

Severe opiate withdrawal in a heroin user precipitated by a massive buprenorphine dose

Nicolas C Clark, Nicholas Lintzeris and Peter J Muhleisen

By diverting his dispensed medication, our patient collected 11 buprenorphine tablets (8 mg each), which he took in one day. The result was not respiratory depression, but instead severe opiate withdrawal lasting four days — this scenario has not previously been reported. This case highlights features of the unique pharmacology of buprenorphine and some key issues for its use in the management of heroin dependence. (MJA 2002; 176: 167-168)

BUPRENORPHINE is a partial opiate agonist that has recently been registered in Australia for use in the management of opiate withdrawal and as an alternative to methadone for long term opiate substitution. In both of these situations, the unique pharmacological properties of buprenorphine give it advantages over existing treatments — its long duration of action allows for dosing every one, two or three days, and as a partial agonist it has ceiling opiate effects (ie, it has high affinity for opiate receptors but low intrinsic efficacy, so higher doses [above 8–12 mg] saturate the receptors for longer, but give only minimal additional opiate effect¹), making it safer in overdose than full opiate agonists. Buprenorphine has low oral bioavailability and is dispensed as a sublingual tablet, with standard maintenance doses of 8–24 mg daily. As with methadone, doses are supervised at a clinic or pharmacy. However, buprenorphine tablets can take 3–8 minutes to dissolve, and in practice it is difficult for busy pharmacists to supervise patients until the tablets have completely dissolved.

Clinical record

We report a patient enrolled in buprenorphine maintenance treatment. At enrolment he was 35 years old, with a 10-year history of heroin use, poorly controlled asthma, and features of depression and anxiety. He started taking buprenorphine at a dose of 8 mg per day, increasing to a maintenance dose of 24 mg daily within three weeks. Consecutive weekly urine samples over six months indicated no heroin use.

After 12 months of continuous therapy, his buprenorphine dose had reduced to 16 mg every second day, and was continuing to be gradually reduced. At this time the patient's long-term relationship ended, he started drinking alcohol heavily and recommenced heroin use. Unbeknown to pharmacy staff at the time, he was not routinely taking his buprenorphine as directed; instead, after dosing he would

leave the pharmacy quickly, spitting out the tablets before they had dissolved. In this way he saved 11 tablets (8 mg each).

After several weeks of regular heroin use without taking buprenorphine (although still attending the pharmacy and continuing to accumulate buprenorphine), he decided to re-initiate treatment of his own accord with the accumulated buprenorphine tablets. He took 40 mg buprenorphine at once, which precipitated uncomfortable opiate withdrawal symptoms (agitation, nausea, sweating, abdominal cramps) within an hour of ingestion. In an attempt to relieve the withdrawal discomfort, he then took a further 24 mg, but this provided no relief. He took a further 16 or 24 mg, but continued to experience persistent agitation, poor sleep, abdominal cramps, diarrhoea and sweating.

The patient presented to the clinic two days later. He appeared restless and agitated and was requesting more buprenorphine. He was dispensed 16 mg buprenorphine, but continued to experience symptoms of opiate withdrawal overnight, despite using heroin. The next morning, still appearing agitated, tense and distressed, he told treatment staff what had happened. He was subsequently transferred to methadone therapy, with resolution of his withdrawal discomfort.

Discussion

This case highlights a number of features of buprenorphine's unique pharmacology which are pertinent to healthcare providers. Firstly, it shows the relative safety of buprenorphine in very high doses. This patient took 88 mg of buprenorphine within one day — almost three times the maximum recommended daily dose (32 mg). This is consistent with another reported case of massive buprenorphine overdose, in which 112 mg was taken orally, also without significant respiratory depression.² This safety is due to the ceiling effects of buprenorphine in high doses.

Secondly, rather than experiencing features of opiate overdose (eg, respiratory depression, sedation), our patient experienced precipitated opiate withdrawal. When buprenorphine is taken soon after opiates with less opiate-receptor affinity, such as heroin and methadone, it displaces them from the receptors. Since buprenorphine is only a partial agonist, this causes a drop in the level of overall opiate

Turning Point Alcohol & Drug Centre, Fitzroy, VIC.

Nicolas C Clark, MB BS, MPH, Medical and Research Officer;
Nicholas Lintzeris, MB BS, BMedSci, Senior Medical and
Research Officer; Peter J Muhleisen, BPharm, Senior Pharmacist.
Reprints: Dr Nicolas C Clark, Turning Point Alcohol & Drug Centre,
54-62 Gertrude Street, Fitzroy, VIC 3065.
nicoc@turningpoint.org.au

activity and is experienced as opiate withdrawal. While we are aware of only three other reported cases of buprenorphine-precipitated withdrawal after heroin use,^{3,4} it is common in methadone patients transferring to buprenorphine therapy, particularly with higher doses of methadone (> 40 mg), a short time between the last methadone dose and the first buprenorphine dose and when higher initial buprenorphine doses are used.⁵⁻⁸ Withdrawal symptoms typically commence within 1–3 hours of the first buprenorphine dose and can last for several days.

