenhydramine at 10,000 ng/mL did not cross react with the fentanyl assay, thereby giving negative result. However, diphenhydramine at 20,000 ng/mL did cross react with the fentanyl assay, thus producing a positive fentanyl result. We also tested specimens provided by a volunteer who consumed 50 mg of diphenhydramine. At 3 h, 6 h, 12 h, and 1.5 days post consumption, fentanyl screen results were negative. Based on these results, we conclude that false positive fentanyl screens can, in part, be attributed to the presence of high levels of diphenhydramine. It is worth nothing that the fentanyl immunoassay also cross reacts with several fentanyl analogs. In our experience, specimens that contain fentanyl analogs also contain fentanyl and norfentanyl, or either fentanyl or norfentanyl.

References:

(1) Diphenhydramine: MedlinePlus Drug Information." *MedlinePlus*, U.S. National Library of Medicine, medlineplus.gov/druginfo/meds/a682539.html.

(2) Rogers, S. C.; Pruitt, C. W.; Crouch, D. J.; Caravati, E. M. Rapid Urine Drug Screens: Diphenhydramine and Methadone Cross-Reactivity. *Pediatric Emergency Care* **2010**, *26* (9), 665–666. https://doi.org/10.1097/PEC.0b013e3181f05443.

(3) Thermo Scientific, DRI Fentanyl Immunoassay package insert. https://assets.thermofisher.com/TFS-Assets/CDD/Package-Inserts/10016007-DRI-Fentanyl-Assay-CJF-EN.pdf

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Editor's Corner: Division News

Dear Readers,
The spring has been a trying time for all of us across the globe due to COVID 2019 pandemic; worldwide, over 23 million people have contracted the virus with about 374,000 deaths. To cope with this extremely contagious virus most countries imposed lockdown, from which they are slowly coming out. But contagion, and hence, social distancing continues. Like everything else, AACC National Meeting has also been affected this year. Whereas we all excitedly plan for AACC National Meeting during every summer, this year the Meeting has been postponed to Dec 13 to 17, though venue remains same (Chicago). I wonder if such postponement is the first time in AACC history. Still enjoy the summer, though with careful social distancing, and, most importantly, keep safe.

Pradip Datta, Editor.

AACC TDM TOX Web Resources:

https://www.aacc.org/community/divisions/tdm-and-toxicology/

Upcoming Conferences/Courses

Most have been postponed.

AACC National Meeting	Dec 13 to 17	Chicago, USA
International Congress of Therapeutic Drug Monitoring & Clinical Toxicology:	Sep13-20,	Banff, Canada
International Federation of Clinical Chemistry	Jan 6-10, 2021	Seoul, Korea

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Announcements:

The editorial board invites ideas and article contributions for this newsletter. Please contact Dr. Pradip Datta at pradip.datta@siemens.com.