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Diabetic ketoacidosis associated with acute methylone consumption in a 21 year-old male patient

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Clinical case

ABSTRACT

Use of methylone has risen recently, traded as a legal substitute for classic drugs and mimicking their effects. It has recently been banned in European and American markets. The case of ketoacidotic diabetes complicated with acute consumption of methylone is described in a 21 year-old Caucasian insulin-dependent male. After ingesting three capsules during a party, he presented to a suburban Buenos Aires State Hospital emergency department in the early hours of January 18, 2012. He advised having experienced dizziness, vomiting, and somnolence, with ketotic breath, dehydration, high heart and breath rates, and hyperthermia. Laboratory exams showed metabolic acidosis and in the toxicology analysis, a methylone level of 0.09 mg/dl was found. The patient was treated in an ICU with fluid replacement, volume restriction, insulin, and potassium. Remission occurred after 48 hours. Suggested mechanisms of action include serotoninergic and noradrenergic effects and antidiuretic hormone release, which produce dehydration, lypolysis, and a raise in ketotic bodies with acidosis greater than expected for hyperglycemia.

Conclusions

In this case, an association was found between acute use of methylone and diabetic ketoacidosis. Epidemiological surveillance and education about the potential risks of methylone use in young people are suggested, especially for those who are predisposed to developing diabetic ketoacidosis.

Key words: Methylone, diabetic ketoacydosis, acute consumption, hyperthermia, dehydration.

RESUMEN

El uso de metilona se ha visto incrementado últimamente, comercializada como sustituto legal de las drogas clásicas e imitando sus efectos. Actualmente ha sido prohibida en los mercados europeo y americano. Se describe el caso de una cetoacidosis diabética complicada por el consumo agudo de metilona en un joven caucásico de 21 años dependiente de insulina. Luego de ingerir tres cápsulas durante una fiesta, se presenta durante la madrugada del 18 de enero de 2012 al departamento de emergencias de un nosocomio del conurbano bonaerense, partido de General Sarmiento (Argentina). Refiere haber experimentado mareos, vómitos y somnolencia, con aliento cetónico, deshidratación, taquicardia, taquipnea, hipertensión arterial e hipertermia. El laboratorio mostró acidosis metabólica y en el análisis toxicológico se encontró un nivel de metilona de 0.09 mg/dl. Se trató en una unidad de cuidados intensivos con reposición de volumen, insulina y potasio. Remitió luego de 48 horas. Como mecanismos se postulan sus efectos serotoninérgicos y noradrenérgicos y la secreción de hormona antidiurética, que producen deshidratación, lipólisis y aumento de cuerpos cetónicos con acidosis mayor de la esperable por la hiperglicemia.

Conclusiones

En este caso se demuestra la asociación entre consumo agudo de metilona y cetoacidosis diabética. Se sugiere la vigilancia epidemiológica y educación sobre los riesgos potenciales del uso de metilona en gente joven especialmente aquellos predispuestos a desarrollar cetoacidosis diabética.

Palabras clave: Metilona, cetoacidosis diabética, consumo agudo, hipertermia, deshidratación.

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INTRODUCTION

According to official reports on drug consumption trends,[1,2] the appearance of new synthetic compounds in the illicit drug market, where consumption is ever higher, has been noted in recent years. Many of these substances are marketed as *legal highs*, whose use and commercialization are not subject to control. As such, they are offered as legal substitutes for classic drugs, imitating their effects. These substances are generally consumed along with other drugs. According to a European study,[3] methylone, including within the group of synthetic cathinones, reached a consumption percentage of

