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Case Reports

Xylazine Dependence and Detoxification: A Case Report

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Introduction

Recreational use of psychoactive substances is highly prevalent throughout the world. Emerging new trends in substance misuse can puzzle medical professionals when confronted with patients with unknown intoxication and withdrawal syndromes.[1] Sharing clinical experience on cases with misuse of new or unknown substances of abuse is highly important to support clinical decision-making and raise attention to potential new trends in substance misuse.

Here, we report a case of severe substance use disorder with the animal sedative xylazine (Rompun). After describing the case, we discuss the existing literature on xylazine misuse, its pharmacological properties, and its effects observed in humans. Finally, we provide recommendations for detoxification.

Case Description

Mr. A, a 35-year-old male veterinarian was admitted involuntarily to our psychiatric clinic for detoxification of the veterinary sedative xylazine (Rompun). He had been taking xylazine for 2 years by subcutaneous injection. Previously, he had been using methylphenidate (MPH) on a daily basis, both oral and intranasal, in an unknown dosage when studying veterinary medicine. As his use of MPH increased, he developed insomnia, anxiety, and a loss of appetite, which led him to start using xylazine injections to sleep. During the months before admission, he was self-injecting xylazine on a daily basis with a self-reported daily dose of 500 mg (1 ampoule). He reported injecting xylazine in the morning and before sleep.

Mr. A did not acknowledge his xylazine use as a problem. He reported no clear tolerance over the years of use, nor did he experience any withdrawal effects when not using. However, his self-reported frequency of use was substantially lower than that reported by his relatives. They reported a substantial escalation of xylazine use over time, with several hours a day spent on using and recuperating from the effects of xylazine. On multiple occasions, he was found unconscious at home. He denied having any problems and declined help offered from family or a psychiatrist. Over the years, his health and daily life functioning deteriorated significantly, which his family attributed to his increasing xylazine use. Over the recent years, he had been unable to work as a veterinarian and became increasingly socially isolated. The increasing frequency of xylazine use and deterioration of his well-being and functioning ultimately led to the involuntary admission in our clinic. Concomitant use of MPH on a daily basis was still present at admission, although there was no reliable information on the exact frequency or

Patient's consent: Written informed consent was obtained from the patient and is available on demand.

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dosage used. Neither the patient nor relatives reported any deterioration of well-being or increase in symptoms related to his use of MPH.

Mr. A's primary complaint was a clenching of the jaw and grinding of his teeth, which he had over the past 2 years. Furthermore, he reported a mildly depressed mood. He denied having delusions or hallucinations, and there were no complaints of anxiety. There was no current abuse of other substances at the time of admission. His psychiatric history included a mild depressive episode at the age of 21, successfully treated with paroxetine. Also, 1 year before admission, he experienced a psychotic episode lasting several weeks, consisting of paranoid delusions and auditory hallucinations, successfully treated with haloperidol (4 mg/d). There was no family history for substance abuse or other psychiatric disorders.

On admission, Mr. A used haloperidol (3 mg/d), lorazepam (1 mg/d), fluvoxamine (250 mg/d), biperiden (6 mg/d), and diazepam (5 mg as needed). Psychiatric assessment showed poor self-care and a lack of insight in his situation. He was well oriented, but showed little initiative. He had difficulty recalling recent events, and showed severe mental slowing. His mood appeared to be normal, with a blunted affect. Physical examination showed a slight clenching of the jaw and injection marks on his abdomen. There were no extrapyramidal symptoms or other abnormalities on physical and neurological examination.

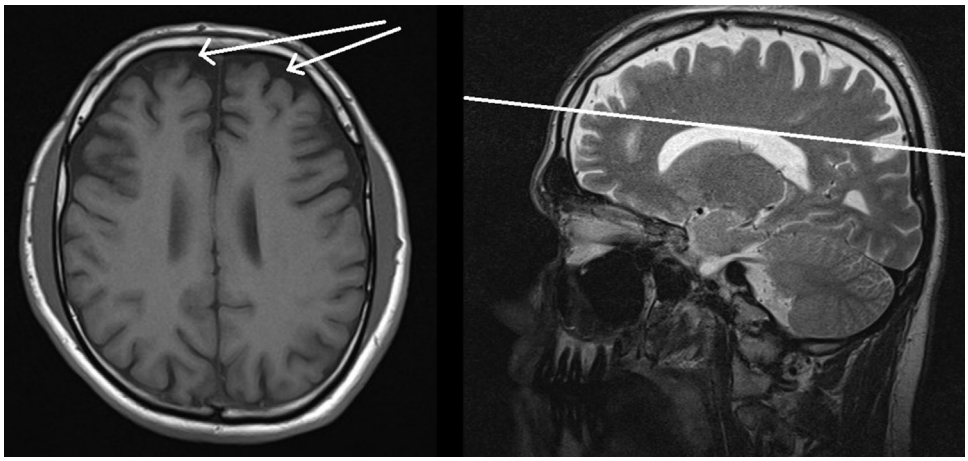
Based on collateral information from his family and psychiatrist, his xylazine use was interpreted as a severe substance use disorder ($\geq$6 criteria—escalation of use suggesting tolerance, inability to stop using, large amounts of time dedicated to use and recuperating, use despite deterioration of his physical condition and psychosocial functioning, interference with his social and occupational functioning, and risky use given the repeated comas). In addition, although information was scarce, the use of MPH could be classified as a mild substance use disorder (continuing use despite health problems, consuming more than planned). Patient did not meet criteria for any other current axis-I disorder, as all other signs and symptoms might be attributed to the use of a psychoactive substance.

