CASE REPORT

Moxonidine for tramadol withdrawal symptoms during detoxification

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SUMMARY

It is well documented in the literature that noradrenergic pathways are key in the manifestation of opioid withdrawal symptoms, which is why clonidine is used as an off-label agent in opioid detoxification regimens given its anti-sympathetic properties. Moxonidine is a selective I1-imidazoline receptor agonist, similar to clonidine but with no α 2-adrenergic agonist activity and subsequently fewer side effects. We report the case of a 33-year-old woman with a 15-year history of tramadol use who was admitted voluntarily for detoxification. She was started on moxonidine and had an uneventful detoxification. Two months after discharge, the patient maintained tramadol abstinence with good tolerability to moxonidine. To the best of our knowledge, this has not been previously reported in the medical literature.

BACKGROUND

Opioid dependence and addiction is a global public health problem. This complex disease has multiple challenging aspects ranging from biological dependence to perpetuating psychosocial factors. Physicians are increasingly encountering patients who need to be acutely detoxified. In many clinical settings, opiates are not available for use in detoxification and clinicians have resorted to using other classes of drugs to help with withdrawal symptoms. One such drug is clonidine, usually used as a treatment for hypertension. Clonidine is an agonist at the α 2-adrenergic receptor as well as at the I1-imidazoline receptor.¹ We hypothesised that due to overlap in the mechanisms of action of clonidine and moxonidine, itself another antihypertensive agent, it is reasonable to consider using moxonidine for opiate detoxification. Most studies indicate that clonidine has equal affinity to both types of receptors,² yet the drug's inhibition of the sympathetic system seems to be mediated by the I1 receptor while its adverse effects such as sedation and dry mouth are mediated by the α 2 receptors.^{1 3} It is well documented in the literature that noradrenergic pathways are important in the manifestation of opioid withdrawal symptoms,⁴ which is why clonidine is used as an off-label agent in opioid detoxification regimens given its antisymphathetic properties. Lofexidine, a structural analogue of clonidine, is a high-affinity α 2 receptor agonist that has been shown to decrease sympathetic outflow.⁵ It has, since 1992, been approved in the UK for opioid detoxification.⁵ Clonidine and lofexidine have been evaluated in a recent Cochrane review and have been found to be more effective than placebo in the management of opioid withdrawal.⁶ Lofexidine was

found to have less effect on blood pressure than clonidine, but both drugs were equally effective at alleviating withdrawal symptoms.⁶ Although it was previously thought that clonidine's effect on opioid withdrawal is solely mediated by the α 2 receptor, recent studies have shown that its action on the I1 receptor is equally important.⁷ Moxonidine is a selective I1-imidazoline receptor agonist,^{1 3} and as such might be useful in treating opioid withdrawal in a manner similar to clonidine and lofexidine, but with fewer side effects.^{1 3} Table 1 summarises the mechanisms of action and common adverse effects of clonidine, lofexidine and moxonidine.

CASE PRESENTATION

A 33-year-old married mother of two children, currently unemployed, with a 15-year history of tramadol use, was admitted voluntarily for detoxification at our hospital. Tramadol is a synthetic opiate that is commonly abused and it acts as a weak mu opioid receptor agonist. The patient's consumption varied between 200 and 400 mg orally daily with no concomitant alcohol or other substance use. She was originally prescribed tramadol 15 years earlier for headaches by a general practitioner and continued using it since then. Her use of tramadol escalated and became problematic once it became a coping mechanism to her marital problems and depression. The patient had reduced her consumption to 100 mg daily 1 week prior to admission, but further attempts to self-taper at home were unsuccessful. On interview, the patient admitted to anhedonia, irritability, anxiety, insomnia and hopelessness. Additionally, she reported a history of seizures related to tramadol use and protracted withdrawal symptoms that led to relapse. Otherwise, her medical and surgical history was unremarkable. No other medication use was reported, besides occasional acetaminophen intake.

