The ToxIC NOSE (Novel Opioid and Stimulant Exposure)

Report #10 from ToxIC's Rapid Response Program for Emerging Drugs

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Hypoglycemia: An Unexpected Complication from Opioid Use

Introduction

Hypoglycemia, a blood sugar dropping below 60 mg/dL, is often due to an adverse effect of some diabetic medications such as insulin. Hypoglycemia can lead to serious complications, such as a fast heart rate, dizziness, confusion, coma, or death if left untreated.

Recent pharmacovigilance studies have also shown an association between hypoglycemia and specific prescription opioids, such as tramadol[1] and methadone.[2] However, this association has not consistently been demonstrated between hypoglycemia and other pharmaceutical opioids, including fentanyl.[3]

There are several hypothesized mechanisms for opioid-induced hypoglycemia. The mu (μ) opioid receptor, the predominant opioid receptor in

The ToxIC Novel Opioid and Stimulant Exposure (NOSE) Reports

Through the ongoing support of the Opioid Response Network (ORN) since 2020, the American College of Medical Toxicology (ACMT) Toxicology Investigators Consortium (ToxIC) has implemented an enhanced sentinel detector field within the ToxIC Core Registry to identify novel and emerging opioid and stimulant exposures. Once an emerging trend or risk is identified, ToxIC releases a quarterly report.

The goal of this project is to disseminate this novel information to the medical toxicology community as well as the ORN as part of a Rapid Response program.

For more information on the ToxIC Core Registry and data collection, please visit: www.toxicregistry.org

humans, inhibits gluconeogenesis leading to decreased glucose production by the liver, which can be detrimental in times of fasting.[1] In addition, hypothalamic-pituitary-adrenal (HPA) axis dysfunction causes hypoadrenalism leading to decreased cortisol production, an essential blood glucose regulator.[4,5] Moreover, during fasting states or starvation, opioids impair other hypoglycemic counterregulatory mechanisms to ultimately prevent blood glucose regulation from multiple angles.[6] While all of these processes are mechanistically plausible, none of these theories account for the differential association between hypoglycemia and specific prescription opioids.

Given the incompletely understood relationship between prescription opioids and hypoglycemia, it is unsurprising that the occurrence of hypoglycemia in the setting of illicit opioid use is even less well-understood. Several recent cases in the ToxIC Core Registry involving unexplained hypoglycemia in opioid overdose patients has raised the question of whether opioids themselves, or potential illicit drug adulterants/contaminants, could account for this phenomenon. This hypothesis-generating NOSE report explores the nature of both licit and illicit opioid exposure-associated hypoglycemia cases within the ToxIC Core Registry with attention towards the specific opioids involved and the co-ingestions or potential adulterants detected.

ToxIC Data Review

Of the 7,710 opioid exposures in the ToxIC Core Registry between 2010-2022, hypoglycemia (blood glucose < 50 mg/dL per our registry definition) was reported in 75 cases (1%). The three most common opioid exposure agents overall were also the three most common exposures associated with hypoglycemia: fentanyl, heroin, and oxycodone (**Figure 1 and 2**). Although tramadol and methadone are emphasized in existing opioid hypoglycemia literature,[1,2] they were not as prevalent in hypoglycemia-related cases and total opioid-exposure cases in our cohort (5.0% vs. 5.9% and 4.0% vs. 5.0%, respectively). Most of the hypoglycemia-associated opioid cases were reported by participating sites in Pennsylvania (N=21, 28%), Phoenix (N=19, 25%), and St. Louis (N=6, 8%).

Of the overall cohort, 25/75 (33%) of these cases were related to drug misuse (e.g. to experience illicit euphoria or prevent withdrawal, using a prescription drug in excess, and/or using someone else's medication), while 19/75 (25%) of these cases involved self-harm attempts. Single agent exposures to opioids occurred in 23/75 (31%) cases. A known concomitant antihyperglycemic medication exposure was involved in 15% of cases: 6 of these involved insulin, 2 involved glimepiride and glyburide, and 1 involved glipizide. It was not

possible to establish whether the patients took these antihyperglycemics in therapeutic doses or in overdose.

