Lessons from practice

Severe GHB withdrawal delirium managed with dexmedetomidine

Clinical record

A 23-year-old woman was sent to our emergency department with severe agitation 12 hours after admission to a private detoxification facility. She had taken γ-hydroxybutyrate (GHB) and methamphetamine that day, and had reportedly presented to the detoxification unit well.

The woman had been dependent on GHB and γ-butyrolactone (GBL) for 2.5 years, and had misused methamphetamine and benzodiazepines. She took up to 36 mL GHB/GBL, 3 points (0.3 g) of methamphetamine, and 25 mg diazepam daily. Her other diagnoses included depression treated with venlafaxine, and mild attention deficit disorder that had previously been treated with methylphenidate.

At the emergency department, she was agitated and responding to hallucinations. She was tremulous, diaphoretic, and tachycardic. She was inattentive, unable to maintain reasonable conversation, and displayed elements of paranoia and thought disorder. She had to be physically restrained. The delirium work-up suggested no alternative diagnoses.

The patient was administered 65 mg diazepam, 50 mg quetiapine and 10 mg olanzapine during the first 24 hours, without marked benefit. Upon transfer to the intensive care unit, dexmedetomidine infusion was commenced. The infusion rate was titrated (1 to 0.2 mg/h) to limit dexmedetomidine-induced bradycardia and hypotension. Ventilation support was not required. She also received 30–55 mg diazepam each day. By Day 5, the patient was still agitated and responding to visual and auditory hallucinations, although to a lesser degree, and the dexmedetomidine infusion was stopped. She continued to require one-to-one nursing care for verbal re-direction, with good effect, as well as diazepam when her agitation increased.

After 2 weeks, most of her symptoms had subsided and the patient was no longer delirious. She was discharged to a private rehabilitation facility. She was still abstinent from GHB/GBL at one-year follow-up. ◆

The effects of GHB were discovered during the 1960s.[1] GHB is both a metabolite and precursor of γ-aminobutyric acid (GABA),[1] an inhibitory central nervous system neurotransmitter. GBL and 1,4-butanediol (1,4-BD) are prodrugs of GHB. GHB, GBL and 1,4-BD can be produced using methods readily available online.[2]

GHB, GBL and 1,4-BD possess anaesthetic properties,[1] but the lack of analgesic and muscle-relaxant properties, together with several adverse effects, has precluded employing GHB as a general anaesthetic agent.[1] Its use in obstetrics, in alcohol and opioid withdrawal, and in the treatment of narcolepsy and cataplexy has been investigated.[2] GHB is reputed to induce euphoria, enhance sexual performance, and promote growth hormone effects, motivating its misuse.[2] Its narrow therapeutic index makes recreational use dangerous, with respiratory depression and coma not uncommon following only small increases in the amount taken.[3]

GHB binds to high affinity GHB-specific receptors and lower affinity $GABA_B$ receptors: physiological levels of GHB activate GHB but not $GABA_B$ receptors.[3] The clinical effects of exogenous GHB are thought to be mediated by $GABA_B$ activation.[3]

GHB is readily absorbed orally, with serum peak concentrations reached within one hour.[1] GHB undergoes significant first pass metabolism in the liver, producing succinic acid, which is metabolised to carbon dioxide and water in the Krebs cycle; a minor proportion is metabolised to GABA.[1] Clearance of GHB via saturable metabolic pathways is dose-dependent.[1] The elimination half-life is 20–60 minutes, with most drug eliminated within 4–8 hours,[1] so that dependent users often take several doses throughout the day.

Early features of GHB withdrawal resemble those of alcohol withdrawal, including autonomic instability, tremor, anxiety, agitation and altered sleep. As with our patient, severe withdrawal can include acute delirium that requires intensive care.[4] Given its short half-life, withdrawal symptoms can start within hours of the last use, and are thought to be due to the loss of GHB-mediated inhibitory effects in the central nervous system, resulting in a hyper-excitatory state. Withdrawal can last 3–21 days.[4]

Benzodiazepines ($GABA_A$ receptor agonists) have been the mainstay of the pharmacotherapy for GHB withdrawal, and large quantities are usually required. Benzodiazepine-resistant patients have been reported, necessitating the use of other sedative agents, including propofol and baclofen.[1] We report the application of dexmedetomidine, a short-acting α_2-adrenoceptor agonist, for managing GHB withdrawal. Dexmedetomidine has the advantage of producing relatively limited respiratory depression and a qualitatively different sedation to benzodiazepines; it reduces the prevalence of

Lessons from practice

- GHB withdrawal syndrome can occur within hours of the most recent use; it can resemble the alcohol withdrawal syndrome, but can be more prolonged.
- Benzodiazepines are the mainstay of pharmacological management of GHB withdrawal, but have undesirable side effects and variable efficacy.
- Early recognition and prompt implementation of appropriate management are crucial in the care of patients with acute drug withdrawal syndromes.
- Dexmedetomidine may facilitate a less invasive and safer approach to the management of delirium associated with drug withdrawal. ◆

Emma MY Tay[1,2]
Robert I Graham[1]
Richard O Day[2,3]

1 Western Sydney Local Health District, Sydney, NSW.
2 St Vincent's Hospital, Sydney, NSW.
3 St Vincent's Clinical School, UNSW, Sydney, NSW.

emma.tay@svha.org.au

doi: 10.5694/mja16.00269

delirium, and possesses analgesic effects, unlike benzodiazepines.[5] However, the duration of intensive care and overall hospital length of stay are similar to benzodiazepine management.[5]

Early recognition and prompt implementation of appropriate care are crucial for preventing the more severe complications of acute withdrawal. Dexmedetomidine sedation may help facilitate a less invasive and safer approach to intensive care management of delirium secondary to drug withdrawal.

Competing interests: No relevant disclosures. ■

References are available online at www.mja.com.au.

1 Schep LJ, Knudsen K, Slaughter RJ, et al. The clinical toxicology of γ-hydroxybutyrate, γ-butyrolactone and 1,4-butanediol. *Clin Toxicol (Phila)* 2012; 50: 458-470.

2 World Health Organization Expert Committee on Drug Dependence. Gamma-hydroxybutyric acid (GHB): critical review report. WHO, 35th meeting, Hammamet, Tunisia, 4–8 June 2012. http://www.who.int/medicines/areas/quality_safety/4.1GHBcritical_review.pdf (accessed July 2016).

3 Snead OC, Gibson KM. γ-Hydroxybutyric acid. *N Engl J Med* 2005; 352: 2721-2732.

4 Meyer R, Jenewein J, Boettger S. Management of γ-butyrolactone dependence with assisted self-administration of GBL. *Case Rep Neurol Med* 2014; 2014: 485178.

5 Reade MC, Finfer S. Sedation and delirium in the intensive care unit. *N Engl J Med* 2014; 370: 444-454. ■