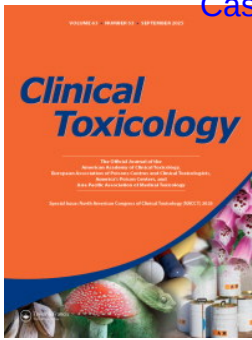


EXHIBIT C



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KEYWORDS

Bromazolam; benzodiazepines; NPS

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29. Case Control study of mitragynine deaths vs. all cause deaths with mitragynine found on autopsy

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Background: Kratom has been used with increasing frequency in the US to manage pain, drug withdrawal, and mental health. The active ingredient, mitragynine (MTG), has been implicated in drug interactions and death. We sought to identify risk factors for death in subjects with MTG compared to polysubstance exposure.

Methods: We contacted each medical examiner (ME) in a single state to obtain the autopsy records and toxicology reports over a 5-year period for all decedents with MTG identified as the cause of death (MD). As a comparison group, we collected all of the patients with MTG present on autopsy, but not deemed to be the cause of death from a single county (PD). Four trained personnel used a standardized data extraction tool to record information on demographics, medications, co-ingestions, medical history, serum drug levels, autopsy findings, location of death, and perimortem circumstances. We used comparative statistics to determine differences in MTG concentration, other drug levels, and medical co-morbidities between the groups.

Results: We obtained 38 cases of MTG attributable death (MD) from medical examiners throughout our state. Using the "WHO-UMC Causality Tool" and the "Liverpool Causality Assessment Tool" experimenters excluded 4 of these due to a likely alternate cause of death. We obtained 111 subjects who died from other causes (PD) but were found to have MTG present at autopsy, 3 of whom were excluded due to MTG likely being the primary cause of death. Demographic factors were similar in both groups with regards to age, BMI, race, and gender. In the PD group, fatal co-ingestions were the most common cause of death including 84 fentanyl (mean level 19.1 ng/mL), 6 morphine, 29 ethanol (mean 63 g/dL), and 49 cocaine. Comparing MD v PD, more had no other substance in their system (19 v 0.9%), pulmonary edema (55.6 v 31.53%), aspiration (5.6 v 4.7%), coronary plaque 21.05 v 14.41%), hepatomegaly (47 v 14%), cerebral edema (47.36 v 0.09%), and cardiomegaly (47.36 v 11.79%). The mean MTG level for the MD group was 2486 ng/mL (95%CI 1607–2863) v 179 ng/mL (95%CI 217–375) for the PD group.

Conclusions: ME sometimes misclassify the cause of death in patients with MTG exposure. Majority of PD deaths are due to fentanyl. Subjects who died from MTG toxicity had significantly higher concentrations compared to those with other fatal substances. Kratom appears to be lethal and its effectiveness in management of addiction, pain, and mental health disorders may be overestimated. This information may be helpful in determining cause of death from polysubstance deaths. Although MTG is sold as a potential aid for withdrawal, a substantial number of users are identified post mortem with opioids on board.

KEYWORDS

Kratom; addiction; mitragynine

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30. Clinical features of five suspected opioid overdose patients with medetomidine and bromazolam detected in biological samples

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Background: Illicit psychoactive substances may contain a wide array of adulterants, including benzodiazepine derivatives and medetomidine, both of which have recently been detected sporadically in North America. We describe the clinical characteristics of five patients with atypical opioid overdose features and medetomidine and bromazolam detected in biological samples.

Case series: Over three hours, five patients presented to one urban emergency department after being found down from suspected opioid use. Due to the presence of bradycardia, hypertension, and sedation refractory to naloxone administration, our poison center was consulted. All patients received prehospital naloxone, one with transiently improved mental status. On hospital arrival, all patients were unresponsive with miosis. Two patients demonstrated hypopnea and received parenteral naloxone, one of whom transiently improved and was placed on a naloxone infusion. All patients developed bradycardia during hospitalization, with median nadir heart rate of 39 beats/min (range 35–47) occurring at median 8.5 hours from presentation (range 0.5–11.5), which normalized in a median of 19 hours (range 10.5–22.5) from presentation. The median peak systolic blood pressure was 188 mmHg (range 152–246), occurred at a median of 0.5 hours from presentation (range 0.5–14.5), and normalized in a median of 16.5 hours from presentation (range 8.5–40). All patients were admitted to an intensive care unit and all ultimately self-discharged, with a median duration of hospitalization of 50 hours (range 18–92.5). Serum ($n=4$) or urine ($n=3$) samples were collected from all patients within 24 hours of presentation and prior to any in-hospital dexmedetomidine administration. Comprehensive qualitative toxicological drug testing was performed by liquid chromatography quadrupole time-of-flight mass spectrometry, and data processed with an extensive database of more than 1,200 substances. Medetomidine, bromazolam, fentanyl, and xylazine were detected across all seven samples. In three samples with sufficient quantity for detection, both medetomidine isomers were detected.

