Fatal intoxication with N-ethylpentylone: a case report

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ABSTRACT
Synthetic cathinones represent the latest genre of new drugs of abuse, which are increasing in popularity in part because they are readily available and because they are not detected by routine drug testing. They provide a cheaper substitute to stimulants such as methamphetamine and cocaine and are sold on the internet and in retail establishments as ‘bath salts,’ ‘plant food,’ or ‘research chemicals.’ We report a case involving a 21-year-old male who suffered arrest-related death due to intoxication with N-ethylpentylone, a new cathinone derivative. He reportedly left his house to smoke marijuana and returned displaying extremely odd behavior. The patient was unresponsive upon presentation to the emergency room and was intubated after suffering cardiac arrest. Clinical laboratory values revealed elevated lactic acidosis, hyperkalemia, rhabdomyolysis, and renal injury. His condition continued to worsen despite medical management. Sudden cardiac arrest occurred again 72 hours into his hospital stay and the patient was pronounced dead. Post-mortem toxicology testing with gas chromatography and mass spectrometry determined the presence of N-ethylpentylone in the urine. This case report details the behavior effects, clinical presentation, and autopsy findings for N-ethylpentylone drug intoxication.

1. Introduction
Cathinone is a beta-ketone amphetamine analog that was originally extracted from the fresh leaves of the khat plant (Catha edulis), native to East Africa and the Arabian Peninsula. Historically the plant was chewed for its stimulant effects [1,2]. The synthesis of synthetic cathinones has created a new and highly dangerous genre of drugs of abuse, available on the internet and in retail establishments as ‘bath salts’ or ‘plant food’ [3].

These drugs provide a cheaper substitute for stimulants such as methamphetamine and cocaine [3]. N-ethylpentylone goes by the street name of bk-Ethyl-k, BK-EPD, or Molly. Clinical effects include euphoria, increased libido, enhanced tactile sensation, and increased alertness, but some effects can be severe reactions such as hyperthermia, seizures, arrhythmia, hallucinations, and death.

In 2011, cathinones such as mephedrone, 3,4-methylenedioxyxymethamphetamine, methedrone, and methylone were named under Schedule I of the Controlled Substances Act. However, N-ethylpentylone currently is not listed as a Schedule I substance in the USA, Canada, or Europe [4,5]. Makers of new designer drugs continue to avoid legal risk by slight alterations of chemical structure, and these drugs have become more readily available. The number of reported emergency room visits and fatal outcomes involving these drugs has increased in recent years [2,6]. This case report illustrates the behavior effects, clinical presentation, and potential fatal outcome of N-ethylpentylone drug intoxication.

2. Case report
A 21-year-old man left his house to reportedly smoke marijuana. When he returned, per his girlfriend, he was ‘acting crazy.’ Law enforcement was dispatched. He was described as combative, confused, and sweating heavily. Paramedics administered 5 mg of intramuscular haloperidol. He went into cardiac arrest shortly thereafter. Advanced cardiac life support protocol was initiated, and return of spontaneous circulation was achieved within 3 minutes. Upon arrival at the emergency room his blood pressure was 95/55 mmHg, heart rate 126 bpm, respiratory rate 25 bpm, and oxygen saturation 99% on 40% FiO2. On physical examination, he was noted to have multiple abrasions on his face, sluggish pupillary reflexes, negative vestibulo-ocular reflex, and myoclonus at the right lower extremity. Initial electrocardiogram showed sinus rhythm with premature atrial complexes, ST depression in inferior leads, and corrected QT interval of 403 ms.

Clinical laboratory analysis revealed potassium 6.8 mmol/L, glucose 28 mg/dL, creatinine kinase
116,550 IU/L, lactic acid 28 mg/dL (without an osmolar gap), aspartate aminotransferase 12,374 IU/L, alanine aminotransferase 7,649 IU/L, and creatinine 1.70. Arterial blood gas showed severe metabolic acidosis with pH 6.80. Other laboratory values revealed elevated troponins and acute kidney injury. The patient was admitted to the intensive care unit and treated with hypothermia cooling measures, intravenous fluids, and bicarbonate.