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41%, behind 2-CB (2,5-dimethoxy-4-bromophenathylamine) which reached 80%. In another American study on detecting synthetic stimulants[4] in 2,000 urine samples, methylone was found in 21% of cases, preceded only by MDPV, which was found in 88%. Until 2010 in Europe, methylone and mephedrone (4-methylmethcathinone) were identified as the most commonly consumed substances within the group of cathinones,[5] and from 2010 onwards, intoxications associated with its use increased significantly.[6] Methylone (3,4-methylenedioxy-n-methylcathinone) is the β-ketonic analog of methylenedioxymethamphetamine (MDMA), known as MDMC, MDMCAT, bk-MDMA, M-1, or M-3. It is a stimulant substance that causes clinical effects similar to, but weaker than, MDMA. It belongs to the chemical family of phenethylamines and within them, to the group of cathinones, primary active alkaloids of the Catha edulis (Khat) plant[7] (Figure 1). Discovered and patented by Jacob Peyton and Alexander Shulgin in 1996 as an antidepressant,[8] it belongs to a new generation of designer phenethylamines, considered as an alternative to the more popular ecstasy [methylenedioxymethamphetamine (MDMA)] or methamphetamine. It appeared in the European market in 2004 under the name "*Explosion*", and in the form of a vanilla-scented room odorizer. The Dutch government prohibited its sale in 2005. The drug was able to avoid the legal restrictions in America by being marketed as *bath salts* "not fit for human consumption". Currently the US Drug Enforcement Administration (DEA) has classified it as a category 1 agent, together with other potentially highly addictive substances such as heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), methaqualone, and peyote.[9] However, this measure has not reduced its availability.[10] Currently, an indeterminate number of young people are exposed to methylone although its use is increasing progressively, spread mostly among young people attending massive "*rave*" parties, such that complications from acute use have grown the most recently.[11,12] Diabetic ketoacidosis occurs when there is a deficiency of insulin and an increase in peripheral resistance to the same, together with an increase in contra-regulatory hormones (cortisol, glucagon, growth hormone, and catecholamines). This produces hyperglycemia, dehydration, electrolyte imbalance, hyperosmolarity, reduced glucose use, and an increase in ketonic bodies: acetoacetate, β-hydroxybutyrate, and acetone. Together with dehydration, it reduces glomerular filtration rate and glycosuria, it worsens hyperglycemia/hyperosmolarity, and it diminishes intracellular K+.[13] If it is not adequately treated with replacement liquids and insulin, this condition can worsen and potentially be fatal.

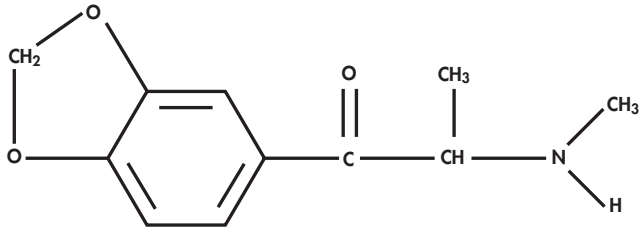

Figure 1. Chemical formula of methylone.

CASE PRESENTATION

In the early hours of January 18, 2012, a young Caucasian man aged 21 was brought by his friends to the emergency room of an urban Buenos Aires hospital, General Sarmiento (Argentina) with symptoms of queasiness, vomiting, and somnolence which started within the previous five hours while he was at a party. As part of his immediate history, his friends advised that he had been dancing wildly the previous night, and drank around six units of low-sodium mineral water (Evian® 500 ml), after having taken three pills to feel more energetic. They denied that he had drunk any alcohol. During questioning, the patient admitted being an insulin-dependent Type 1 diabetic since the age of 12, medicated with insulin glargine at a dose of 50 units/day (30 units in the morning and 20 at dinner time), and 10 units of insulin lispro (five units before main meals) for the last nine years. He also advised that in recent weeks, he had noted an increased volume of urine, polyuria, polydipsia, and polyphagia, as well as raised levels of capillary glycemia, with some readings of up to 20 mmol/l; however, this was ignored by the patient. He denied having missed any doses of insulin or having had a fever, dysuria, cough, or throat pain. When questioned about his drug use, he said that the substances taken at the party were his first experience and he denied having combined them with any other illicit drug. His family members advised that some three months previously, he had been admitted to another hospital with symptoms compatible with diabetic ketoacidosis of unknown origin. He improved rapidly with insulin treatment and broad-spectrum antibiotics, leading to suspicion that there had been an undetected infection. His most recent HbA1c had been 11%, revealing poor control of his diabetes. In the physical exam, he had ketonic breath, signs of dehydration, tachycardia (148 beats per minute), tachypnea (26 breaths per minute), arterial pressure of 155/95 mmHg, a temperature 100.04F, and a central venous pressure of 1 mmHg. His mental state revealed a discrete tendency to sleep, but he remained oriented throughout. There were no signs of lateralization or meningismus. Abdominal palpation showed diffuse pain without signs of peritoneal inflammation or defense. Pulmonary auscultation showed a good entry of air in both fields and thorax radiography did not show any abnormalities. Urine analysis showed the presence of ketonic bodies, absence of pyuria, and negative cultures (unlike the previous admission three months before). Arterial gases showed severe metabolic acidosis with normal lactate and elevation of serum osmol and anion gap. The metabolic acidosis was more severe than expected due to raised

