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Emerging characteristics of isotonitazene-involved overdose deaths: a case-control study

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Abstract

Objectives: Case reports of fatal overdoses involving the novel synthetic opioid isotonitazene have prompted the U.S. Drug Enforcement Administration to consider an emergency scheduling of the drug in June 2020. We aimed to epidemiologically characterize deaths involving isotonitazene.

Methods: We conducted a case control study using publicly available mortality records from January 1, 2020-July 31, 2020 in Cook County, IL and Milwaukee County, WI. Cases (all deaths involving isotonitazene) and controls (all deaths involving other synthetic opioids) were compared on demographic characteristics, number of substances involved in fatal overdose, and co-involvement of other substances.

Results: We identified 40 fatal overdoses involving isotonitazene and 981 fatal overdoses involving other synthetic opioids. Isotonitazene deaths involved a significantly greater number of substances, and were significantly more likely to involve the designer benzodiazepine flualprazolam.

Discussion: Isotonitazene was involved in a substantial minority of synthetic opioid overdose deaths in the first seven months of 2020. Future studies characterizing its prevalence in other markets are warranted. Emergence of highly potent novel synthetic opioids underscore the need for comprehensive health services for people with opioid use disorder.

Keywords

synthetic opioids; isotonitazene; overdose; epidemiology

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INTRODUCTION

Deaths involving synthetic opioids have increased ten-fold from 2013 to 2018 in the United States, with 36,509 nationwide in 2019.[1,2] Though the largest share of synthetic opioid deaths involve fentanyl and its analogues, novel synthetic opioids are continuously emerging. Overdose deaths involving to the novel synthetic opioid isotonitazene have been reported in Europe, Canada, and the midwestern U.S.[3–6]

Isotonitazene belongs to the 2-benzylbenzimidazole group of compounds, including etonitazene, metonitazene and clonitazene that are structurally distinct and is known to be a highly potent, full mu-opioid receptor agonist in a recent *in vitro* study.[3,4] First synthesized in the 1950s, it has a similar potency to fentanyl and does not have an established medical use.[7]

Information on the pharmacological and toxicological properties of isotonitazene is limited because it has not been formally studied in humans. For example, experimental data is needed on its half-life, binding potentials, intrinsic efficacy, receptor affinity, dissociation rates, and other pharmacokinetic measures. Details of the hypothesized metabolism of isotonitazene have been recently proposedand were derived from a case series of 18 decedents with exposure.[6] There is limited information on the dosage regimens. However, isotonitazene can be present in powder, tablet or solution and can be insufflated, injected, and inhaled by smoking or vaporizing.[5] The naloxone dosing required to reverse an isotonitazene overdose has not been established; however, studies of other potent synthetic opioids suggest a higher standard dose may be required in some cases.[4,8]

In June 2020, the U.S. Drug Enforcement Administration temporarily added isotonitazene to Schedule I of the Controlled Substances Act.[9] U.S. deaths involving isotonitazene have not been epidemiologically characterized. We conducted a case-control study to compare deaths involving isotonitazene to deaths involving other synthetic opioids in two major midwestern jurisdictions.

METHODS

We reviewed publicly available mortality records from Cook County, IL and Milwaukee County, WI from January 1, 2020 to July 31, 2020 to conduct a case-control study of deaths involving isotonitazene compared to other synthetic opioid overdose deaths during the same period. These counties were chosen because among the few U.S. jurisdictions with rapidly available mortality records,[10] they are the only ones to our knowledge that had any cases involving isotonitazine. Cases included any death involving isotonitazene. Controls included deaths not involving isotonitazene where another synthetic opioid was present, including fentanyl, fentanyl analogs, 4-ANPP (despropionyl fentanyl, a fentanyl precurser), brorphine, carfentinil, U-47700, tramadol, methadone, buprenorphine or meperidine. Cases and controls were compared based on other drug involvement and demographic characteristics. Chi-square, Fisher’s exact, and t-tests (alpha level 0.05) were conducted to compare synthetic opioid overdose deaths by isotonitazene involvement. As it

involved only publicly available data, this study was designated as exempt from oversight by the Stanford University School of Medicine Institutional Review Board.

RESULTS

From January 1, 2020 through July 31, 2020, we identified 1,021 deaths involving synthetic opioids: of these, 40 (4%) involved isotonitazene (Table 1). Cases and controls did not significantly differ by age, sex, race/ethnicity, or county. Cases had an average of 4.2 drugs listed as cause of death (range 2 – 8), significantly greater ($p<0.001$) than the average of 3.1 drugs (range 1 – 13) listed for other synthetic opioid overdoses. The most common co-involved substance with isotonitazene was the designer benzodiazepine flualprazolam, which was detected in 33 of 34 Cook County deaths, and two of the six Milwaukee County deaths. Fentanyl was detected in two Milwaukee County isotonitazene-involved deaths, along with 25 of the Cook County deaths. Synthetic opioid overdose deaths that did not involve isotonitazene were significantly more likely to involve fentanyl. Beyond flualprazolam in isotonitazene deaths, fentanyl, the fentanyl precurser 4-ANPP, acetyl fentanyl, heroin, cocaine, and alcohol were the most commonly co-involved substances for both cases and controls. Two substances were uniquely detected in overdose deaths involving isotonitazene: cyclopropyl fentanyl and the antidepressant paroxetine.

