Adjunctive dexmedetomidine for treatment of delirium tremens: Case report and brief review

Amit Chail, Amresh Dubey, Yujal Man Singh, Nikahat Jahan
Department of Psychiatry, Command Hospital (Southern Command), Department of Anaesthesiology, AFMC, Pune, Maharashtra, India

Address for correspondence:
Dr. Amresh Dubey,
Department of Psychiatry,
Command Hospital,
Pune, Maharashtra, India.
E-mail: drdubeyamresh1980@gmail.com

Received: 18 June 2020
Accepted in Revised Form: 03 July 2020
Published: 14 August 2020

Alcohol withdrawal delirium (delirium tremens [DT]) is a medical emergency. Gamma-aminobutyric acid type A agonists (benzodiazepines [BZDs]) are the mainstay of treatment. Resistant alcohol withdrawal requires adjunctive medications along with BZDs and supportive care. DT is associated with significant autonomic dysfunction (sympathetic hyperactivity). Dexmedetomidine is a selective α2-adrenergic receptor agonist which reduces sympathetic over-activity and agitation in delirious patients. We present a case of alcohol withdrawal delirium (DT) who responded well to adjunctive dexmedetomidine infusion resulting in reduced sympathetic activity and reduced dose requirement of BZDs.

Keywords: Alcohol withdrawal state, alpha-2 agonist, delirium tremens, dexmedetomidine, resistant alcohol withdrawal

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Chail A, Dubey A, Singh YM, Jahan N. Adjunctive dexmedetomidine for treatment of delirium tremens: Case report and brief review. Ind Psychiatry J 2019;28:321-4.
of alcohol withdrawal from a peripheral centre. He had a history of multiple hospitalizations and relapses in the last 2 years. In the current episode, he developed generalized tremulousness, nausea and excessive sweating, within a day of stoppage of regular heavy drinking. He had two Generalised Tonic-Clonic Seizures (GTCS) on the same day which led to his hospitalisation in the peripheral centre.

On initial evaluation at 0800 h Day 1, he was disoriented to time and place. He had tachycardia (heart rate [HR]: 120/min), raised blood pressure (BP) (150/100 mmHg), generalized tremulousness, and profuse sweating. He was restless, uncooperative, and agitated.

His hematological and biochemical investigations showed mean corpuscular volume of 101 fL and hypokalemia and hypomagnesemia with serum potassium level of 2.8 mEq/L and serum magnesium of 1.3 mg/dl, respectively. His noncontrast computed tomography head was essentially normal.

He was diagnosed with a case of alcohol withdrawal delirium. His initial CIWA-ar score was 29. He was given 08 mg of injection lorazepam over 01 h. He had minimal symptom control with the same. A total of 36 mg lorazepam was given on D1. He was also given, tab Haloperidol 5 mg orally and injection haloperidol 5 mg I/M, adequate hydration, electrolytes and injection Thiamine 1000 mg/day. In view of hypokalaemia and hypomagnesemia, injection Potassium Chloride (KCl) 100 meq/L intravenous (IV) over 24 h, and injection magnesium sulphate 4 g slow IV over 48 h were administered. However despite this, his RASS score varied from +3 to +2 and CIWA-Ar was around 14–16.

His BZD was switched to midazolam infusion on D3 and augmented with dexmedetomidine infusion on D4, as shown in Table 1. By day 5, individual was oriented and cooperative and his vital parameters stabilized (HR 82/min and BP 128/84 mmHg). His oral BZDs were tapered off and tab acamprosate (neuro-protective) (333 mg Thrice a day (TDS) and naltrexone (50 mg OD) (in view of hedonistic drinking) was started. He was also given benefit of motivational enhancement therapy and cognitive behavioral therapy for relapse prevention. He was subsequently discharged after 4 weeks of inpatient care.

