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CLINICAL REPORT

Use of dexmedetomidine for the treatment of alcohol withdrawal syndrome in critically ill patients: a retrospective case series

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Abstract Alcohol withdrawal syndrome (AWS) continues to be a challenge to manage in the ICU setting, and the ideal pharmacological treatment continues to evolve. Dexmedetomidine is a newer agent approved for short-term sedation in the ICU, but its use in the treatment of AWS has been limited. We report a retrospective case series of ten patients who were identified as receiving dexmedetomidine for AWS as designated by electronic pharmacy records. All subjects were male, with a mean age of 53.6 years, and a mean ICU length of stay of 9.3 days. They were all diagnosed with AWS by DSM-IV criteria. All the study patients received dexmedetomidine during their hospital course as a treatment for AWS. Studied variables included demographic data, dose and duration of dexmedetomidine, other pharmaceutical agents, and hemodynamics. Dexmedetomidine was safe to use in all patients, although mechanical ventilation was still required in three patients. With dexmedetomidine, the autonomic hyperactivity was blunted, with a mean 12.8 % reduction in rate pressure product observed. Consideration should be given to the combined use of dexmedetomidine with benzodiazepines in the treatment of AWS.

Keywords Dexmedetomidine · Alcohol withdrawal syndrome · Pharmacological therapy · Alcohol · Critical care

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Introduction

The treatment of alcohol withdrawal syndrome (AWS) is challenging to intensivists. Benzodiazepines remain the mainstay of treatment [1–3]. Complications of therapy include hemodynamic instability and respiratory depression.

Clonidine, a centrally acting alpha-2 adrenergic agonist, is used to ameliorate the autonomic dysfunction associated with AWS [4]; however, it is associated with bradycardia and hypotension [5]. Limitations to clonidine use in the intensive care unit (ICU) include its long duration of action and the nonintravenous route of administration (p.o. or transdermal).

Dexmedetomidine is indicated for sedation with mechanical ventilation and conscious sedation [6]. Dexmedetomidine was designed from clonidine to maximize the sedative effects by having an α2:α1-adrenoreceptor ratio of 1,600:1, making it eight times more potent [7]. It is an alpha-2 adrenergic agonist, with anesthetic, anxiolytic, analgesic, and sympatholytic effects [8]. Dexmedetomidine has a 2-h half-life, with linear pharmacokinetics [9]. Bradycardia and hypotension are the most common adverse events. Dexmedetomidine is FDA approved for a maximum of 24 h; however, there is experience for longer-term use [10]. In animal models [11–13], dexmedetomidine significantly diminished the ethanol withdrawal reaction. There have been isolated case reports of the use of dexmedetomidine as an infusion in the ICU for the treatment of AWS [14–17].

Case series

We conducted a retrospective chart review at Winthrop University Hospital of all patients who received

dexmedetomidine in the ICU during a 12-month period. Our institution is a tertiary 590-bed hospital with 55 adult ICU beds. The study was conducted from pharmacy records in all patients who received dexmedetomidine during the calendar year 2010. This study received Investigational Review Board approval.

We reviewed 330 records and determined which patients received dexmedetomidine for AWS. The diagnosis of AWS was made according to DSM-IV criteria [18]. We collected multiple variables including demographics, location, ICU length of stay (LOS), operations, duration of mechanical ventilation, pneumonia, illicit drug history, admission alcohol level, duration of AWS, dose and duration of dexmedetomidine, adjunct drugs for AWS, and hemodynamics before and 4 h after the initiation of dexmedetomidine. All data were tabulated in a spreadsheet (Microsoft Office Excel 2007) for analysis. The rate pressure product (RPP) was calculated from the formula RPP = SBP × HR (SBP = systolic blood pressure, HR = heart rate) [19].

We identified ten patients (Table 1); all were male with a mean age of 53.6 years of age (range, 20–90 years). All the patients had a history of alcohol abuse, and 60 % of them were agitated within 48 h of admission. Three of the patients required mechanical ventilation for 1–9 days (mean, 5.3 days), despite dexmedetomidine infusion at the maximum recommended dose of 0.7 μg/kg/h in two patients, and one patient at 1.2 μg/kg/h. Seven patients developed AWS in the postoperative period after an invasive procedure requiring intubation; the remaining patients had no procedure. The average hospital LOS was 14.2 days (range, 2–55 days), and the mean ICU LOS was 9.3 days (range, 1–33 days). No clinical seizure activity was noted, and no mortalities occurred.