Table 1. Laboratory values at admission and discharge

Laboratory (normal range)	Admisssion	Discharge
Hematocrit/hemoglobin	41.6%/12.4 g/dl	43.7%/13.9 g/dl
Leukocytes	12.100/mm3	4.820/mm3
Neutrophils	7.599/mm3	2.633/mm3
Sodium (135-142 mmol/L)	115.0 mmol/l	134.0 mmol/l
Potassium (3.5.4.4 mmol/L)	3,1.0 mmol/l	4.1 mmol/l
Glycemia (3–7.8)	25.0 mmol/l	4.5 mmol/l
β-hydroxybutyric acid (<0.6).	3.2 mmol/l	0.5 mmol/l
Urea/creatinine	41/1.4 mg/dl	31/0.32 mg/dl
Creatine phosphokinase serum (CPK) (0–110 U/l)	498 U/l	121 U/l
pH (7.35-7.45)	7.01	7.40
Bicarbonate (24–30)	2.1 mmol/l	23.2 mmol/l
Chlorine	109.0 mEq/l	98.0 mEq/l
Anion gap** (12±5)	31.4 mmol/	9.1 mmol/l
Osmol gap	37.0 mmol/l	9.3 mmol/l
Serum osmolarity*	234.0 mmol/l	316.0 mmol/l
Urinary osmolarity	756.0 mmol/kg	237.0 mmol/kg
Urinary ketones**	+++	–

* Serum osmolarity: 2 x [Na+ (mEq/L)] + glucose (mg/dl)/18 = mOsm/kg.
** Anion gap: [(Na+)–(Cl-+HCO3-(mEq/L)].

β-hydroxybutyric acid and the rest of the ketonic bodies (Table 1). The laboratory ruled out liver, thyroid, adrenal, pancreatic, and renal failure. Levels of creatine phosphokinase serum (CPK) were raised, (495 units/l, normal range being 0-110). After performing the toxicology analysis, an intense yellow color was observed in the sample with Marquis reagent (Figure 1).[14] A confirming analysis was then carried out with 100µL of centrifuged plasma assessed with liquid chromatography/mass spectrometry (Agilent Technologies). A methylone level of 0.09mg/dl was found. The rest of the toxicology panel did not show any residues of salicylates, amphetamines, cannabinols, ethanol, or methanol.

Treatment was administered in an intensive care unit with volume replacement with saline serum 0.9% at a dose of 1L/h, human crystalline insulin applied by continuous infusion (0.1U/kg weight/hour) and potassium replacement. However, in spite of an improvement in glycemic levels, the young man's acidosis persisted with raised levels. Because of this, venous hemofiltration was carried out to try and reduce the anion gap, which was achieved in approximately three hours of treatment (pH 7.4, bicarbonate 17 mmol/l). Later, the patient improved progressively and achieved complete remission from his symptoms after 48 hours. He was discharged from hospital four days after admission. He was prescribed insulin glargine daily at a dose of 60U/day.

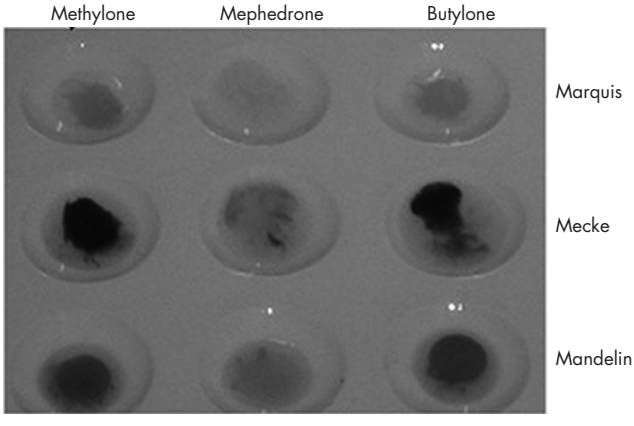

Figure 2. Panel of reagents for detection of cathilones.

