Suicide Due to Cyclizine Overdose

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Cyclizine is an antihistamine with sedative effect used to treat motion sickness. A few studies have reported on cyclizine abuse among teenagers, and cyclizine abuse has been reported among opioid dependants receiving methadone, with the combination having been reported to produce strong psychoactive effects. Few reports exist on the possible toxic effects of cyclizine, and it is regarded as a safe drug most often sold as a non-prescription/over-the-counter drug. Very few cases of fatalities resulting from cyclizine overdose can be found in the literature. We present a case where a 22-year-old female was found unconscious in a park and was declared dead at the hospital after 1 h of attempted resuscitation. She had previously attempted suicide several times by drug overdose. In a nearby car belonging to the victim a bottle of beer, acetaminophen, and venlafaxine in addition to ethanol. Further specified in the report from the police. Information from the literature (2–4), and nothing from the last 20 years. We report on a case of suicide where cyclizine was found to be the principal drug and question the safety of this drug.

Introduction

Cyclizine is an antihistamine with sedative effect most often used to treat nausea, vomiting and dizziness associated with motion sickness. The usual dose for adults and teenagers is 50 mg taken orally 30 min before travel. The dose may be repeated every 4–6 h, but no more than 200 mg should be taken during 24 h. A therapeutic concentration range is reported to be 0.1–0.25 mg/L (1). Few reports exist on the possible toxic effects of cyclizine and it is regarded as a safe drug, most often sold as a non-prescription/over-the-counter drug. Very few reports of fatalities resulting from cyclizine overdose can be found in the literature (2–4), and nothing from the last 20 years. We report on a case of suicide involving cyclizine.

Case history

A 22-year-old woman was found unconscious in a park and was declared dead at the hospital after ~1 h of attempted resuscitation. She had previously attempted suicide several times by drug overdose. In a nearby car belonging to the victim a bottle of beer, empty packages for tablets and plastic bags containing drugs were found. Types and amounts of drugs and empty packages were not further specified in the report from the police. Information from next of kin suggested that she could have taken meclozine, paracetamol and venlafaxine in addition to ethanol.

The deceased was a slender, young woman, length 153 cm, weight 53 kg. During autopsy no injuries or signs of violence were observed. Multiple scars on the skin suggested foregoing self-inflicted mutilation. Remnants of tablets were found in the stomach with aspiration into the airways. The lower lobes of the lungs were congested, with a total lung weight of 955 g. Furthermore, histological examination revealed an excess of fluid in the pulmonary tissue (large areas with edema), aspirated material in small bronchioli, early signs of inadequate myocardial circulation and cellular necrosis in liver tissue. No signs of edema were seen in other organs, and no further findings were made at autopsy.

Permission to publish the case was obtained from next of kin.

Methods

Whole blood from the femoral vein, urine and stomach content were collected during autopsy and screened for drugs of abuse and medicinal drugs. GC–MS screening of the stomach contents revealed presence of cyclizine and meclozine. Cyclizine and meclozine concentrations in blood were determined using a UPLC–MS-MS method. Quantification of femoral blood revealed a high concentration of cyclizine (16 mg/L), a low concentration of meclozine (0.2 mg/L) and ethanol 0.16 g/dL. No other medicinal drugs or drugs of abuse were detected. We report on a case of suicide where cyclizine was found to be the principal drug and question the safety of this drug.

Determination of cyclizine and meclozine

Cyclizine was supplied by Sigma (Sigma-Aldrich Norway AS, Oslo, Norway), meclozine by Alltech (Alltech Associates, Inc. Deerfield, IL, USA) and imipramine-d3 (internal standard) from Cerilliant® (Round Rock, TX, USA). Methanol (HPLC-grade) and acetonitrile (ACN, far UV HPLC) were purchased from LAB-SCAN (Dublin, Ireland). Deionized water was obtained from a Milli-Q UF Plus water purification system (Millipore, Bedford, MA, USA). Human whole blood was supplied by the Blood Bank at Oslo University Hospital, Ullevaal, Norway. Stock solutions of cyclizine and meclozine were prepared in methanol and
working standard solutions (0.05–1.3 mg/L for cyclizine and 0.08–2.0 mg/L for meclozine) were prepared in water from the stock solutions. Quality control (QC) samples were prepared independently at two concentration levels (0.08 and 0.8 mg/L for cyclizine, 0.1 and 1.2 mg/L for meclozine). The sample was diluted 100 times with blank blood bank blood before analysis of cyclizine. To an aliquot of 100 μL whole blood were added 25 μL of internal standard solution imipramid-d₃ (1.4 mg/L) and 250 μL of cold acetonitrile. The samples were immediately agitated for 1 min and thereafter put in a deep freezer for a minimum of 10 min. The samples were centrifuged at 4500 rpm (3900 × g) for 10 min. One hundred microliters from ACN layer was transferred to the autosampler vials and diluted with 100 μL water.