INVESTIGATIONS

Physical examination on admission to the detoxification unit showed bilateral mydriasis, diaphoresis and mild generalised tremulousness. Vital signs were within normal parameters. Urine drug toxicology was positive for acetaminophen. However, in our hospital, the standard urine toxicology does not include tramadol. The purpose of the drug testing in this case is to rule out concomitant drug use. Basic laboratory testing including complete blood count, basic blood chemistry, electrolytes and liver enzymes were within normal parameters.

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Table 1 A comparison of the properties of clonidine, lofexidine, and moxonidine

	Mechanism of action	Common adverse effects
Clonidine	Agonist at α_2 -adrenergic receptors Agonist at imidazoline-1 receptors (equal affinity to both receptors)	Sedation Hypotension Orthostatic hypotension Dry mucous membranes Dizziness Asthaenia Headache
Lofexidine	Agonist at α_2 -adrenergic receptors Minimal agonist affinity at imidazoline-1 receptors	Insomnia Sedation Dry mucous membranes Dizziness Asthaenia
Moxonidine	Agonist at imidazoline-1 receptors Minimal affinity at α_2 -adrenergic receptors	Dry mucous membranes Asthaenia Headache

TREATMENT

The patient was started on mirtazapine 30 mg at bedtime, diazepam 5 mg twice daily as needed, loperamide 4 mg as needed for diarrhoea and ibuprofen as needed for pain.

The tramadol was gradually tapered by 50 mg over 2 days and then discontinued. Moxonidine was initiated on the second day at a dose of 0.2 mg once daily and increased to 0.2 mg twice daily on the fifth day.

OUTCOME AND FOLLOW-UP

The patient had an immediate response at the initiation of moxonidine: she felt less irritable and restless, had decreased mydriasis and tremor, with no abdominal cramps and no diarrhoea. She did not report any adverse effects and her vital signs remained stable, and no hypotension was noted. Increasing moxonidine to twice a day caused a significant reduction in the residual tramadol withdrawal symptoms and reduced cravings for the drug. The patient's vital signs remained within normal limits and no hypotension or bradycardia was noted at the higher moxonidine dosage. Her mood improved during her hospital stay and her depressive symptoms, including sleep and appetite, improved significantly. After 10 days in the hospital, she was discharged on moxonidine 0.2 mg twice daily and mirtazapine 30 mg at bedtime. On discharge, the patient declined to join a substance abuse counselling programme. The patient followed up in the clinic 8 weeks later and during the visit it was noted that she was still abstinent from tramadol use, and reported good compliance and tolerability to moxonidine. Her mood was euthymic and her functionality was good. The abstinence and sustained improvement was confirmed by her mother, who accompanied her to the follow-up visit. The patient also reported that she rarely had a craving for tramadol. No adverse medication side effects were mentioned by the patient. She was advised to stay on her current medication regimen and advised to schedule follow-up on a monthly basis. She continued to decline entering into a substance abuse counselling programme.

DISCUSSION

To the best of our knowledge, this is the first case reporting the use of moxonidine for management of opioid withdrawal symptoms. However, multiple studies have revealed the potential role of α_2 receptor agonists, including moxonidine, in the management of pain:⁸ when introduced intrathecally, it was found to have an analgesic effect without acting on the α_2 receptor subtype, which mediates most of the side effects associated with clonidine.⁹ Similarly, imidazoline receptors have been detected in brain areas responsible for perception of pain and have also been found to interact with the opioid system in the central nervous system.¹⁰ This conceptual framework provides feasibility to the hypothesis that imidazoline-modulating drugs are effective in the management of opioid withdrawal; moxonidine seems to be a viable alternative to clonidine in terms of pharmacological efficacy and safety.³ However, randomised controlled trials are needed to further evaluate moxonidine as a drug suitable for opioid detoxification and potential treatment for opioid dependence.

Learning points

- Moxonidine was effective in the management of tramadol withdrawal in a 33-year-old woman with a history of chronic tramadol addiction.
- Moxonidine possibly helped in abstinence and reduced cravings, at least in the short term.
- Moxonidine had a favourable side effects profile and was well tolerated.
- Randomised controlled trials are needed to evaluate moxonidine as a drug for opioid detoxification and possible long-term treatment.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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