In five of the patients, no alcohol level was sent on admission; in three patients, it was negative, and in the remaining two it was significantly elevated, to 309 and >500 mg/dl, respectively. In nine patients, a heavy alcohol consumption history was elicited; the tenth patient was intoxicated on admission. No illicit drug abuse was found in any of the patients, by history or toxicology screen.

Dexmedetomidine and benzodiazepines were used to treat AWS at the discretion of the intensivist. Dexmedetomidine was used as a continuous infusion without a bolus in all ten patients, at a mean dose of 0.63 μg/kg/h (range, 0.2–1.2 μg/kg/h) for a mean period of 92.7 h (range, 13–247 h). In three patients, dexmedetomidine was the only agent used. None of the patients developed aspiration or pneumonia while on dexmedetomidine. None of our patients was simultaneously started on a continuous infusion of a benzodiazepine or propofol. Five patients were administered lorazepam as an intravenous injection 2 mg every 6 h, which is equivalent to 0.31 mg/h (range, 0.1–0.46 mg/h). In two patients, midazolam was given at 1 mg every 4 h intravenously.

Dexmedetomidine failed to control severe agitation in three patients, and it was discontinued, despite two of the three patients receiving lorazepam simultaneously. These patients required both a benzodiazepine plus propofol infusion to control the agitation, which also required mechanical ventilation. Those who failed the dexmedetomidine treatment were given a propofol infusion ranging from 40 to 88 μg/kg/min; in addition, they were given ativan 2 mg every 6 h, and the third received midazolam infusion at 7 mg/h, which was continued for 12–97 h. Once the propofol was started, the dexmedetomidine was discontinued because of cost consideration. The duration of the AWS in our patients closely paralleled the duration of dexmedetomidine, with a mean time of 106.7 h.

In 70 % of the patients, antipsychotics were also administered, with haloperidol being the most common agent used, intravenously at 5-mg doses every 6 h to control agitation. The atypical antipsychotics quetiapine and risperidone were also used. Postoperative pain was managed with a fentanyl infusion, at a range of 25–100 μg/h titrated to a pain score.

The use of dexmedetomidine did not produce a significant change in our patients' vital signs 4 h into the infusion (Table 2); however, there was a downward trend. Although all patients were on beta-blockers, the autonomic hyperactivity was blunted after initiation of dexmedetomidine. The symptoms of AWS, including agitation, improved in 1–2 h. Mean heart rate decreased by 10.5 %, although no patient had bradycardia requiring discontinuation of dexmedetomidine. Reduction of systolic pressure as well as mean arterial pressure of 2.8 % occurred in both parameters, with a similar reduction in diastolic blood pressure of 2.7 %. Also, the RPP decreased by 12.8 %. However, on statistical analysis, none of these was a significant change from baseline. By not using a bolus, hypotension and bradycardia were avoided.

Discussion

Dexmedetomidine has utility in the management of AWS. Although our retrospective case series is limited in size, it demonstrates the successful use in AWS patients. Our series, with the exception of severe cases, demonstrates the safety of combining dexmedetomidine with multiple pharmacological agents without significant side effects. There was a trend toward decreasing the RPP, corresponding to an improvement in the autonomic hyperactivity of these patients. Although the FDA cautions against prolonged use of dexmedetomidine because of the possibility of withdrawal symptoms, this was not observed in

Table 1 Summary of the patients with alcohol withdrawal syndrome (AWS) treated with dexmedetomidine