Given the potentially severe withdrawal syndromes observed in alpha-$_2$-adrenergic agonists, such as clonidine, including ventricular tachycardia and myocardial infarction,[2–4] we chose to start a low dose of clonidine (0.025 mg twice daily), while closely monitoring withdrawal symptoms, blood pressure, and pulse. In line with Dutch detoxification guidelines we used the subjective and objective withdrawal scales (OOS and SOS), covering a broad range of withdrawal symptoms. During titration, blood pressure and pulse were stable at approximately 130/85 mm Hg and 60–70 bpm. Objective and subjective withdrawal scores gradually decreased from 10–3 (out of 34) and from 25–8 (out of 132), respectively, indicating mild withdrawal. The most reported symptoms were muscle twitching and restlessness at onset, and later mild fatigue and increased appetite. Clonidine was discontinued after 1 week with no change in symptoms, blood pressure, or heart rate.

After detoxification, Mr. A showed persisting cognitive impairments. Extensive neuropsychological testing* 2 weeks after detoxification revealed severe cognitive deficits. In contrast to his academic training, he scored 87 on verbal intelligence and 68 on perceptual intelligence, indicating low intellectual abilities. Speed of information processing was below average, with normal visuo-constructive skills. Working memory was on the level of intellectual disability, with impaired storage of new information. Once memorized, recollection was adequate. He had severe impairments in executive functions, particularly in planning. Performance on a social cognition task was at the level of a 14–15-year-old subject. Lumbar puncture showed a small increase in tau protein (367 ng/L; reference range $<$300 ng/L) and neuron-specific enolase (19.8 ug/L; reference range $<$17.5 ug/L) in the cerebrospinal fluid, which is indicative of axonal damage, but not specific for any neurodegenerative disorder. Magnetic resonance imaging of the cerebrum revealed generalized supratentorial cortical atrophy (global cortical atrophy grade 2) with widened sulci and volume loss of the gyri, most prominent in frontotemporal brain regions (Figure). Cognitive decline and findings at brain imaging and lumbar puncture could be related to substance misuse (MPH and possibly xylazine), but potential cognitive deficits

* Instruments used for neuropsychological testing include Wechsler Adult Intelligence Scale IV-NL, Stroop color-word test, Trail making test, complex figure drawing, 15-words test, Dutch reading test for adults, Rivermead Behavioral memory test (stories), Behavioral assessment of the Disexecutive Syndrome, D-Kefs Tower test, Wisconsin card sorting test, social interpretation test, visual association test, clock-drawing test, Utrecht copinglist, and short test for mental status orientation.

FIGURE. **MRI Showing Cortical Atrophy. Left: T1 Magnetic Resonance Imaging of the Brain, Showing Generalized Cortical Atrophy with Widened Sulci and Loss of Volume of the Gyri (Global Cortical Atrophy Grade 2). Arrows Indicate Most Significant Areas of Cortical Volume Loss. Right: T2 Image Showing the Slice Position. 341 × 160 mm (300 × 300 DPI).**



as part of a developing schizophrenia or early-onset frontotemporal dementia could not be ruled out.

Discussion

To the best of our knowledge, this is the first report on continuous excessive xylazine (Rompun) use and its detoxification. Xylazine, or 2-(2,6-dimethylphenylaminno)-4H-,5,6-dihydro-1,3-thiazine, is a thiazine-derivative with sedative, hypnotic, local anesthetic, hypotensive, analgetic, and muscle relaxant properties.[5] It has strong agonistic properties for the presynaptic alpha-$_2$-adrenergic receptors in the central nervous system, where it inhibits the release of noradrenaline. This mediates its sedative, analgetic, and muscle relaxant effects. By binding to postsynaptic alpha-$_2$-adrenergic receptors, it causes peripheral vasoconstriction. Compared with other alpha-$_2$-adrenergic agonists (such as clonidine), it has a low affinity for all 4 types of alpha-$_2$-receptors, which translates into a relatively high dose to establish sedative effects.[6] It may also have effect on other receptor systems, although evidence is limited.[7]