DISCUSSION

As an emerging synthetic opioid, isotonitazene-involved deaths differed in key ways from other deaths involving synthetic opioids. As observed in case reports, flualprazolam was present in most deaths involving isotonitazene.[6] Our findings suggest that this reflects co-use or co-distribution of flualprazolam and isotonitazene, rather than rising background use, since flualprazolam was involved in only 8% of other synthetic opioid overdose deaths. Polysubstance involvement is common across synthetic opioid overdose deaths, but it is worth noting that isotonitazene deaths involved significantly more substances compared to other synthetic opioid overdose deaths. The spread of another lethal opioid underscores the importance of expanding health services for people with opioid use disorder.[11]

Limitations

We were only able to consider jurisdictions with recent, publicly available mortality data that also routinely test for isotonitazene. Deaths involving isotonitazene would not be detected in settings where medical examiners do not test for it, so by including only Cook County and Milwaukee, this analysis may understate the true prevalence regionally. For a previous analysis of synthetic opioid mortality, we reviewed January - April 2020 mortality records from seven other U.S. counties that have publicly available detailed drug-involved mortality.[10] Of these, none had any cases where isotonitazene was listed as a cause of death.

It is thus important for medical examiners to test for novel synthetic opioids to monitor their spread across U.S. drug markets, and for future studies to consider a broader range of U.S. drug markets as data become available. The numbers reported here may underestimate the number of isotonitazone and other synthetic opioid overdose fatalities, if some pending autopsies are later found to be positive for one or more of these substances.

CONCLUSIONS

Future studies covering more cities can shed light on whether emerging trends reported here reflect persistent differences in isotonitazone use and mortality patterns. Determining whether isotonitazone-involved overdoses require higher doses of naloxone is also a key priority, and along with the spread of fentanyl, may support increasing the standard dose of naloxone.[7,8]

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Table 1.

Characteristics of synthetic opioid overdose deaths by Isotonitazone involvement, Cook County, IL and Milwaukee County, WI, January - July 2020, n=1,021

	Isotonitazene (Case)		Other synthetic opioids (Control)		χ^2 / t-test
County					p=0.8
Cook County, IL	34	85%	815	83%	
Milwaukee County, WI	6	15%	166	17%	
Sex					p=0.5
Male	32	80%	734	75%	
Female	8	20%	247	25%	
Age (mean, SD)	44.9 (2.0)		44.9 (0.4)		p=0.5
Race/Ethnicity					
Asian	0	0%	8	1%	p=0.6
Black, non-Hispanic	20	50%	450	46%	p=0.6
Hispanic/Latino	3	8%	117	12%	p=0.4
Other/Unknown	1	3%	16	2%	p=0.7
White, non-Hispanic	16	40%	390	40%	p=1.0
Number of substances (mean, SD)	4.2 (0.2)		3.1 (0.04)		p<0.001
Synthetic opioids					
Fentanyl	27	68%	939	96%	p<0.001
4-ANPP/despropionyl-fentanyl	22	55%	635	65%	p=0.2
Acetyl fentanyl	3	8%	94	10%	p=1.0
Carfentinil	1	3%	5	1%	p=0.2
Methoxyacetyl fentanyl	1	3%	1	0.1%	p=0.07
Cyclopropyl fentanyl	1	3%	0	0%	p=0.04
Valeryl fentanyl	0	0%	5	1%	p=1.0
Butyr fentanyl	0	0%	1	0%	p=1.0
Brorphine	0	0%	4	0.4%	p=1.0
U-4770	1	3%	1	0.1%	p=0.07
Methadone	5	13%	115	12%	p=0.9
Tramadol	0	0%	44	4%	p=0.4
Buprenorphine	0	0%	9	1%	p=1.0
Flualprazolam	35	88%	75	8%	p<0.001
Cocaine	15	38%	390	40%	p=0.8
Heroin/Morphine	15	38%	467	48%	p=0.2
Alcohol	8	20%	240	24%	p=0.5
Alprazolam	3	8%	93	9%	p=0.5
Gabapentin	2	5%	57	6%	p=1.0
Methamphetamine	1	3%	30	3%	p=1.0
Oxycodone	1	3%	28	3%	p=1.0
Diphenhydramine	1	3%	24	2%	p=1.0
Xylazine	1	3%	14	1%	p=0.5

	Isotonitazene (Case)		Other synthetic opioids (Control)		χ^2 / t-test
Topiramate	1	3%	2	0.2%	p=0.1
Paroxetine	1	3%	0	0%	p=0.04
MDMA	1	3%	13	1%	p=0.5
Cyclobenzaprine	1	3%	13	1%	p=0.5
Chlorpheniramine	1	3%	1	0%	p=0.07
Total	40	100%	981	100%	