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Abstract: INTRODUCTION: Methoxphenidine is a novel dissociative designer drug of the diarylethylamine class which shares structural features with phencyclidine (PCP), and is not at present subject to restrictive regulations. There is very limited information about the acute toxicity profile of methoxphenidine and the only sources are anonymous internet sites and a 1989 patent of the Searle Company. We report a case of analytically confirmed oral methoxphenidine toxicity. CASE DETAILS: A 53-year-old man was found on the street in a somnolent and confusional state. Observed signs and symptoms such as tachycardia (112 bpm), hypertension (220/125 mmHg), echolalia, confusion, agitation, opisthotonus, nystagmus and amnesia were consistent with phencyclidine-induced adverse effects. Temperature (99.1°F (37.3°C)) and peripheral oxygen saturation while breathing room air (99%) were normal. Laboratory analysis revealed an increase of creatine kinase (max 865 U/L), alanine aminotransferase (72 U/L) and gamma-glutamyl transpeptidase (123 U/L). Methoxphenidine was identified by a liquid chromatography tandem mass spectrometry toxicological screening method using turbulent flow online extraction in plasma and urine samples collected on admission. The clinical course was favourable and signs and symptoms resolved with symptomatic treatment. CONCLUSION: Based on this case report and users’ web reports, and compatible with the chemical structure, methoxphenidine produces effects similar to those of the arylcyclohexylamines, as PCP.

DOI: https://doi.org/10.3109/15563650.2014.974264
Acute toxicity associated with the recreational use of the novel dissociative psychoactive substance methoxphenidine

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Running head
Acute toxicity associated with the recreational use of methoxphenidine.

The paper is written in UK English.

Word count (excluding references, figures, and abstract): 1536

References: 15

Figure: 2
Key words:
diarylethylamine, drug of abuse, NMDA receptor, designer drug, phencyclidine, ketamine, psychedelic, 2-MeO-diphenidine

Declarations of interest
None of the authors has conflicts of interest concerning commercial or financial involvements. No author is affiliated with an organization whose financial interests may be affected by material in the manuscript.
Abstract

Introduction: Methoxphenidine is a novel dissociative designer drug of the diarylethylamine class which shares structural features with phencyclidine (PCP), and is not at present subject to restrictive regulations. There is very limited information about the acute toxicity profile of methoxphenidine and the only sources are anonymous internet sites and a 1989 patent of the Searle company. We report a case of analytically confirmed oral methoxphenidine toxicity.

Case details: A 53-year-old man was found on the street in a somnolent and confusional state. Observed signs and symptoms such as tachycardia (112 bpm), hypertension (220/125 mmHg), echolalia, confusion, agitation, opisthotonus, nystagmus, and amnesia were consistent with phencyclidine-induced adverse effects. Temperature (99.1 °F, 37.3°C) and peripheral oxygen saturation while breathing room air (99%) were normal. Laboratory analysis revealed an increase of creatine kinase (max 865 U/L), alanine aminotransferase (72 U/L), and gamma-glutamyl transpeptidase (123 U/L). Methoxphenidine was identified by a liquid chromatography tandem mass spectrometry toxicological screening method using turbulent flow online extraction in plasma and urine samples collected on admission. The clinical course was favourable and signs and symptoms resolved with symptomatic treatment.

Conclusion: Based on this case report and users’ web reports, and compatible with the chemical structure, methoxphenidine produces effects similar to those of the arylocyclohexylamines, as PCP.
Introduction
Methoxphenidine (MXP) or 2-MeO-diphenidine (1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine), is a diarylethylamine compound that shares structural features with the arylcyclohexylamines, such as phencyclidine (PCP), ketamine, and methoxetamine (MXE), and with the diarylethylamine diphenidine (Figure 1). These recreational psychoactive substances with dissociative effects are highly addictive because of their ability to produce intense psychedelic effects. Shortly after the 2013 UK ban on arylcyclohexylamines, methoxphenidine became available on the grey market. It is advertised and sold through the internet as a research chemical in form of a white powder or crystals. Methoxphenidine, which possesses a lower affinity for N-methyl-D-aspartate (NMDA) receptors than the related compound diphenidine, was first reported in a 1989 patent as a potential treatment for neurotoxic injury. As a consequence of structural similarity, the effects of methoxphenidine might be assumed to be similar to those of other dissociative drugs. There is no reliable information on the pharmacology, effects and toxicity of this substance, and established analytical methods are lacking. The only sources of information are drug users’ web discussion forums, in which euphoria, feeling of happiness, stimulating effects, disorientation, dissociative effects (starting at 80 mg methoxphenidine), and transient anterograde amnesia lasting for 3-6 h are mentioned. Some users report undesired effects including tachycardia, hyperthermia, panic attacks, and, after ingestion of higher doses, seizures requiring hospitalisation. Methoxphenidine is generally used orally, in doses of 80-150 mg (in some reports up to 500 mg), and users report a steep dose-response curve. Effects are described to begin after 60 min, with a duration up to 18 h. We report a case of acute toxicity after oral methoxphenidine use confirmed by the identification of the substance and its metabolites in serum and urine by a liquid chromatography tandem mass spectrometry toxicological screening method.