Patient	Age (years)	Gender	Unit	Vent	Diagnosis	Procedure	Home EtOH usage	Past medical history	Duration of dexmedetomidine (h)	Max infusion of dexmedetomidine (μg/kg/h)	Duration of AWS (h)	Hospital LOS	ICU LOS
1	32	M	SICU	N	Head trauma, sz post assault	None	8 beers daily	None	84	0.7	91	8	5
2	29	M	SICU	N	Facial trauma	ORIF of facial fx	1 bottle bourbon daily	None	145	1.0	148	12	6
3	55	M	SICU	N	Diverticulitis	Hartmann reversal	12 beers daily	HTN, hyperlipidemia	13	0.4	17	10	3
4	82	M	SICU	Y	Diverticulitis	Sigmoid colon resection	1 bottle vodka/ weekend	DM, HTN, hyperlipidemia, anemia, afib	161	0.7	183	55	33
5	39	M	MICU	N	AWS	None	12 beers daily	HTN	61	0.3	62	13	6
6	68	M	NeuroICU	N	SAH	VP shunt	4 beers daily	HTN	247	0.4	257	17	17
7	20	M	SICU	Y	Scalp laceration TBI	Repair of scalp laceration	Intoxicated on admission, EtOH = 309	ADHD	6	1.2	21	2	1
8	90	M	NeuroICU	N	SDH from fall	None	4 scotch daily	CHF	135	0.7	141	12	12
9	57	M	NeuroICU	Y	Carotid stenosis	Angiogram and carotid stent	"Daily"	DM, HTN, hyperlipidemia	20	0.7	97	10	8
10	64	M	MICU	N	Right inguinal hernia	Repair of RIH	3 beers daily	HTN	48	0.2	50	3	2
Mean	53.6	100 % male		30 %					92.7	0.63	106.7	14.2	9.3

M male, *N* no, *Y* yes, *EtOH* alcohol, *LOS* length of stay, *SICU* Surgical Intensive Care Unit, *NeuroICU* Neurosciences Intensive Care Unit, *MICU* Medical Intensive Care Unit, *AWS* alcohol withdrawal syndrome, *SAH* subarachnoid hemorrhage, *TBI* traumatic brain injury, *RIH* right inguinal hernia, *SDH* subdural hematoma, *HTN* hypertension, *DM* diabetes mellitus, *afib* atrial fibrillation, *ADHD* attention deficit hyperactivity disorder, *VP* ventriculoperitoneal, *ORIF* open reduction internal fixation, *CHF* congestive heart failure

Table 2 Vital signs pre- and post dexmedetomidine

	Pre infusion of dexmedetomidine	Post infusion of dexmedetomidine (4 h after drug initiated)	Change (%)	Statistics (P value)[a]
HR (bpm)	91.1	81.5	−10.5	0.13, NS
MAP (mmHg)	93.3	90.7	−2.8	0.75, NS
SBP (mmHg)	133.5	129.7	−2.8	0.75, NS
DBP (mmHg)	73.2	71.2	−2.7	0.77, NS
RPP (mmHg)	12084.2	10539.7	−12.8	0.24, NS

NS not significant

[a] Student's t test

our AWS patients. We believe that the lack of any bradycardia or hypotension in our patients is the result of the already existing excessive adrenergic autonomic dysfunction that is a hallmark of AWS. However, caution must be used in nonhypertensive, volume-depleted critically ill patients.

Although the manufacturer warns about a dose reduction in the elderly, in our patients more than 65 years of age no adjustment was necessary, with no noted increase in adverse effects. Lack of early response at the maximum dexmedetomidine dose signals the failure of the drug to control the AWS.

Our protocol initiates dexmedetomidine for AWS starting at 0.1 μg/kg/h, titrating rapidly to a target HR < 100, and a Ramsay scale of 2, with the maximum dose used 1.2 μg/kg/h. Concurrently, we use β-blockers (metoprolol 5 mg intravenously every 6 h) plus lorazepam 2 mg intravenously every 6 h, and haloperidol as needed for agitation. If no response is seen, an extra dose of lorazepam 2 mg is given. If this is adequate, then we initiate a continuous benzodiazepine infusion, and if this fails the dexmedetomidine is switched to propofol infusion with intubation and mechanical ventilation.

Dexmedetomidine allowed lower doses of other agents to be used, which avoids accumulation of benzodiazepines, excessive sedation and obtundation, need for airway protection, respiratory depression, and mechanical ventilation, as well as possible ventilator-associated pneumonia (VAP). Also, it may reduce unnecessary neurological workups [e.g., head computed tomography (CT)] because patients on dexmedetomidine can still be examined and are capable of interactions.

