Use of propofol infusion in alcohol withdrawal-induced refractory delirium tremens

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ABSTRACT

INTRODUCTION: Delirium tremens is a potentially fatal complication of alcohol withdrawal. In severe delirium, very large dosages of benzodiazepines can be required and in refractory cases, sedation with propofol can be used. Treatment of refractory delirium tremens with propofol is mainly described in case reports. We aimed to evaluate the treatment of delirium tremens with propofol infusion for 48 h.

MATERIAL AND METHODS: This study was a single-centre retrospective cohort analysis of 15 patient journals covering the period from May 2012 to September 2013.

RESULTS: Five women and ten men were included. Their mean age was 50.9 years. Prior to propofol treatment, conventional treatment with up to 1,500 mg of benzodiazepines, 2,000 mg of chlordiazepoxide or 1,200 mg of phenobarbital was attempted in the medical or psychiatric ward, without effect (sleep). Patients were sedated, intubated and mechanically ventilated in the intensive care unit. The mean propofol infusion rate was 4.22 mg/kg/h. Thirteen patients received supplemental infusion of opioids, whereas seven required concomitant vasopressor infusion. Once propofol infusion was discontinued after 48 h, 12 patients had a long awakening, displaying symptoms of prolonged sedation. Twelve of the 15 patients treated for delirium tremens with propofol for 48 h were successfully treated. Three patients needed further treatment.

CONCLUSION: Our study suggests that treatment with propofol is viable. Establishing indication, dose, duration, and long-term effects of propofol treatment of delirium tremens requires further investigation.

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Alcohol dependency and abuse is common in the Western world. Of the 5.5 million people living in Denmark, it is estimated that at least 585,000 people have a detrimental alcohol use, and 140,000 are suffering from alcohol addiction [1].

Acute alcohol ingestion causes central nervous system depression through excitation of inhibitory γ-aminobutyric acid-A ($GABA_A$) receptors, inhibition of the N-methyl-D-aspartate (NMDA) component of excitatory glutamate receptors as well as interaction with serotonin and dopamine receptors. Excitation of the $GABA_A$ receptor leads to anxiolysis, sedation and impaired motor coordination. Chronic alcohol ingestion induces tolerance through reduction of $GABA_A$ receptor function as well as up-regulation of NMDA receptors, which results in a compensatory increase in excitatory neurotransmission. Lack of inhibition by alcohol due to reduced or discontinued alcohol use leads to excessive central nervous system excitation (symptoms of withdrawal) [2]. Withdrawal symptoms arise within hours to days of alcohol abstinence and range in degree from sympathetic hyperactivity, nausea or vomiting to hallucinations and withdrawal seizures and, most severely, delirium tremens (DT). Clinically, DT presents as disorientation, agitation, hallucinations, tremors, diaphoresis, tachycardia, hypertension and pyrexia (i.e. symptoms corresponding to hyperactive delirium). DT occurs in 5-20% of alcohol withdrawals, typically 1-5 days after alcohol abstinence, and DT carries a mortality rate of up to 25% although treatment can reduce this to 0-1% [3]. Mortality is caused by complications to the clinical manifestations of DT, i.e. myocardial infarction due to autonomic hyperactivity [2]. Delirium usually lasts from three to five days, up to two weeks, though rare cases of even longer DT periods do exist [4].

Treatment of withdrawal

Benzodiazepines are the preferred treatment for withdrawal symptoms owing to cross-tolerance with alcohol through modulation of $GABA_A$ receptors [5]. The most commonly used benzodiazepines are chlordiazepoxide and diazepam. Adjuvant treatment with clonidine or haloperidol is also used. Treatment for withdrawal is normally administered at medical and psychiatric wards. In situations of severe withdrawal symptoms, very large dosages of benzodiazepines can be required, and intravenous barbiturates can be used in these cases. These cases typically require close monitoring due to a narrow therapeutic window and lack of antidote [3, 6]. An alternative to this is propofol, which is a short-acting, intravenous sedative-hypnotic agent commonly used for sedation during surgery as well as in the intensive care unit (ICU). Like benzodiazepines, propofol interacts with $GABA_A$ receptors, though not at the same binding site [7-9]. Propofol also inhibits the NMDA subtype of glutamate receptors and thus has a dual effect. The effect is inhibition of the central nervous system and reduction of withdrawal symptoms.

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Delirium tremens is the most severe manifestation of alcohol withdrawal.

The literature regarding propofol sedation for the treatment of alcohol withdrawal is limited, although the two topics are well-studied separately. The aim of this study was to evaluate the effect of treatment of refractory DT with propofol infusion for 48 h.

MATERIAL AND METHODS

The study was a single-centre retrospective cohort analysis. Data were extracted through a retrospective review of patient journals from May 2012 to September 2013. Extraction and review of the data from patient journals was done independently by two authors.