Case report
A 53-year-old Caucasian male with a history of diabetes mellitus and multiple substance abuse, was found on the street in a somnolent and confusional state, with transient echolalia and unable to communicate. His current medication included buprenorphine as opiate substitution therapy (16 mg/day), amlodipine (5 mg/day), candesartan (32 mg/d) dihydrochlorothiazide (25 mg/day), metformin (2000 mg/d),
subcutaneous insulin, and simvastatin (40 mg/d). He carried a packet containing a white powder labelled “methoxphenidine”, which was later analytically confirmed by gas chromatography mass spectrometry (Scientific Forensic Service of Zurich) to be pure methoxphenidine.

On arrival at the emergency department the patient suddenly lost consciousness, and developed opisthotonus, horizontal nystagmus, and conjugate eye deviation. He was immediately transferred to the intensive care unit, where he arrived with central nervous system depression and a Glasgow Coma Scale score of 10. The physical examination revealed hypertension (220/125 mmHg) and tachycardia (112 bpm); body temperature was 99.1 °F (37.3°C), respiratory rate was 14/min, and the peripheral oxygen saturation was 99% while breathing room air. The pupils were miotic, non-reactive, and horizontal nystagmus was still present. Deep tendon reflexes were normal and the Babinski sign was negative. The muscle tone was normal and there was no clonus. The general physical examination was unremarkable. The ECG was normal, except for mild sinus tachycardia (105 bpm) and mild QTc-prolongation (465 ms). There were no signs of trauma, and the CT scan showed neither cerebral hemorrhage nor injury of the cervical spine. Laboratory analysis revealed an increase of creatine kinase (max 865 U/L; reference <190 U/L), alanine aminotransferase (72 U/L; reference < 41 U/L), and gamma-glutamyl transpeptidase (123 U/L; reference < 61 U/L). Serum bilirubin and alkaline phosphatase as well as other parameters including blood glucose level (9.9 mmol/L, on admission), serum electrolytes, creatinine, INR and the complete blood count were normal. ELISA urine toxicology screen was positive for benzodiazepines, but negative for cocaine, amphetamine, tetra-hydro-cannabinol, opioids, barbiturates, methadone, tricyclic antidepressants, 3,4-methylenedioxymethamphetamine, and methamphetamines. Ethanol was not detectable in serum.

Lorazepam (2 mg intravenously) was initially administered for treatment of hypertension and tachycardia, with a decrease of blood pressure and heart rate within 30 min to 172/90 mmHg and 103 bpm, respectively. Concomitantly, nystagmus and miosis resolved. The patient developed urinary retention requiring catheterization, and lidocaine was used as topical anaesthetic. 90 min after admission the patient regained consciousness, but was confused, disoriented and showed fumbling movements. He was progressively more agitated, and was therefore managed by further lorazepam administration (6 mg intravenously,
cumulative dose). The subsequent clinical course was uneventful and the next morning the patient was asymptomatic except for amnesia of the event and was therefore discharged home.

Plasma and urine samples collected on admission were analysed by a liquid chromatography tandem mass spectrometry toxicological screening method using turbulent flow online extraction. The method uses a linear ion trap mass spectrometer to acquire MS² and MS³ spectra in positive as well as negative mode in the same run. Identification of compounds is based on MS² and MS³ spectral libraries. Urine samples are analysed twice, once natively and once after enzymatic cleavage of the glucuronide metabolites. Serum is analyzed only once. Methoxphenidine was added to the spectral libraries (MS² and MS³) using pure reference compound that has been provided by the Scientific Forensic Service of Zurich. For the identification of methoxphenidine metabolites, the urine sample was analysed in untargeted mode with the same liquid chromatography high resolution mass spectrometry toxicological screening method using turbulent flow online extraction.