The samples were analyzed in accordance with a previously published UPLC–MS-MS method (A) on a Waters Aquity UPLC-system (Waters Corporation, Milford, MA, USA), applying an Acquity HSS T3-column 100 × 2.1 mm ID (Waters Corporation, Milford, MA, USA), with an average pore size of 100 Å and a particle diameter of 1.8 μm. The mobile phases consisted of A: 10 mM ammonia formate buffer, pH 3.1, and B: methanol. A Waters Quattro Premier XE tandem mass spectrometer, equipped with a Z-spray electrospray interface, was used for all analyses. Positive ionization was performed in the multiple reaction monitoring mode, with one transition for cyclizine (267.2 > 167.1) and imipramide-d₃ (284.1 > 89.0) and two transitions for meclozine (391.2 > 201.1, 391.2 > 166.1). Quantification was performed with Targetlynx using Masslynx 4.1 software. The retention times were 3.5, 3.7 and 5.0 min, respectively. A five-point calibration curve was used for cyclizine quantification, and a three-point calibration curve for meclozine. They were linear with correlation coefficients greater than 0.997 for both analytes. QC samples (two replicates at each level) had <15% deviation from nominal values. The lowest calibrator had signal-to-noise ratios >10 for all transitions. The blank blood sample had no interfering signals.

Results
The initial screening of femoral blood and urine for a number of selected alcohols, drugs of abuse and medicinal drugs only revealed the presence of ethanol in a concentration of 0.16 g/dL in blood and 0.18 g/dL in urine. The ingestion of ethanol was confirmed by the presence of the metabolites ethyl glucuronide (1.9 mg/L) and ethyl sulfate (1.2 mg/L) in blood. No other illicit or medicinal drugs include in the screening program were found. Further screening of the stomach contents did however revealed the presence of cyclizine and meclozine, which lead to the quantification of these drugs in femoral blood. Quantification of femoral blood revealed a high concentration of cyclizine (16 mg/L) and a low concentration of meclozine (0.2 mg/L).

Discussion
We report on a case of suicide where cyclizine was found to be the principal drug. Cyclizine is viewed as having low risk of adverse outcome, with few reports of adverse but non-lethal outcomes after ingestion of large amounts of the drug (10, 11). Also very few reports of lethal intoxications exists (2–4), and some cases it is the combination of cyclizine and dipipanone (strong opioid analgesic) that is thought to be the cause of death (12, 13). Cyclizine is antihistamine which also exerts a central anticholinergic effect. The mechanism for its antiemetic effect is however not well understood. Cyclizine is used as an antiemetic in many countries, it is regarded as well tolerated and most often sold as an over-the-counter drug, even though few studies exist. As mentioned, however, a few reports exists as to the use of cyclizine as a drug of abuse known to produce strong psychoactive effects (10, 14, 15), and two previous reports have found the drug to be involved in suicide (3, 4). A few studies have reported on cyclizine abuse among teenagers (14) due to its anticholinergic properties with the possibility of inducing hallucinations. Also cyclizine abuse has been reported among opioid dependents receiving methadone (15), with the combination having been reported to produce strong psychoactive effects with intense stimulation and often hallucinations. The adverse effects can include drowsiness, tachycardia and hypertension, and overdosage can cause central nervous system depression, euphoria, convulsions, coma and death (9). In the case presented cyclizine was found in a concentration far above the therapeutic concentration range, in a concentration that compared with the literature is considered to be within the lethal level. In the two cases previously reported where cyclizine is regarded as the drug responsible for death, postmortem blood concentrations of 15 and 80 mg/L are reported. Little is known as to the possibility of postmortem redistribution of cyclizine; however, some post-mortem redistribution may be expected due to large lipid solubility and high volume of distribution of the drug.

As cyclizine is regarded as a fairly safe drug regarding intoxications, it is not included in the targeted LC–MS-MS screening approach currently in use at our institute for postmortem cases, and therefore only looked for if suspected. It should be mentioned that without the suspicion that the victim had committed suicide by ingestion of specific drugs such as meclozine, the findings of empty packages for tablets and plastic bags containing drugs at the scene, and without screening of stomach contents, the cause of death might not have been determined in this case. This is one of the major problems using a targeted screening approach versus a more comprehensive screening approach. Cyclizine is easy accessible and regarded as a safe drug, with no reports of adverse effects in the literature over the last decade. The question is if this drugs potential as a drug of abuse and as a means of suicide suggests otherwise. Cases such as this could question the safety of this drug as an over-the-counter drug without restrictions.

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References
cyclizine poisoning in a child. Beiträge zur Gerichtlichen Medizin, 36, 429.