Health-care professionals at the ICU at Glostrup Hospital, Denmark, follow a regional instruction in which propofol is suggested for refractory cases of DT (**Figure 1**). Patients admitted for alcohol detoxification were assessed with the Withdrawal Syndrome Scale for Alcohol [10], a validated assessment scale for registering, graduating and monitoring of withdrawal symptoms. The inclusion criteria were symptoms requiring up to 2,000 mg of benzodiazepines without effect (sleep) and DT as diagnosed either by a psychiatric or an intensive care physician. Patients were admitted to the ICU, sedated, intubated and mechanically ventilated. To assess the sedation level, we used the Richmond Assessment-Sedation Scale (RASS) [11] (**Table 1**), a validated tool for quantifying sedation in the ICU. The target sedation level to control agitation was RASS –4 to –5, and this level was kept for 48 h after which the sedation was discontinued and the patient extubated when deemed ready. After extubation, clinical evaluation as well as assessment was performed twice daily with the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [12], a validated assessment tool for evaluating the presence of delirium in critically ill patients in the ICU setting.

The evaluation and the assessment were performed when the patient was awake to determine whether symptoms of delirium were present.

Ethics

The Regional Ethics Committee was asked for permission to conduct the study, and as this was a retrospective study of a recommended treatment protocol in our region (consisting of 1.7 million inhabitants), no further ethical evaluation was necessary. Informed consent prior to treatment was not possible due to the state of DT.

Trial registration: not relevant.

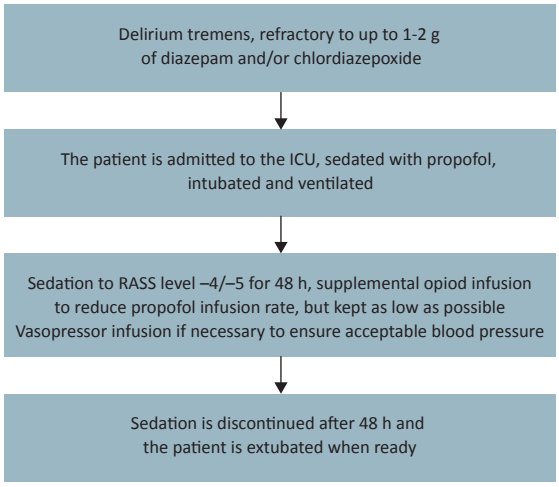
RESULTS

Five women and ten men were included. Their mean age was 50.9 years (36-69 years). See Table 2 for patient characteristics. All patients had prior contacts to the health-care system for alcohol withdrawal; one patient had been diagnosed with DT during an earlier admission. Apart from one patient who was registered as having an abuse of benzodiazepines (30 mg diazepam daily), no other medicine or substance abuse was registered. The average reported alcohol consumption was 22 U (1 U = 12 g, or 1.5 cl of 100% alcohol) daily. Treatment for alcohol withdrawal and DT was started in the medical or psychiatric ward, a total of 14 patients were treated with diazepam, seven received phenobarbital, while 12 received chlordiazepoxide. Medication was given over approximately two days without adequate effect (sleep) before admittance to the ICU.

To reach the target sedation level, the propofol dose averaged 4.22 mg/kg/h (**Table 3**). Thirteen patients received a supplemental infusion of opioids, whereas

FIGURE 1

Treatment protocol for 48-h propofol sedation entitled "Alkohol delir og Propofol sedation, Glostrup Hospital, Operations- og Anæstesiologisk Afdeling Y" (http://vip.regionh.dk).



ICU = intensive care unit; RASS = Richmond Assesment-Sedation Scale.

seven required concomitant norepinephrine infusion. All patients received antibiotics prophylactically, and seven were diagnosed with pneumonia radiologically either at admission or the following days. After propofol infusion was discontinued, 13 patients displayed symptoms of prolonged sedation, not responding to verbal stimuli (Table 3). The time from propofol was discontinued until the patient was deemed sufficiently awake was 3.4 days (0-7 days), which meant that the ICU stay was prolonged. Twelve of 15 patients were clinically judged to be orientated and cooperative and thus deemed free of delirium symptoms after awakening. Three patients needed further treatment; two patients showed symptoms of delirium for five and six days, respectively, whereas one was deemed to be free of delirium only after another 11 days.

DISCUSSION

The use of propofol in the treatment of refractory DT is described in the literature, although the evidence is mainly case-based [7, 8, 13, 14]. Thus, no recommendations as to dosage or duration have been established. As propofol has a rapid onset and short half-life, it is titratable and allows for short recovery after prolonged infusion. This does, however, require ICU admission for concomitant ventilation and monitoring. Due to its dual effects on both $GABA_A$ and NMDA receptors, propofol provides a reasonable alternative in cases of benzodiazepine-resistant DT, where also barbiturates are suggested. However, the number of prospective studies of the use of barbiturates is limited [15, 16].