In our experience, dexmedetomidine is safe and effective in the treatment of AWS. It can be used for prolonged courses in combination with low-dose benzodiazepines and antipsychotics. We noted that in the severe AWS cases it was not effective at our current maximum dose of 1.2 μg/kg/h; however, it remains to be seen if higher doses would be more efficacious. Because of the autonomic hyperactivity, and lack of bradycardia or hypotension, it is an open question whether higher maximum doses of dexmedetomidine would be tolerated and effective in the severe AWS patient, thus preventing the patients who required mechanical ventilation, and possibly decreasing overall LOS. Although our series is small, and retrospective, the AWS patients are a challenging group to study [20]. Further research should be done, on a randomized, prospective basis, to select the patients who will have the best outcomes with this agent and to accumulate further experience.

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References

1. Kaim SC, Klett CJ, Rothfeld B. Treatment of the acute alcohol withdrawal state: a comparison of four drugs. Am J Psychiatry. 1969;125:1640–6.
2. Sarff M, Gold J. Alcohol withdrawal syndromes in the intensive care unit. Crit Care Med. 2010;38(suppl):S494–S501.
3. Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. N Engl J Med. 2003;348:1786–95.
4. Cushman P Jr. Clonidine and alcohol withdrawal. Adv Alcohol Subst Abuse. 1987;7:17–28.
5. Kamibayashi T, Maze M. Clinical uses of α2-adrenergic agonists. Anesthesiology. 2000;93:1345–9.
6. Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. Ann Pharmacother. 2007;41:245–52.
7. Abramov D, Nogid B, Nogid A. The role of dexmedetomidine (Precedex) in the sedation of critically ill patients. P&T. 2005;30:158–61.
8. Lakhlani PP, MacMillan LB, Guo TZ, McCool BA, Lovinger DM, Maze M, Limbird LE. Substitution of a mutant a2A-adrenergic receptor via 'hit and run' gene targeting reveals the role of this subtype in sedative, analgesic, and anesthetic-sparing responses in vivo. Proc Natl Acad Sci USA. 1997;94:9950–5.
9. Dexemetomidine (package insert). Lake Forest: Hospira, Inc.; 2008.
10. Reiter PD, Pietras M, Dobyns EL. Prolonged dexmedetomidine infusions in critically ill infants and children. Indian Pediatr. 2009;46:767–73.
11. Riihioja P, Jaatinen P, Oksanen H, Haapalinna A, Heinonen E, Hervonen A. Dexmedetomidine, diazepam, and propanolol in the treatment of ethanol withdrawal symptoms in the rat. Alcohol Clin Exp Res. 1997;21:804–8.
12. Riihioja P, Jaatinen P, Haapalinna A, Kiianmaa K, Hervonen A. Effects of dexmedetomidine on rat locus coeruleus and ethanol withdrawal symptoms during intermittent ethanol exposure. Alcohol Clin Exp Res. 1999;23:432–8.
13. Le AD, Harding S, Juzytsch W, Funk D, Shaham Y. Role of alpha-2 adrenoreceptors in stress-induced reinstatement of alcohol seeking and alcohol self-administration in rats. Psychopharmacology. 2005;179:366–73.

14. Darrouj J, Puri N, Prince E, Lomonaco A, Spevetz A, Gerber DR. Dexmedetomidine infusion as adjunctive therapy to benzodiazepines for acute alcohol withdrawal. Ann Pharmacother. 2008;42:1703–5.
15. Maccioli GA. Dexmedetomidine to facilitate drug withdrawal. Anesthesiology. 2003;98:575–7.
16. Rovasalo A, Tohmo H, Aantaa R, Kettunen E, Palojoki R. Dexmedetomidine as an adjuvant in the treatment of alcohol withdrawal delirium: a case report. Gen Hosp Psychiatry. 2006;28:362–3.
17. Baddigam K, Russo P, Russo J, Tobias J. Dexmedetomidine in the treatment of withdrawal syndromes in cardiothoracic surgery patients. J Intensive Care Med. 2005;20:118–23.
18. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edn., text revision. Washington, DC: American Psychiatric Association; 2000. p. 216.
19. Jones R, Knight PR, Hill AB. Rate pressure product. Anaesthesia. 1980;35:1010–1.
20. Williams D, McBride AJ. The drug treatment of alcohol withdrawal symptoms: a systematic review. Alcohol Alcohol. 1998;33:103–15.