K56 The Use of Liquid Chromatography/Time-Of-Flight (LC/TOF) Data-Mining Techniques to Evaluate Evidence of Use of Dipyrone and Levamisole in Conjunction With Fentanyl and Other Illicit Recreational Drugs

Brian Holsey, BS, NMS Labs, 3701 Welsh Road, Willow Grove, PA 19090; Sherri L. Kacinko, PhD, 3701 Welsh Road, Willow Grove, PA 19090; and Barry K. Logan, PhD, NMS Labs/CFSRE, 3701 Welsh Road, Willow Grove, PA 19090*

After attending this presentation, attendees will be familiar with the popular cutting agent dipyrone, its pharmacology and metabolism, and will be able to assess the significance of its presence in addition to certain popular drugs of abuse.

This presentation will impact the forensic science community by highlighting the use of potentially toxic drugs mixed with certain street drugs and narcotics.

Dipyrone is an antipyretic and non-narcotic analgesic drug not available in the United States. It has been associated with a variety of toxicities, including hematologic toxicity (blood dyscrasias), and has been associated with bronchospasm and anaphylaxis in asthmatics. Similar to another popular cocaine cutting agent, levamisole, the reported side effects of dipyrone use include agranulocytosis, aplastic anemia, hypersensitivity reactions, toxic epidermal necrolysis, and porphyria. Like other bulk white powders, such as diltiazem, phenacetin and levamisole, dipyrone has been reportedly used as a cutting agent with illicit drugs. This study evaluated five months of postmortem toxicology screening data between February and June 2016, to assess which illicit drugs were found in combination with dipyrone and levamisole.

Methods: Cases submitted to NMS Labs for drug testing in postmortem investigations between February and June 2016 were analyzed by LC/TOF, using an Agilent® 1290 Infinity® High-Performance Liquid Chromatography (HPLC) coupled with an Agilent® 6230 Time-Of-Flight/Liquid Chromatography/Mass Spectrometry (TOF/LC/MS). Retrospective reprocessing of data was performed to identify cases in which dipyrone (based on the presence of its metabolites and breakdown products noramidopyrone, 4-formylaminoantipyrine, and 4-acetylaminoantipyrine) and other popular cutting agents, such as levamisole and diltiazem, were present. Also evaluated were drugs subject to abuse (cocaine, Benzoylecgonine (BZE), morphine, 6-monoacetylmorphine (6-MAM), fentanyl, norfentanyl, acetyl fentanyl, despropionyl fentanyl, butyryl fentanyl, furanyl fentanyl, β-hydroxythiofentanyl, and 3-methylfentanyl).

Results: Data from a total of 13,268 runs were evaluated. The drugs of interest were found as follows: fentanyl/norfentanyl 1758 (13.2%); acetyl fentanyl 257 (1.9%); butyryl fentanyl 16 (0.1%); furanyl fentanyl 229 (1.7%); morphine/6-MAM 2528 (19.0%); and cocaine/BZE 1220 (9.2%).

Evaluating combinations of the above drugs in the 1,758 cases in which fentanyl was detected revealed it was present alone in 675 cases (38%), while in 386 cases (22%), it was present with morphine/6-MAM, in 139 (7.9%) cases it was present with cocaine/BZE, and in 62 cases (3.5%), it was present with acetyl fentanyl. Fentanyl was detected with butyryl fentanyl and furanyl fentanyl in less than ten cases.

Table 1, below, represents the positivity rate of drugs discussed here with common cutting agents dipyrone, levamisole, and diltiazem. Cases in which fentanyl and norfentanyl were present were removed to avoid confounding from dipyrone associated with fentanyl.

Drug	Positives (%)	Dipyrone present	Diltiazem present	Levamisole present
Fentanyl/norfentanyl	1758 (13.2%)	13.2%	3.3%	16.9%†
Acetyl fentanyl*	31 (0.2%)	3.2%	3.2%	16.1%†
Butyryl fentanyl*	14 (0.1%)	0%	7.1%	35.7%†
Furanyl fentanyl*	202 (1.5%)	1.5%	0%	24.3%†
Morphine/6-MAM*	1812 (13.6%)	1.6%	3.3%	11.5%†
Oxycodone*	1386 (10.4%)	0.4%	3.0%	11.5%†
Cocaine*	1087 (8.2%)	1.3%	2.2%	62.9%

**Excludes cases in which fentanyl or norfentanyl were present. † Excludes cases in which cocaine was present.*

Levamisole was the most commonly observed cutting agent and was most frequently found in combination with cocaine (62.9%) and furanyl fentanyl (24.3%) and less frequently with other drugs (11-17%). Dipyrone was present most frequently in cases involving fentanyl (13.2%), followed by acetyl fentanyl (3.2%), and seen less than 2% of the time in combination with the other drugs. Diltiazem was seen infrequently (3.3% or less) in any combination. There are limitations to the data, including the fact that all the compounds have different half-lives, so residual cutting agents from previous ingestions cannot be ruled out as a source. In the case of diltiazem, it may have been ingested therapeutically. Nonetheless, the data are beneficial in identifying the high prevalence of levamisole and dipyrone, compounds that may contribute to the toxicity of these street drugs in drug user deaths.

Dipyrone, Levamisole, Drug-Related Deaths