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Non-fatal overdose with a new synthetic opioid

SHORT CASE REPORT

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A young man experienced respiratory arrest at home, and cardiopulmonary resuscitation was performed. The patient received naloxone with good effect and was admitted to hospital. He disclosed opioid use, but no substances were detected in routine drug screenings.

A young man who had experienced respiratory arrest was found in his bedroom. The Emergency Medical Communication Centre was alerted, and cardiopulmonary resuscitation was performed for 25 minutes before the air ambulance arrived. The initial rhythm analysis showed sinus rhythm, and 0.8 mg of intravenous naloxone was administered based on clinical indication (1). The patient then regained consciousness. On the way to the hospital, 0.8 mg of naloxone was also administered intramuscularly, followed by an additional 0.4 mg intramuscularly in the emergency department, totalling 2.0 mg of naloxone.

The patient was alert and oriented upon arrival at the emergency department. His vital parameters were stable: pulse 108 beats per minute, blood pressure 152/92 mmHg, oxygen saturation (sO_2) 86 %, respiratory rate 14 and temperature 36.8°C. Arterial blood gas without supplemental oxygen showed pH 7.36 (reference range 7.36–7.44), pO_2 7.1 kPa (> 10.1), pCO_2 6.5 kPa (4.5–6.1), lactate 1.6 mmol/L (0.4–1.3) and HCO_3^- 27 mmol/L (22–26). Blood tests showed leukocytes 18.4 × 10^9/L (4.1–9.8 × 10^9/L), glucose 11.5 mmol/L (4.0–6.0), troponin T 23 ng/L (< 15) and CRP < 1 mg/L (< 5). The blood test was negative for ethanol. In the emergency department, oxygen therapy was initiated with 2 litres via nasal cannula, and the pO_2 levels normalised before discharge.

The patient stated that he had purchased what was supposed to be opioids in a nasal spray bottle from an acquaintance a few weeks earlier, but he had not used the spray until the evening of the incident. The nasal spray was intended for relaxation purposes, and he had been instructed to titrate the dose to achieve the effect. On the night in question, he claimed to have taken two doses without noticing any effect and subsequently took two more doses in quick succession. The time between the first dose and when he was found by his family was likely just under an hour.

The patient had used cannabis in the past, but denied using other drugs. Suspecting that the nasal spray contained fentanyl, serum and urine samples were taken for drug analysis, two and nine hours after the first dose, respectively. A negative result in the drug screening for urine was reported the same morning, and the patient was discharged. The nasal spray container was destroyed before anyone thought to analyse its contents.

Based on a clinical suspicion of opioid poisoning, a specific analysis was ordered in the hope of detecting the agent, but the analysis yielded no results other than naloxone (5.77 µmol/L). The duty doctors in clinical pharmacology and intensive care decided to conduct a 'broad substance search' to look for a

synthetic high-potency opioid outside the standard repertoire of drugs. After a couple of weeks, we found 1.6 nmol/L and 0.32 nmol/L of protonitazene in the blood and urine samples, respectively.

Protonitazene is a highly potent synthetic opioid that has not previously been detected in Norway. The Norwegian CBRNe Centre of Medicine was notified, who further informed relevant organisations and institutions that a highly potent opioid could be in circulation. Users were advised not to consume substances when alone and were informed that repeated doses in the absence of effect increases the risk of overdose (2).

Discussion

Drug testing can be carried out using non-specific or specific analysis methods (3). Most non-specific methods are based on the principle of immunoassay testing (antibody-antigen binding). As the non-specific analysis was negative, a specific analysis was performed using liquid chromatography quadrupole time-of-flight mass spectrometry (LC-Q-TOF-MS). This was also negative. Using the same instrument, a broad substance search was then carried out against a large catalogue of substances, where thousands of different drugs and medications can potentially be detected.

It was known that nitazenes were in circulation in Europe due to the warning issued by the European Monitoring Centre for Drugs and Drug Addiction (4). We observed that the clinical and chemical properties of the substance, such as fragmentation patterns and retention time, might be consistent with that reported in the literature about nitazenes, also known as 2-benzyl benzimidazole opioids.

Using reference material with different nitazenes, we confirmed that the blood sample contained protonitazene and two metabolites. A very low concentration of the substance was detected in the serum, which may indicate high potency, short half-life and/or potent metabolites. Protonitazene can be 3–10 times as potent as fentanyl (5, 6).