Toxicology screening was positive only for cannabionoid and revealed an ethanol level of 12 mg/dL. Special testing for synthetic cannabionoid metabolites and 25I-NBOMe (5-HTA2 receptor agonist) was negative. Computed tomography of the head showed no abnormalities. However, magnetic resonance imaging of the brain showed bilateral restricted diffusion in the posterior parietal and occipital regions suggesting profound cerebral hypoxia. During the hospital course his lactic acidosis improved to 3.2 mmol/L with intravenous fluids, but his kidney function continued to worsen and creatinine kinase rose to 451,126 IU/L. On day 2, the patient was started on continuous renal replacement therapy due to oliguria and rising creatinine levels. Despite supportive treatment, he developed hypothermia with a temperature of 34.3°C, persistent hypocalcemia, and disseminated intravascular coagulation. On day 3, he developed severe hypotension requiring vasopressors for hemodynamic support. Approximately 72 hours after admission he went into cardiac arrest. Cardiopulmonary resuscitation was performed for 30 minutes and the patient was pronounced dead. Lab results during his hospitalization confirmed profound organ dysfunction and metabolic derangement in a previously healthy individual (Table 1).

An autopsy was performed at the Office of the Chief Medical Examiner in response to a concern about possible misconduct by law enforcement. Post-mortem toxicology testing using gas chromatography and mass spectrometry found N-ethylpentylone in the urine. The official cause of death was drug intoxication with N-ethylpentylone based on these autopsy findings, the clinical presentation, and the hospital course.

### 3. Discussion

N-ethylpentylone is a designer drug that is misused as a ‘legal high’ for its stimulant and psychoactive effects. The Drug Enforcement Agency reported 121 cathinones identifiers during the first half of 2017, and N-ethylpentylone accounted for approximately 50% of the identifiers [7]. Based on our case and a similar case [8], N-ethylpentylone toxicity appears to adversely effect every organ system. Our patient experienced cardiac arrest, rhabdomyolysis, renal

| Test                           | Day 1 (initial labs) | Day 1 | Day 2 | Day 3 |
|--------------------------------|----------------------|-------|-------|-------|
| pH                             | <6.80                | 7.27  | 7.41  | 6.85  |
| pCO2, mmHg                     | 48.0                 | 29.4  | 29.4  | 61.2  |
| pO2, mmHg                      | >500.0               | 207   | 98.1  | 41.1  |
| HCO3, mEq/L                    | 6.3                  | 13.7  | 18.4  | 8.4   |
| Oxygen saturation              | 100                  | 98    | 99    | 100   |
| Fraction of inspired oxygen, % | 100                  | 40    | 40    | 30    |
| Na, mEq/L                      | 142                  | 134   | 138   | 137   |
| K, mEq                         | 6.8                  | 5.7   | 3.7   | 3.6   |
| Chloride, mg/dL                | 109                  | 101   | 104   | 101   |
| CO2, mg/dL                     | 9                    | 16    | 20    | 8     |
| Blood urea nitrogen, mg/dL     | 24                   | 21    | 42    | 16    |
| Creatinine, mg/dL              | 1.70                 | 2.21  | 4.94  | 2.60  |
| Glucose, mg/dL                 | 204                  | 116   | 105   | 213   |
| Estimated glomerular filtration rate, mL/min | >60 | 24 | 18 | 39 |
| Calcium, mmol/L                | 6.6                  | 5.9   | 5.4   | 6.0   |
| Magnesium, mg/dL               | 3.0                  | 5.8   | 2.2   | 2.5   |
| Phosphorus, mg/dL              | 9.5                  | 9.1   | 7.0   | 6.6   |
| Anion gap mEq/L                | 24                   | 17    | 18    | 28    |
| Aspartate Aminotransferase, IU/L| 681                  | 3,218 | 12,374| 6,611 |
| Alanine aminotransferase, IU/L | 755                  | 1,556 | 7,649 | 4,674 |
| Total billirubin, mg/dL        | 0.5                  | 1.54  | 5.2   | 2.30  |
| Albumin, g/dL                  | 3.9                  | 2.7   | 2.0   | 3.3   |
| Lactic acid, mmol/L            | >15.5                | 11.4  | 9.5   | 15.8  |
| White blood cell count, K/UL   | 5.7                  | 25.2  | 20.3  | 0.5   |
| Red blood cell count, K/UL     | 4.48                 | 5.82  | 4.72  | 3.51  |
| Hemoglobin, g/dL               | 12.9                 | 17.2  | 13.5  | 9.9   |
| Hematocrit, %                  | 42.4                 | 47.7  | 39.7  | 31.2  |
| Platelet count, K/UL           | 241                  | 250   | 83    | 13    |
| Neutrophil, %                  | 58.7                 | 86.6  | 91.6  | 17.3  |
| Lymphocyte, %                  | 35.5                 | 6.3   | 2.3   | 65.2  |
| Creatinine kinase, IU/L        | 116,550              | –     | 451,160 | 420,032 |
| Troponin I, ng/mL              | 18.900               | –     | –     | –     |
| Prothrombin Time, seconds      | 24.8                 | 17.0  | >100.0| >100.0|
| Activated partial thromboplastin time, seconds | – | 37.9 | – | – |
| International normalized ratio | 2.2                  | 1.4   | >13.4 | >13.4 |
failure, hepatic failure, anoxic brain injury, coagulopathy, and death.