Despite the limitation that we have had to rely on the patient's own retrospective estimate of the amount of buprenorphine and other drugs that he consumed, this case supports the notions that precipitated withdrawal can occur in heroin users not taking methadone, and that high initial doses of buprenorphine produce more severe precipitated withdrawal. It also suggests that further doses of buprenorphine may not be useful in trying to relieve precipitated withdrawal symptoms.

This case also demonstrates the difficulties in effectively supervising patients taking buprenorphine. The risks associated with diverted buprenorphine include precipitated withdrawal if used by dependent heroin or methadone users (the people most likely to use diverted buprenorphine^{9,10}); and problems associated with injection of the tablets, including thrombosis, cellulitis, and systemic infections with oral bacteria or fungi. Even though the risk of overdose is less than with heroin or diverted methadone, overdose and death can still occur in combination with other sedatives.¹¹ One strategy for dispensing buprenorphine to patients suspected of diversion is to crush the tablets in a commercial tablet crusher and then dispense the sublingual "powder" under supervision. A fast-dissolving sublingual tablet is being developed to help overcome these problems.

Despite the potential problems of precipitated withdrawal and diversion, buprenorphine is a very useful medication which will greatly increase the range of effective treatment options for heroin dependence in Australia, and it is

important for all healthcare providers to be aware of this very unusual opioid. For more information, national clinical guidelines for the use of buprenorphine are available online.^{11,12}

Acknowledgements

We acknowledge the Victorian Government "Turning the Tide" Initiatives for funding for the New Pharmacotherapies Project and Reckitts Benckiser for supplying buprenorphine free of charge. We thank staff and clients at Turning Point Alcohol and Drug Centre, and Dr Alison Ritter, Head of Research.

References

- Walsh SL, Preston KL, Stitzer ML, et al. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther* 1994; 55: 569-580.
- Houdret N, Asnar V, Szostak-Talbodec N, et al. [Hepatonephritis and massive ingestion of buprenorphine]. [In French]. *Acta Clin Belg Suppl* 1999; 1: 29-31.
- Gourarier L, Lowenstein W, Gisselbrecht M, et al. [Withdrawal syndrome in 2 drug addicts after intravenous injection of buprenorphine?]. [In French]. *Presse Medicale* 1996; 25: 1239-1240.
- Jacobs EA, Bickel WK. Precipitated withdrawal in an opioid-dependent outpatient receiving alternate-day buprenorphine dosing. *Addiction* 1999; 94: 140-141.
- Jasinski DR, Henningfield JE, Hickey JE, Johnson RE. Progress report of the NIDA Addiction Research Centre, Baltimore, Maryland, 1982. In: Harris LS, editor. Problems of drug dependence. NIDA Research Monograph Series. Washington, DC: DHHS (ADM), 1983: 92-98.
- Walsh SL, June HL, Schuh KJ, et al. Effects of buprenorphine and methadone in methadone-maintained subjects. *Psychopharmacology (Berl)* 1995; 119: 268-276.
- Bouchez J, Beauverie P, Touzeau D. Substitution with buprenorphine in methadone- and morphine sulfate-dependent patients. Preliminary results. *Eur Addict Res* 1998; 4 (Suppl 1): 8-12.
- Lintzeris N, Clark N, Ritter A, Muhleisen P. Transferring from methadone maintenance to buprenorphine maintenance: a clinical guideline. *Heroin Addict Related Clin Problems* 2000; 2(1 Suppl): 35-36.
- O'Connor J, Moloney E, Travers R, Campbell A. Buprenorphine abuse among opiate addicts. *Br J Addict* 1988; 83: 1085-1087.
- Quigley AJ, Bredemeyer DE, Seow SS. A case of buprenorphine abuse. *Med J Aust* 1984; 140: 425-426.
- Reynaud M, Petit G, Potard D, Courty P. Six deaths linked to concomitant use of buprenorphine and benzodiazepines. *Addiction* 1998; 93: 1385-1392.
- Lintzeris N, Clark N, Ritter A, et al. Clinical guidelines and procedures for the use of buprenorphine in the treatment of heroin dependence. Published March 2001. <<http://www.dhs.vic.gov.au/phd/buprenorphine/index.htm>>

(Received 20 Aug, accepted 20 Dec, 2001)

□