DISCUSSION

Methylone presents as a white-colored, crystalline powder with a bitter taste, which is prepared in the form of pills or liquid, although it can also be inhaled with weaker effects. It can be administered orally, intranasally, sublingually, intravenously, or rectally. Oral administration seems to be the most popular for its positive and consistent effects, possibly due to the copious quantity of serotonin receptors present in the intestinal walls. The estimated dose ranges between 60mg and 300mg, but some informal records report that doses between 100mg and 250mg are usual. Doses above 250mg are considered "dangerous" (*heavy doses*). In a recent publication, a dose of 120mg was reported (albeit mixed with 76mg of methoxy-tryptamine [5-MeO-MITP]).[15] Pharmacokinetically, it is rapidly absorbed by the digestive tract, with action starting after 30 minutes. It has a maximum ef-

fect of between 60 and 90 minutes after ingestion. Its average duration is eight to 10 hours, and total duration can last for 24 hours. Bioavailability is 65% and after a first hepatic step, it is metabolized by N-demethylation followed by O-methylation, mediated by catechol-O-methyl transferase. The metabolism of these compounds occurs through phase I, with the microsomal enzymatic system of cytochrome CY450, and phase II through conjugation with glucuronides and sulfates and urinary excretion. N-dealkylation is a metabolic route of lower importance. Pharmacodynamically, methylone acts as a non-selective substrate for dopamine transporter (DAT), serotonin (SERT), and noradrenaline (NET), blocking their reuptake. It has an affinity three times lower with SERT and 13 times lower with vesicular monoamine transporter 2 (VMAT2) in terms of the MDMA transporter, but its affinity with dopamine and norepinephrine receptors is almost identical.[16] It also increases vesicular exocytosis of serotonin, dopamine, acetylcholine, histamine, and noradrenaline in the synaptic space, increasing the cytosolic [Ca^{2+}] of the synaptic terminals.[17] When reducing the activity of tyrosine-hydroxylase and tryptophan-hydroxylase enzymes, it also reduces levels of dopamine and serotonin in the dopaminergic D2 receptors in the frontal lobe and the hippocampus. On the other hand, methylone increases levels of serotonin and dopamine in the nucleus accumbens/subcallosal gyrus (motivation mediators), which form part of the mesocorticolimbic reward circuit, together with orbitofrontal gyrus, the amygdala, and the anterior cingulate (anticipation of reward). This series of actions release glutamatergial transmission in the prefrontal area, substrate of psychostimulant actions. However, there is no direct correlation between the subjective effects of methylone and the inhibition of one or other monoamine transporters.[18] The increase of norepinephrine partly explains the sympathomimetic effects on the brain and the cardiovascular system, given that the administration of reboxetine, a selective NET inhibitor, reduces the effects of MDMA and cathinones on the increase in arterial pressure and cardiac frequency, as well as weakening subjective euphoria and emotional excitation.[19] Upon increasing the activity of the antidiuretic hormone, it produces hyponatremia and hypo-osmolarity. Acute consumption of methylone, added to the physical and mental stress induced by the substance, produces activation of the hypothalamic-hypophyseal-adrenal (HPA) axis. As a result, they increase levels of norepinephrine, corticotropin-releasing hormone (CRH), adrenocorticotropin (ACTH), cortisol, and luteinizing hormone, at the same time as it reduces plasmatic levels of prolactin.[20] Its sympathomimetic effects extend to the digestive, skin, and genito-urinary systems.[21] In summary, methylone has a potency comparable to its compounds of reference, d-amphetamine, MDMA, and cocaine. The overall effects of this drug include stimulating, entactogenic, and hallucinogenic properties, as well as euphoria, an increase in physical and social activity, acute perception of sounds and tactile stimulation, intensified appreciation of music, an increase in self-esteem with a reduction in the judgment of risk, hallucinations and paranoia, raised mood, reduced hostility, greater mental clarity, and moderate sexual stimulation. Among its secondary effects are headaches, queasiness, vertigo, insomnia, balance disorders, nausea/vomiting, impotence, palpitations/extrasystoles, excessive sweating, acrocyanosis (cold and blue extremities), xerostomia (dryness of the corneas), bruxism, epistaxis, hot flashes, throat pain, appetite suppression, blurred vision, mydriasis, increased muscle tone, psychmotive unease, increased arterial tension, and anxiety, which can lead to paranoid ideation and states of confusion. Gastro-duodenal ulcers may also be developed, as well as intestinal infarctions and ischemic colitis, vasculitis of the skin, and pleural effusions. The most serious reactions can include fatal arrhythmias, hyperpyrexia, rhabdomyolysis, acute renal failure, hyponatremia, convulsions, intracranial hemorrhage, and hypo- or hyperglycemia. Serotonin release, along with a block in its transporter (SERT), can develop serotonergic syndrome,[22] including dehydration, disseminated intravascular coagulation, convulsions, and rhabdomyloysis. This syndrome and its concomitant neurological alteration can be even more aggravated in cases of diabetic ketoacidosis, which produces an increase in tryptophan and 5-hydroxyindoleacetic acid (precursors of serotonin) in cerebrospinal fluid and plasma.[23] Hyperthermia, which can reach 107.6F, is due to the action of methylone on the CNS, along with prolonged exercise (wild dancing), and environmental conditions (crowds, high temperatures). Hyponatremia and hypo-osmolarity due to increased ADH is aggravated by psychogenic polydipsia which can cause convulsions, cerebral edema, and trastentorial herniation. Users of methylone describe its effects as a mix of dextroamphetamine, MDMA, and cocaine, due to which it is extremely addictive, with a high level of dependency and consumption by increasing numbers of people. This can lead to toxic doses with frequent visits to emergency rooms and even to fatal outcomes.[24] In the present case, diabetic ketoacidosis with concomitant hyperglycemia and ketonuria contributed only in part to the low pH, as the levels of β-hidroxybutyric acid were not sufficient to explain the anion gap. Methylone can cause serious complications in insulin-dependent diabetes patients for various reasons: reticence to seek prompt medical advice, masking of serious symptoms by concurrent use of other drugs, lack of compliance with insulin regime, hyperglycemia and ketosis associated with lipolysis induced by sympathetic hyperactivity, dehydration, and hyponatremia due to insufficient water consumption. The aforementioned patient had consumed almost three liters of low-sodium water during the night, leading to difficulty replacing water and lost electrolytes. Symptoms of diabetic ketoacidosis have been detected in insulin-dependent subjects who had taken acute MDMA in crowded rave-type