Since the 2000s, numerous new psychoactive substances (often abbreviated to NPS) have appeared. These are defined as substances with the potential for misuse, either in pure form or in a preparation, which are not scheduled under the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances and can pose a threat to public health.

Over the past decade, the prevalence of synthetic opioids has increased. Fentanyl derivatives, largely produced in China, initially dominated the market. Nitazenes entered the market after China introduced stricter regulations on the production of fentanyl derivatives (7, 8). Nitazenes were developed in the 1950s but were never utilised due to the high risk of overdose, partly as a result of potent metabolites (5). In 2019, isotonitazene was the first drug that was discovered, and this dominated the market until it was made illegal in the United States and other nitazenes took over (8).

The time from the production of a new substance to its discovery is often lengthy. Where there is a strong suspicion of drug use, clinicians should not settle for a negative result. The laboratory should be contacted when a clinician believes the test result is incorrect. In the case of our patient, it took two weeks to conclude that the samples contained protonitazene.

In this patient, identification of the drug had no implications for the treatment. The finding was important, nevertheless, because it meant the public could be informed and warned of the risk, thereby hopefully preventing further overdoses. Another case with a fatal outcome was identified in a different part of the country during the same period. Nitazenes have subsequently been listed in Norway's regulations on narcotics (9).

Since submission of the manuscript, new cases of nitazene poisonings have been reported in Norway (10, 11).

The patient has consented to publication of this article.

The article has been peer-reviewed.

LITERATURE

1. Giftinformasjonen. Fentanyl - behandlingsanbefalinger ved forgiftning. https://www.helsebiblioteket.no/forgiftninger/legemidler/fentanyl-behandlingsanbefaling-ved-forgiftning Accessed 30.6.2023.

2. Kalveland J. Oslo universitetssykehus advarer mot farlig stoff i omløp. Dagens medisin 18.11.2022. https://www.dagensmedisin.no/oslo-universitetssykehus-advarer-mot-farlig-stoff-i-omlop/199637 Accessed 3.1.2024.

3. Farmakologiportalen. https://www.farmakologiportalen.no/ Accessed 30.6.2023.

4. EMCDDA. New psychoactive substances: 25 years of early warning and response in Europe. https://www.emcdda.europa.eu/publications/rapid-communication/update-eu-early-warning-system-2022_en Accessed 20.12.2023.

5. The Center for Forensic Science Research & Education. New synthetic opioid protonitazene increasing in prevalence as "nitazenes" gain traction across the United States and Canada. https://www.cfsre.org/nps-discovery/public-alerts/new-synthetic-opioid-protonitazene-increasing-in-prevalence-as-nitazenes-gain-traction-across-the-united-states-and-canada Accessed 30.6.2023.

6. WHO. Critical review report: protonitazene. https://cdn.who.int/media/docs/default-source/controlled-substances/45th-ecdd/protonitazene_draft.pdf?sfvrsn=dfb007b3_1 Accessed 30.6.2023.

7. Prekupec MP, Mansky PA, Baumann MH. Misuse of novel synthetic opioids: a deadly new trend. J Addict Med 2017; 11: 256–65. [PubMed]

[CrossRef]

8. Montanari E, Madeo G, Pichini S et al. Acute intoxications and fatalities associated with benzimidazole opioid (nitazene analog) use: A systematic review. Ther Drug Monit 2022; 44: 494–510. [PubMed][CrossRef]

9. Helse- og omsorgsdepartementet. Forskrift om narkotika (narkotikaforskriften). https://lovdata.no/dokument/SF/forskrift/2013-02-14-199 Accessed 20.11.2023.

10. Solås VS, Andersrød BV, Strømbeck SM. Overdosedødsfallet i Halden: Har funnet stoff 100 ganger sterkere enn morfin. NRK 20.10.2023. https://www.nrk.no/osloogviken/overdosedodsfallet-i-halden_-pavist-metonitazen-1.16603675 Accessed 20.11.2023.

11. Five ML. Advarer mot livsfarlig stoff: – Finnes over hele landet. TV2 11.12.2023. https://www.tv2.no/nyheter/innenriks/advarer-motlivsfarlig-stoff-finnes-over-hele-landet/16287608/ Accessed 13.12.2023.

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