Little is known about the exact pharmacology of N-ethylpentylone, and we have limited understanding of synthetic cathinone pharmacokinetics in general. Similar to amphetamines, synthetic cathinones act on the central nervous system by inhibiting monoamine neurotransmitters dopamine, serotonin, and norepinephrine via facilitation of extracellular release and reuptake inhibition [3], which explains reported effects of euphoria, increased libido, interpersonal openness, and alertness [9]. Despite structural similarities, synthetic cathinones differ from amphetamines in their affinity against transporters and their mechanisms of function. These differences have the potential to change the psychoactive and physiological impact of each synthetic cathinone [8,10].

In the current case, haloperidol may have contributed to the patient’s cardiac arrest. Haloperidol can abnormally prolong corrected QT (QTc) interval, potentially leading to torsade de pointes, a life-threatening arrhythmia [11]. The combination of N-ethylpentylone with a relatively high dose of haloperidol may have augmented the cardiac effects of haloperidol. We do not have a documented heart rhythm during the event because our patient regained return of spontaneous circulation in 3 minutes. However, cardiac arrest as a result of haloperidol is unlikely in this patient because QTc was not prolonged on initial electrocardiogram. His clinical outcome may have been a result of extreme sympathetic activity resulting in vasoconstriction and hypoperfusion [12], or it may have been due to direct cell drug toxicity. This question has not been well studied.

Clinicians should be aware of this drug and should recognize signs and symptoms of intoxication with N-ethylpentylone, including behavioral effects, tachycardia, acidosis, rhabdomyolysis, and multi-organ failure. Guidelines for clinical management are not yet available. Therefore, supportive measures with intravenous fluids, bicarbonate, and mechanical ventilation should be considered standard treatment for cathinone drug intoxication. The role of early renal replacement therapy to improve outcomes has not been studied. However, N-ethylpentylone is a small water-soluble molecule [2] and theoretically can be removed by renal replacement therapy. This therapy is worth consideration if there is a high clinical suspicion for intoxication with synthetic drugs.

There has been only one report of fatal intoxication with N-ethylpentylone [8]. In contrast to that patient, our patient did not have any other comorbidities or confounding illness that may have contributed to his death. His unfortunate clinical outcome seems to have resulted exclusively from drug intoxication with N-ethylpentylone.

N-ethylpentylone is a new synthetic cathinone that is a serious health concern due to its ease of availability, psychological effects, and potential for addiction. The rapid spread of synthetic cathinones [13–16] and their unpredictable effects, warrants consideration for clinical research to understand the pharmacology and to develop effective treatment to prevent death.

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