Discussion: Medetomidine and bromazolam have been reported as illicit substance adulterants, but prolonged hypertension in addition to bradycardia and sedation has not been previously described. Hypertension may be attributable to medetomidine, the dex-isomer of which produces a biphasic effect on arterial blood pressure, with a decrease at low doses and elevation with increasing concentrations. Precipitated

opioid withdrawal could also have contributed to the elevated blood pressure seen in these patients, as all received naloxone, and the highest blood pressure was recorded in the only patient who received a naloxone infusion. Bromazepam likely also contributed to sedation, though the extent cannot be determined from this series. Though these patients did not provide details related to their exposure and presented independently, all had a prior history of presentations for opioid use, and their close temporal and geographical proximity suggests exposure from the same adulterated supply.

Conclusions: Medetomidine and bromazepam may co-occur as adulterants in the illicit psychoactive substance supply and produce prolonged and marked bradycardia, hypertension, and sedation. Clinicians should be aware of these effects, and their presence in a patient with suspected opioid overdose should prompt consideration of these adulterants.

KEYWORDS

Adulterant; contaminant; overdose

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31. Inappropriately controlled and inappropriately understood – risk factors associated with Kratom deaths in a single state

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Background: Kratom, or as it is more commonly known as thang, thom, or ketum is a drug sold without regulation in the US. Kratom, and its active ingredient mitragynine (MTG) has been implicated in many deaths. The concentration of MTG and specific cause of death are largely uncertain. The objective of this study is to identify risk factors and mechanism for death in patients with MTG exposure.

Methods: We contacted each medical examiner (ME) office in a single state to obtain the ME records and autopsy reports over a 5-year period for all decedents with MTG identified as the cause of death. Using the WHO-UMC causality tool and the Liverpool causation assessment tool, we excluded cases in which there was another more likely cause of death identified. Two trained personnel used a standardized data extraction tool to record information on demographics, medications, co-ingestions, medical history, serum levels of drugs, autopsy findings, location of death, and perimortem circumstances. We used descriptive statistics to identify trends amongst decedents and determined mean and ranges for MTG concentration in.

Results: Forty cases of death by MTG were identified from the ME in a single state who responded to our initial request. Four were excluded due to likely alternative causes of death. In the remaining subjects, 24 (63.16%) were male, 35 (92.1%) were white, mean BMI was 27.25, mean age was 39.8 years, and 35 cases were deemed to be accidental death. Mean MTG levels were 2486ng/mL (range 12–6100). Postmortem toxicology revealed the presence of another medication or substance in 81.6% of cases including: 7 ethanol (median level 0.067mg/dl), 3 cannabis, 2 methamphetamine, 10 benzodiazepines, and 31 with other prescription drugs. None of these patients had fentanyl, heroin, or morphine detected, but 3 had nontoxic concentrations of other narcotics. Autopsy findings were variable: 8 (21.05%) had signs of minor trauma (most commonly

facial abrasions), none had tongue biting, 18 (47.36%) had cardiomegaly, 8 (21.05%) had coronary plaques, none had MI, 20 (55.26%) had pulmonary edema, 2 (5%) had aspiration, 18 (47.37%) had hepatomegaly, and 6 (15.79%) had cerebral edema. None of these physical findings were deemed.

Conclusions: Although the mechanism remains uncertain, MTG deaths may be multifactorial. Subjects who died from kratom exposure were likely to be white males taking other medications, and have high concentrations of MTG.

KEYWORDS

Kratom; mitragynine; demographics

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32. Characterizing presence of novel psychoactive substances present in positive urine drug screen samples in central Illinois

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Background: A recent rise of novel psychoactive substances (NPS) that are increasingly being added to recreational substances to enhance the effects and stretch the supplies poses an additional threat in an already complex opioid crisis. The effects of these synthetic drugs are not well-researched. From a public health perspective, it is imperative to understand the multi-faceted nature of the opioid epidemic in order to appropriately prevent and respond to fatal and non-fatal drug overdoses. While a majority of studies and preventative efforts are conducted in an urban setting, there is a lack of surveillance of these drugs in rural communities. We implemented a short-term toxicology surveillance program to survey the rate of illicit drugs in the local urban and surrounding rural communities and to understand the presence of novel psychoactive drug adulteration in individuals that test positive for illicit drugs in order to improve future drug contamination monitoring and overdose intervention efforts.

Methods: We performed a cross-sectional analysis of discarded urine samples collected from patients from urology and pelvic wellness clinics in central Illinois during a 5-month period (February 2024–July 2024) to survey the presence of illicit drugs in the community. Urine specimens considered biowaste were collected from urology and pelvic wellness clinics at the end of each day. Any patient under 18 years of age was excluded. Patient data were extracted from electronic health records. Urine was tested for fentanyl (Germain Laboratories Inc., San Antonio, TX) and a panel of 14 drugs of abuse (McKesson, Annandale, VA). Samples that tested positively for fentanyl or any of the 14 illicit drugs except THC or TCA were sent for further laboratory testing of NPS (NMS Labs, Horsham, PA), which included a panel of 42 analytes (i.e., designer benzodiazepines, designer opioids/synthetic fentanyl derivatives, stimulants and hallucinogens) and xylazine.

Results: We analyzed 800 urine specimens from which 1.5% ($n=12$) had a positive fentanyl strip and 35.5% ($n=282$) had a positive drug panel, with THC, TCA, benzodiazepines, and morphine having the highest positivity. Patients that had