Methoxphenidine was identified in the plasma as well as in the urine sample (Figure 2). In the urine sample, the following methoxphenidine metabolites were identified in addition to the parent compound: three different hydroxylation products, the product of O-demethylation, and three different glucuronidated hydroxylation products. Furthermore, trace amounts of benzoylecgonine, amlodipine and metabolite, buprenorphine and metabolite, norfentanyl, hydrochlorothiazide, metformin, lidocaine and metabolite, as well as nicotine and metabolite were detected. In the plasma, in addition to methoxphenidine, lorazepam, lidocaine and metabolite, and amlodipine were detected.

**Discussion**

Dissociative drugs including PCP and ketamine are used recreationally for their mind-altering effects. Starting with the first dissociative designer drug, 4-MeO-PCP in 2008, the dissociative designer drug market has rapidly evolved, and several of these compounds have reached widespread use internationally. This is true for MXE, which has therefore been scheduled in recent years as a controlled substance in many countries. Drug-selling sites now specifically promote methoxphenidine as a
legal replacement for the banned arylcyclohexylamines such as MXE and 4-MeO-PCP. Methoxphenidine seems to be rapidly gaining popularity, and forum posts on this compound are steadily increasing. Concomitantly to the appearance of methoxphenidine on the grey market, diphenidine, another dissociative designer drug of the diarylethylamine class with a very close chemical structure and similar effects to methoxphenidine, emerged. As is usually the case for novel psychoactive substances, also for the arylcyclohexylamines and diarylethylamines, little is known about their health risks when they enter the recreational drug scene.

Methoxphenidine users describe the effects as similar to those of ketamine and MXE. Actually, signs and symptoms observed in our patient such as hypertension, tachycardia, confusion, sedation, shifts in perception of reality, agitation, nystagmus, opisthotonus, amnesia, and urinary retention are compatible with the effects induced by MXE, ketamine, and PCP. Moreover, speech disorders such as pressured speech, verbigerations, and echolalia have been regularly reported by users of PCP and ketamine.

Hypertension and nystagmus, which were observed in our patient, are hallmarks of PCP intoxication, and both have been reported to occur in about 57% of the cases and to resolve within 4 h of PCP consumption. Also miosis is common in PCP intoxication and was observed in our patient. A major contribution by buprenorphine seems unlikely as the patient had no respiratory depression and showed a rapid resolution of the central nervous system depression.

The initial neurological presentation of our patient with loss of consciousness associated with opisthotonus is compatible with a tonic seizure. Seizures have been reported after use of PCP and also rarely by MXP users. Furthermore, the analgesic drug lefetamine, which is structurally related to methoxphenidine and which was abused in Japan and Europe and has been withdrawn from the market, has been reported to cause seizures in rats.

In our patient, all detected substances other than methoxphenidine, norfentanyl, and benzylecgonine (i.e. buprenorphine, amlodipine, candesartan, dihydrochlorothiazide, metformin, lorazepam, and lidocaine) were used therapeutically. Norfentanyl and traces of benzylecgonine slightly above the detection limit in absence of the parent compounds were found in the urine sample only, and this is compatible with the...
prolonged detectability (up to 72 hours) of norfentanyl, the major metabolite of fentanyl,\textsuperscript{11} and benzoylcegonine.\textsuperscript{12} We are therefore persuaded that there is enough evidence to reject the hypothesis of a simultaneous abuse of fentanyl and/or cocaine, which could have influenced the clinical course.

Because methoxphenidine is at present not subject to restrictive regulations, it seems plausible that the consumption of this substance might increase internationally. For this reason, further studies are needed to determine the pharmacological and toxicological properties of methoxphenidine, and to analyse patterns of acute toxicity in humans and possible long-term effects, including neuropsychiatric disorders as well as urinary bladder, liver, and brain injury, which were observed after long-term abuse of PCP and ketamine.\textsuperscript{13,14,15}

In conclusion, methoxphenidine appears to have a similar acute toxicity profile to other arylcyclohexylamines, such as PCP, ketamine, and MXE. On the basis of the very limited evidence available, management of patients presenting with acute toxicity related to methoxphenidine use should be as for other dissociative drugs.

**Patient’s consent**
A document showing the patient’s written consent to this publication is available on request.

**Acknowledgements**
We thank Dr. Hugo Kupferschmidt, Swiss Toxicological Information Centre, for valuable discussions during the preparation of the manuscript, and Ms. Rose-Marie Hauser-Panagl for secretarial assistance.
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