With respect to clinical presentation, 75/75 cases (100%) were listed as "symptomatic." Common clinical findings included: hypotension (23/75; 31%), respiratory depression (38/75; 51%), aspiration pneumonitis (11/75; 15%), central nervous system depression or coma (52/75; 69%), and acute kidney injury (29/75; 39%). The most common treatments rendered included naloxone (43/75; 57%), mechanical ventilation (29/75; 39%), glucagon (4/75; 5%), and octreotide (5/75; 7%); data regarding dextrose administration was not available. Death occurred in 6/75 (8%) patients. Of these deaths, 2 were listed as related to misuse/abuse, 2 were from self-harm attempts, 1 was from therapeutic administration, and 1 was listed as an intentional non-pharmaceutical exposure with an unknown motive.

Figure 1. *Frequency of opioids involved in all opioid exposures in ToxIC Core Registry (N = 7710)*

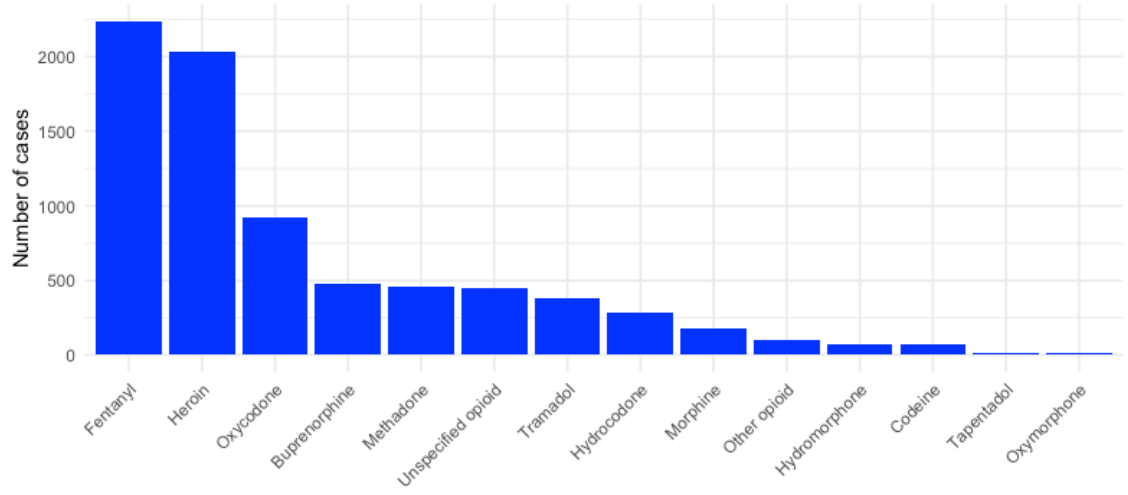
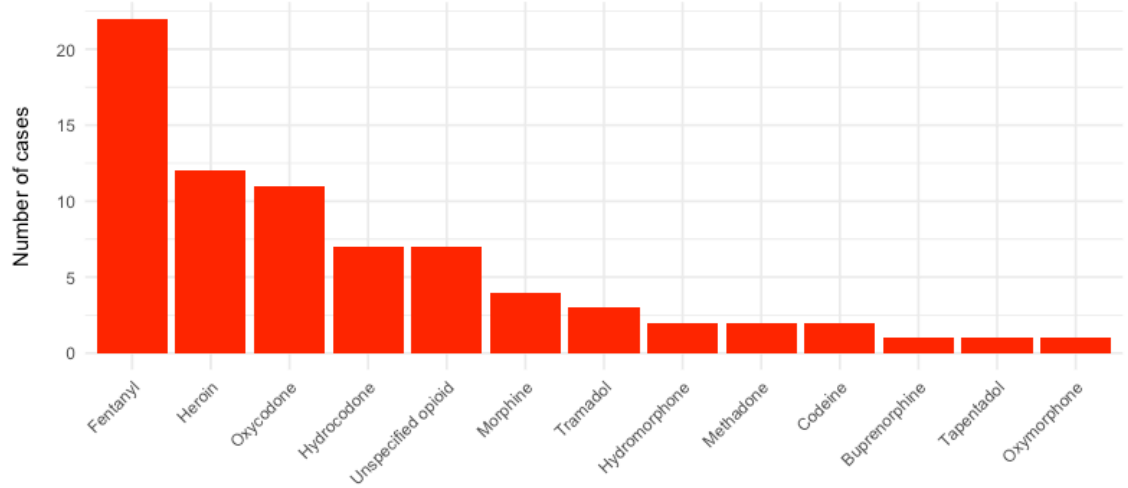


Figure 2. *Frequency of specific opioids in hypoglycemia-related opioid exposures in ToxIC Core Registry (N = 75)*



ToxIC NOSE Cases

Since the inception of the ToxIC NOSE sentinel detector field within the ToxIC Core Registry in January 2021, 10 cases with unexplained hypoglycemia in the setting of opioid overdose have been submitted. Sulfonylurea testing was obtained in 2 cases and reported positive in 1 case, described in the case presentation below.