There is no available literature on the pharmacokinetics or pharmacodynamics of xylazine in humans. For its use in veterinary medicine, where it is used for its sedative properties, the dose typically ranges between 0.25 and 4 mg/pound intramuscularly or 0.5 mg/pound intravenously.[8–10] Xylazine is rapidly absorbed and distributed (peak plasma 12–14 minutes) and is rapidly metabolized in the liver through the cytochrome P450 enzymes (elimination half-life ranging from 23–49 minutes). Concerning its toxicity, LD50 (median lethal dose) is only available for dogs (47 mg/kg) and horses (60–70 mg/kg).[11]

As a drug of abuse, recreational use of xylazine has been reported in Puerto Rico and Philadelphia where it is mainly used as an adulterant to opioids and cocaine.[12,13] A survey in 89 drug users in Puerto Rico showed that 80.7% had used xylazine before, most often mixed with either cocaine (38%) or "speedball"; a combination of heroin and cocaine (42.3%).[14] In another study (also in Puerto Rico), traces of xylazine were present in 34.8–38.7% of syringes, mostly combined with speedball (90.6%).[12] Xylazine is commonly injected and can cause skin lesions, such as ulcers, at the injection sites, related to skin hypo-oxygenation.[15] Xylazine intoxication symptoms include sinus bradycardia, cardiac arrhythmias, hypotension, apnea, and disorientation or coma.[16–18,7,19–22] The severity of these effects of xylazine are dose-dependent and occur within a broad range between 0.73 and 22 mg/kg.[8,20] There is no clear distinction between blood levels associated with nonfatal intoxication and those resulting in death.[8]

To date, reports on the xylazine dependence and withdrawal are lacking. Although we anticipated a syndrome resembling clonidine withdrawal (hypertension and ventricular tachycardia), we observed limited withdrawal symptoms in our patient, without

clear cardiac effects. On the one hand, this could indicate that xylazine does not lead to a clinically relevant withdrawal syndrome. On the other hand, the dosage of xylazine may have been too low to produce significant withdrawal effects. Lastly, the low-dose clonidine could have been sufficient to dampen withdrawal symptoms. In future cases, a symptom-triggered approach of clonidine administration to prevent severe withdrawal could be considered. Importantly, even without a significant withdrawal syndrome, a patient can meet criteria of severe substance use disorder. In this case, despite the absence of a significant withdrawal syndrome, the patient described here still met at least 6 criteria of substance use disorder, indicating a severe use disorder (according to DSM-5)—escalation of use suggesting tolerance, inability to stop using, large amounts of time dedicated to use and recuperate from it, use despite deterioration of his physical condition and psychosocial functioning, interference with his social and occupational functioning, and risky use given the repeated comas.

Long-term adverse effects of excessive xylazine use are unknown. The relationship between xylazine use and the severe cognitive decline in our patient is unclear. There is, however, increasing evidence indicating neuroinflammatory effects of substance abuse.[23] Recent animal studies on alcohol abuse have shown a relation with long-term cognitive dysfunction.[24] Moreover, psychostimulant abuse has been linked with cerebral microangiopathy.[25] Others observed a relationship between substance-induced comas and cognitive decline, as also suggested in the context of GHB dependence.[26] Whether xylazine or MPH produce similar effects remains unknown. In this case, we cannot rule out the possibility that the cognitive symptoms resulted from schizophrenia with predominantly negative symptoms or cognitive symptoms related to a single psychotic episode (that might also have been related to substance use, MPH in particular). Yet, the fast disease progression and age of onset described here are not typical for schizophrenia. Another possible explanation of cognitive decline is an early-onset frontotemporal dementia. This might explain his cognitive decline, apathy, and lack of insight into his situation and fits with the atrophy observed on the MRI and the cerebrospinal fluid findings. However, frontotemporal dementia at the age of 35 is rather unlikely. Finally, toxic effects of long-term MPH-abuse might have contributed to the observed cognitive deficits. A recent case report indeed suggests that prolonged stimulant abuse might cause cognitive dysfunction.[27] However, our patient had a much shorter time of abuse (10 years vs >30 years) and different abnormalities on MRI (frontotemporal atrophy vs subcortical white matter lesions).[28]

Taken together, we report the first case of xylazine dependence. We observed no significant withdrawal syndrome after detoxification of xylazine, with a low dose of clonidine (0.025 mg twice daily). We did observe persisting severe cognitive deficits after detoxification, with accompanying abnormalities on MRI and in the cerebrospinal fluid in our patient. We recommend that patients with potential xylazine dependence are monitored for cardiovascular dysregulation during withdrawal and for neurological changes after a period of controlled abstinence. A low dose of clonidine could potentially alleviate possible withdrawal symptoms associated with xylazine detoxification, although systematic studies on xylazine detoxification are lacking.

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