Brief review
Dexmedetomidine (an imidazole compound) is the pharmacologically active dextroisomer of medetomidine and a selective α2-adrenoceptor agonist. Its dexmedetomidine is 08 times more specific for α2-receptors than clonidine. The α2:α1 specificity of clonidine is 220:1, whereas for dexmedetomidine its 1620:1.[9] The actions of dexmedetomidine are suggested to be mediated through presynaptic α2-adrenoceptors which activate pertussis toxin-sensitive G proteins, thereby increasing conductance through potassium ion channels. It inhibits the release of norepinephrine from synaptic vesicles. This leads to an inhibition of sympathetic activity, thereby leading to sedation and anxiolysis.[10] Healthy individuals treated with dexmedetomidine at low concentrations have been demonstrated to have decreased norepinephrine levels and decreased HRs.[11]

Pharmacokinetics
It has a half-life of 6 min and terminal half-life 2 h. The average protein binding is 94%. Biotransformation involves both direct glucuronidation as well as cytochrome P450-mediated metabolism. 95% is excreted in urine and 4% in feces.[10]

Dosing
As per the US Food and Drug Administration

| Table: 1 Course in hospital |
|-----------------------------|
| Medication | Name of medicine | Route | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
| Lorazepam | | IV | 36 mg | 48 mg | 21 mg | - | - | - | - |
| Haloperidol | | PO | 5 mg | 7.5 mg | - | - | - | - | - |
| | | IM | 5 mg | 10 mg | 5 mg | - | - | - | - |
| Midazolam | | IV | - | - | 72 mg | 24 mg | - | - | - |
| Dexametomidine | | IV | - | - | - | 180 µg | - | - | - |
| Diazepam | | PO | - | - | - | - | 50 mg | 100 mg | - | - |
| Total (BZD) Diazepam dose equivalent* | | | 360 mg | 480 mg | 480 mg | 140 mg | 150 mg | 100 mg | 60 mg |

Assessment scale

| Clinical Assessment | Minimum | Maximum |
|---------------------|---------|---------|
| CIWA-Ar score | 14 | 18 |
| RASS score | 3 | 3 | 14 | 4 |

*See discussion for BZD dose equivalence. CIWA-Ar – Clinical Institute Withdrawal Assessment for Alcohol revised; RASS – Richmond Agitation-Sedation Scale; IV – Intravenous; IM – Intramuscular; PO – Per Os (Orally)
recommended dose of dexmedetomidine for conscious sedation is between 0.2 and 0.7 $\mu$g/kg/h.[13] However, doses in the studies varied widely, from 0.2 $\mu$g/kg/h up to 4.6 $\mu$g/kg/h. In a study by Tolonen et al., patients received very high-infusion rates (>2.7 $\mu$g/kg/h) and experienced a high rate of adverse events, including pneumonia, respiratory failure, and the need for noninvasive mechanical ventilation.[13] Taking these outcomes into account, best practice at this time seems to be slow titration with maximum dose individualized based on response and adverse effects.

**Adverse effects**

Some of the notable adverse effects include bradycardia, sinus arrest, and hypotension.[10]

**Clinical benefits of dexmedetomidine versus propofol**

Studies indicate that dexmedetomidine may offer advantages over propofol in terms of decrease in the length of intensive care unit (ICU) stay, risk of delirium, and need for mechanical ventilation.[14,15] Dexmedetomidine reduces the need for BZDs and is a promising and effective adjuvant treatment for AWS.[8]

**DISCUSSION**

Prolonged alcohol use leads to downregulation of gamma-aminobutyric acid (GABA) receptors and increased expression of NMDA receptors. Abrupt cessation of chronic alcohol consumption unmasks these changes with a glutamate-mediated CNS excitation resulting in autonomic over activity which involves noradrenergic system.[13] BZDs (GABAergic agonists) reduce withdrawal symptom severity, duration, risk of delirium, and incidence of seizure.[15] Dose equivalence of BDZ is usually calculated as: 10 mg Diazepam is approximately =1 mg Lorazepam= 2.67 mg Midazolam.[10] Patients with severe or RAW are more likely to require intubation and mechanical ventilation and experience longer ICU and hospital stays.[11] Such cases require treatment augmentation with anesthetic agents (propofol), phenobarbital, or alpha agonists (dexmedetomidine).