Another cluster of cases was submitted by one site in which 4 patients used what they believed to be cocaine, but all developed an opioid toxidrome with profound hypoglycemia. One of the patients died at the scene. No testing for sulfonylureas was reported for these cases.

Case Presentation: A 37-year-old man was found unresponsive and hypoglycemic by EMS. Field glucometer read "low." EMS gave 2 mg of naloxone with no response followed by 1 ampule of D50 with some improvement in mental status. In the Emergency Department he had recurrent episodes of hypoglycemia <20 ng/dL refractory to D50 boluses; he was placed on a 10% dextrose infusion at 100 ml/hr. The patient was later given octreotide 50 mcg subcutaneously for persistent hypoglycemia. Hypoglycemic events recurred until 16 hours after presentation. Once his mental status was clear, the patient reported no history of diabetes, use of diabetic medications, or self-harm attempt. He did report using THC, methamphetamine, and fentanyl (M30 illicit pills), all confirmed on his urine drug screen and confirmatory drug testing. The Confirmatory drug test was also positive for the sulfonylurea glimepiride. The patient was not a known diabetic and denied knowingly taking this medication.

Discussion

Hypoglycemia associated with opioid exposure, particularly methadone and tramadol, is a known phenomenon.[1,2] It is unknown whether a similar risk is associated with chronic fentanyl use, though it has been postulated. In this NOSE report, however, cases of opioid exposure in which hypoglycemia was secondary to a suspected hypoglycemic adulterant in the illicit drug supply were identified.

The existence of various contaminants and/or adulterants in the recreational drug supply is well established. Motivation for drug adulteration can vary widely and includes the desire to use a cheaper but potent form of the drug intended (fentanyl in heroin), to augment the desired effect (xylazine in fentanyl), or to surreptitiously increase the bulk of a drug for increased profit (levamisole in cocaine).[7,8,9] It remains uncertain if the sulfonylurea found in this case was a true

adulterant to the opioid, a contaminant from the clandestine environment the drug was produced or packaged, or an accidental concomitant ingestion by the patient.

Sulfonylurea adulteration of opioids is not described in the literature, however it may be an underreported phenomenon given difficulties inherent in sulfonylurea detection. Benefits of substituting a hypoglycemic agent into an opioid or stimulant drug are not evident. Notably, however, glimepiride does come in a small blue pill formulation, similar in appearance to M30's (fentanyl) used by the patient **(Figure 3)**. Their similar appearance may allow for a similar appearing final product after the bulk agent is added and pressed into a new M30 pill.

Figure 3. *M30 fentanyl pill compared to glimepiride*
(Left: photo provided by Christopher Dion, Right: photo from drugs.com[10])

M30 Glimepiride

Conclusion

Our review of a single case with hypoglycemia after opioid exposure from the ToxIC Core Registry points to illicit drug contamination or adulteration with a sulfonylurea as a potential cause of the hypoglycemia. Given that it is only a single case, continued toxicosurveillance will be vital to determine the exact mechanism of opioid-related hypoglycemia, and to determine which patients are at greatest risk. Animal and human laboratory studies may be particularly useful to address this potential mechanistic linkage. In this context, the role of sub-overdose vs. overdose levels in opioid exposure, and acute vs. chronic opioid exposure in hypoglycemia can be further examined. Increased clinician awareness of hypoglycemia after opioid use is essential to the appropriate treatment of this secondary deadly condition.

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About the *Opioid Response Network (ORN)*:

ORN provides free, localized training and education for states, communities, organizations and individuals in the prevention, treatment and recovery of opioid use disorders and stimulant use. Learn more and submit a request at www.OpioidResponseNetwork.org.

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