parties where they had danced continuously.[25] In all cases, they had good clinical development after replacement of liquids and insulin, although in one case there was pneumonia which required mechanical ventilation.[26] In another study on 19 insulin-dependent patients with ketoacidosis, it was found that in the six who had previously consumed MDMA, the level of acidosis was higher than in the other patients who had not consumed it.[27] In a more recent study, it was found that mephedrone, chemically related to methylone, was associated with diabetic ketoacidosis in a young insulin-dependent diabetic consumer .[28] In an investigation into consumption of psychoactive substances in Argentina,[29] in a sample of 12,589 cases aged 12 - 65, there was a life prevalence of having taken stimulants (MDMA and related substances) of 0.6% (0.9% for men and 0.3% for women), of whom almost 80% were aged between 18 and 34, and belonged to middle-class socioeconomic groups. The average age for a first experience with MDMA, methylone, or mephedrone was 20 years old (14-31 years). The profile of the methylone consumer includes young men who are heterosexual, single, consumers of multiple substances, with a secondary or higher level of education, belonging to middle and high-level socio-economic groups. This is a pattern similar to that encountered in other countries.[30-32] Some researchers have indicated that drug use can be included as a marker of poor control of diabetes, in particular in the adolescent population, who frequently ignore complications of their use, increasing risk of sudden death among that sector.[33] This danger should be emphasized in all medical interventions with adolescents. In spite of treatment for diabetic ketoacidosis with insulin being satisfactory, these symptoms should arouse suspicion of etiologies other than the traditional ones, such as lack of insulin or infection. A current focus of this pathology should emphasize not only the early treatment of diabetic decompensation, but also the identification of what leads to it.[34] Calculating the anion gap allows for identification of unreported consumers, whose acidosis could be due, at least in part, to drug use. Although treatment is supportive, not recognizing drug use can produce a rapid clinical deterioration. Early recognition of these patients can facilitate timely referral for advice and counseling.

Methylone use can trigger diabetic ketoacidosis in patients with previous diabetes. In this case, this association was demonstrated, where fatigue associated with extenuating physical exercise, together with consumption of the drug, can be the cause of the problem. Frequently, patients do not wish to discontinue drug use in spite of the potential risks, therefore better monitoring, together with epidemiological vigilance and education about the potential risks of methylone use is necessary in young people, especially those predisposed to developing diabetic ketoacidosis.

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Conflict of Interest

No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter included in this manuscript.

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