Our patient had RAW. Dexmedetomidine was preferred over other options as it is sympatholytic, sedating, and reduces agitation along with reducing the risk of respiratory depression and mechanical ventilation. He had a rapid response in the severity of symptoms and was shifted out of ICU a day after initiation of dexmedetomidine. This highlights the potential efficacy and safety of dexmedetomidine as an adjunct in alcohol withdrawal delirium.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

This study was financially supported by the Department of Psychiatry, Command Hospital, Pune and Department of Anaesthesia, AFMC, Pune, India.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Gururaj G, Varghese M, Benegal V, Rao GN, Pathak K, Singh LK, et al. National Mental Health Survey of India, 2015-16: Prevalence, patterns and outcomes. Bengaluru, National Institute of Mental Health and Neuro Sciences, NIMHANS Publication No. 129. 2016. Available from: http://indianmhs.nimhans.ac.in/Docs/Report2.pdf [Last accessed on 2020 Apr 28].

2. Subodh BN, Umamaheswari V. Synopsis of the Clinical Practice Guidelines on management of Alcohol Use Disorders. In: Basu D, Dalal PK, eds. Synopsis of the Clinical Practice Guidelines on Substance Use Disorders. New Delhi: Indian Psychiatric Society; 2015. p. 21-35.

3. Taylor DM, Barnes TR, Young AH editors. The Maudsley Prescribing Guidelines in Psychiatry. 13th ed. Hoboken, NJ: Wiley Blackwell; 2018.

4. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O’Neal PV, Keane KA, et al. The Richmond agitaton-sedation scale: Validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338-44.

5. Hack JB, Hoffmann RS, Nelson LS. Resistant alcohol withdrawal: Does an unexpectedly large sedative requirement identify these patients early? J Med Toxicol 2006;2:55-60.

6. Rayner SG, Weinert CR, Peng H, Jepsen S, Broccard AF, Study Institution. Dexmedetomidine as adjunct treatment for severe alcohol withdrawal in the ICU. Ann Intensive Care 2012;2:12.

7. Kalabalik J, Sullivan JB. Use of Dexmedetomidine in the Management of Alcohol Withdrawal Syndrome in Critically Ill Patients. Int J Crit Care Emerg Med 2015;1:1-5.

8. Muzyk AJ, Kerns S, Brudney S, Gagliardi JP. Dexmedetomidine for the treatment of alcohol withdrawal syndrome: Rationale and current status of research. CNS Drugs 2013;27:913-20.

9. Giovannitti Jr JA, Thomis SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: A review of current clinical applications. Anesth Prog 2015;62:31-9.

10. DEXMEDETOMIDINE C13H16N2 PubChem. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Dexmedetomidine. [Last accessed on 2020 Jun 14].

11. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colino CM. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000;93:382-94.

12. FDA US. Prescribing Information DEXMEDETOMIDINE Hydrochloride Injection; 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206628s000lbl.pdf [Cited on 2020 April 30].

13. Tolonen J, Rossinen J, Alho H, Harjola VP.
Dexmedetomidine in addition to benzodiazepine-based sedation in patients with alcohol withdrawal delirium. Eur J Emerg Med 2013;20:425-7.

14. Wong A, Benedict NJ, Kane-Gill SL. Multicenter evaluation of pharmacologic management and outcomes associated with severe resistant alcohol withdrawal. J Crit Care 2015;30:405-9.

15. Jesse S, Bråthen G, Ferrara M, Keindl M, Ben-Menachem E, Tanasescu R, et al. Alcohol withdrawal syndrome: Mechanisms, manifestations, and management. Acta Neurol Scand 2017;135:4-16.

16. Benzodiazepine Equivalents Conversion Calculator. Available from: https://clincalc.com/Benzodiazepine/default.aspx. [Last accessed on 2020 Jun 15].