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### Proton Pump Inhibitors and Tetrahydrocannabinol Urine Drug Screens: An Update

Jennifer L. Powers and Frederick G. Strathmann

The question of whether or not pantoprazole and other proton pump inhibitors cause false positives in tetrahydrocannabinol (THC) urine drug screens is one that comes up frequently in discussions with physicians who manage patients on pain medication. As proton pump inhibitors have become more widely prescribed and even available over-the-counter, this is an important question for laboratories or assay manufacturers to address. For several years, evidence for this interference only pointed back to the pantoprazole drug insert which states that there have been reports of false positive THC drug screens, but does not provide data or references. Then, in 2015 a case report appeared in which a 13-year-old with cyclic vomiting syndrome had a false positive THC screen attributed to pantoprazole; however, this report did not provide convincing evidence or give the name of the THC screen used (1). Many different THC immunoassays are FDA-approved for screening purposes and have different cross-reactivity with metabolites and interferences. Most detect the 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH). If a positive result is obtained, confirmation is recommended.

Recently, information on specific THC urine drug screens has begun to appear in literature (2, 3). Gomila and coworkers (2) examined the cross-reactivity of pantoprazole in three cannabinoid immunoassays: the Alere Triage TOX Drug Screen, the kinetic interaction of microparticles in solution (KIMS) Cannabinoids II assay performed on a Cobas c502 analyzer, and the DRI Cannabinoids Assay performed on an Architect C16000 analyzer. Their approach utilized both spiked samples and pediatric patient samples. Drug-free urine samples from healthy volunteers
were spiked with pantoprazole at varying concentrations (1 - 12,000 \( \text{g/mL} \)). Using a cutoff of 50 ng/mL, negative results were obtained with the DRI and KIMS assays at all concentrations; however, the Alere Triage TOX Drug Screen gave positive results at pantoprazole concentrations >1,000 \( \text{g/mL} \). All samples showed negative results by GC-MS confirmation using a 15 ng/mL cutoff. For the eight consented patients (ages 10-13), urine was obtained before treatment with pantoprazole and twice during treatment with 20-40 mg pantoprazole per day. These were examined in the same manner as spiked samples. No false positive findings were obtained before pantoprazole treatment, and no false positives obtained during treatment when screening with the DRI Cannabinoids Assay. However, for samples collected during treatment with pantoprazole, 1 out of 16 samples examined with the KIMS Cannabinoids II immunoassay and 13 out of 16 samples examined with the Alere Triage TOX Drug Screen screened positive for THC, but negative by GC-MS. Package inserts for the Alere and DRI assays do not state anything about cross-reactivity with pantoprazole, while the KIMS package insert specifies pantoprazole does not cross-react to 100 \( \text{g/mL} \). Cross-reactivity of pantoprazole metabolites was not examined by the manufacturer.

In a separate study by Powers and coworkers (3), THC immunoassay screening was performed using the EMIT II Plus Cannabinoid Assay on a Beckman AU5810 with a 20 ng/mL cutoff. A THC-negative urine sample spiked with 10,000 ng/mL pantoprazole gave a negative result. Thirty-two patient samples were collected from consented adults self-reporting to be taking a proton pump inhibitor (PPI), as well as residual samples from patient specimens submitted for a drug screen with a list of expected drugs. PPIs taken by this group included pantoprazole, omeprazole, esomeprazole, lansoprazole, and dexlansoprazole. None of the 32 patient samples gave a positive result for THC in this immunoassay screen. One sample with a raw OD reading near the cutoff was examined by LC-MS/MS for confirmation and found to contain THC (THC-COOH at 7.3 ng/mL). In a different approach, urine samples that screened positive for THC by immunoassay, but failed to confirm by LC-MS/MS were de-identified for examination of possible presence of a PPI. Samples that confirmed with very low concentrations of THC-COOH (6 – 25 ng/mL) were also examined. Using an in-house developed LC-TOF-MS assay, samples were analyzed for the presence of a PPI by comparing results to a compound library containing data from several known PPIs. Mass match, isotope ratios, and chromatographic retention time were the criteria for evidence of a known PPI. No evidence of a PPI was found in any of the 50 samples examined, suggesting there may be other unknown molecules or metabolites of the drug causing the false positives seen with the EMIT II Plus Cannabinoid Assay. However, we cannot exclude the possibility that the patients ingested hemp-containing foods or experienced passive inhalation.
According to literature (4), >80% of pantoprazole is excreted as metabolites in urine. This, coupled with the fact that a spike of >1000 g/mL pantoprazole was required to see false positives with the Alere Triage TOX Drug Screen (2), suggests a metabolite may be the more likely cause of false positives. Although manufacturers will typically screen for interference by certain common drugs, the drug metabolites are not included, likely due to the many metabolites that form as well as lack of availability. Powers et al (3) took the approach of utilizing molecular modeling studies to compare the main metabolite of pantoprazole with the THC metabolite commonly measured by most THC screens. Lack of similarity found upon comparison of overall shape and electrostatics, as well as the calculated Tanimoto score, suggests very low likelihood of cross-immunoreactivity for these two compounds.

Conclusion: Taken together, the above data suggests that the explanation of THC false positives resulting from cross-reactivity of PPIs in urine screens has little validity for most methods. While the potential does exist for at least one available THC immunoassay (Alere Triage TOX Drug Screen), the wide availability of confirmatory assays can easily distinguish THC use or exposure from a false positive. As with any unexpected toxicology findings, secondary testing, preferably using a more specific method is highly recommended.

References:
Editor's Corner: National Meeting in Chicago (July 30–August 2)

Dear Readers,

Division Events:
1. Division Mixer, Sunday July 29, after AACC Plenary
2. **Division Annual Meeting and Luncheon**, Monday July 30, 2018 from 12:00 – 2:00 pm in Hyatt Regency McCormick Place (Burnham A/B on Level 2).

Educational Sessions:

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Pradip Datta, Editor.

From the Chair:

The TDM-Tox Division had another relatively productive year in 2017 and is on a similar track for 2018. Thanks to each and every one of you who supports it.

We look forward to seeing many of you at the 70th AACC Annual Scientific Meeting in Chicago. As always there are numerous educational sessions and other events including our luncheon meeting on Monday July 30. My favorite talks tend to be the plenary sessions since they essentially always leave me with a desire to learn more. This year, 38 posters will be presented under the auspices of this division on Wednesday August 1st and I am sure that everyone will find several of particular interest. See you there.
AACC TDM TOX Web Resources:
https://www.aacc.org/community/divisions/tdm-and-toxicology/

Upcoming Conferences/ Courses
AACC/ASCLS
July 29-Aug 2
Chicago, IL

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