The incidence of benzodiazepine-resistant DT is generally unknown although a Danish study found benzodiazepine resistance in 9% of benzodiazepine-treated DT patients [16]. It is hypothesised that this resistance may be caused by saturation of $GABA_A$ receptors with high doses of benzodiazepines, thus diminishing the effect of further increases. Another theory is that severe withdrawal is not controlled by benzodiazepines due to their lack of effect on NMDA receptors [8]. In these cases, continued escalation in benzodiazepine use is ineffective and potentially harmful since the risk of respiratory depression increases [15]. Patients with benzodiazepine-resistant DT often need to be endotracheally intubated, they have an increased risk of nosocomial pneumonia and a longer ICU stay [6]. Indeed, although all patients were treated with antibiotics, seven of our patients were diagnosed with pneumonia.

Propofol is formulated as an emulsion containing lipids. Observation of the patient's lipid profile is recommended for prolonged infusion periods (beyond 72 h) as prolonged infusion may cause hyperlipidaemia, which may be associated with pancreatitis [8]. Whereas propofol is generally considered safe, high-dose propofol infusion may be associated with the rare, but serious propofol infusion syndrome (PRIS). The reported incidence of PRIS is 1% and PRIS is associated with a mortality in the 18-80% range [17]. Several risk factors for PRIS have been hypothesised. These risk factors include long-term high propofol dose (> 5 mg/kg/h for > 48h), low carbohydrate supply, and concomitant vasopressor therapy [18]. Symptoms include acute and treatment-resistant bradycardia, severe lactic acidosis, rhabdomyolysis and circulatory collapse. Suspicion of PRIS should lead to immediate discontinuation of propofol infusion and supportive treatment.

Six of our patients were treated with an average

TABLE 1

The Richmond Agitation-Sedation Scale [11].

+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behaviour toward staff
+2	Agitated	Frequent non-purposeful movement or patient-ventilator dys-synchrony
+1	Restless	Anxious or apprehensive, but movements not aggressive or vigorous
0	Alert and calm	
–1	Drowsy	Not fully alert, but has sustained (> 10 sec.) awakening, with eye contact, to voice
–2	Light sedation	Briefly (< 10 sec.) awakens with eye contact to voice
–3	Moderate sedation	Any movement (but no eye contact) to voice
–4	Deep sedation	No response to voice, but any movement to physical stimulation
–5	Unarousable	No response to voice or physical stimulation

TABLE 2

Patient characteristics (n = 15).

Sex, men/women, n	10/5
Age, mean (range), yrs	50.9 (36-69)
Weight, mean (range), kg	73.3 (60-87)
Daily alcohol consumption, mean (range), U	22 (10-42)
SAPS II, mean (range)	31.3 (19-68)
APACHE II score, mean (range)	10.7 (1-19)
Treatment time prior to ICU admission, mean (range), days	1.87 (1-6)
Diazepam	
Patients treated with diazepam prior to ICU, n	14
Diazepam dose these patients received, mean (range), mg	843.6 (360-1,500)
Chlordiazepoxide	
Patients treated with chlordiazepoxide prior to ICU, n[a]	12
Chlordiazepoxide dose these patients received, mean (range), mg[a]	1,281.8 (200-2,000)
Phenobarbital	
Patients treated with phenobarbital prior to ICU, n	7
Phenobarbital dose these patients received, mean (range), mg	708.6 (300-1,200)
Patients treated with diazepam and chlordiazepoxide prior to ICU, n	11
Patients treated with diazepam, chlordiazepoxide and phenobarbital prior to ICU, n	4

APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; SAPS = Simplified Acute Physiology Score.
a) 1 patient was treated with an unregistered/unknown dosage.

TABLE 3

Characteristics of sedation and intensive care unit stay (n = 15).

Propofol	
Cumulative dose in 48 h, mean (range), mg	16,651.5 (5,496-26,287)
Infusion rate over 48 h, mean (range), mg/kg/h	4.22 (1.43-6.17)
Maximum infusion rate, not bolus, mean (range), mg/kg/h	5.65 (1.75-12.0)
Supplemental remifentanil infusion, n[a]	11
Remifentanil	
Cumulative dose, mean (range), µg	14067.7 (540-92,576)
Infusion rate over 48 h, mean (range), µg /kg/min.	5.83 (1.6-20.0)
Supplemental sufentanil infusion, n[a]	4
Sufentanil	
Cumulative dose, mean (range), µg	538.8 (480-639)
Infusion rate over 48 h, mean (range), µg /h	11.25 (5-15)
Concomitant vasopressor (norepinephrine), n	7
Norepinephrine	
Cumulative dose, mean (range), µg	22,481.9 (12,014-48,966)
Infusion rate over 48 h, mean (range), µg /kg/min.	0.14 (0.08-0.25)
Time from propofol discontinuation after 48 h, mean (range), days	
Until extubation	1.60 (0-10)
Until awake	3.4 (0-7)
Total length of ICU stay, mean (range), days	4.67 (3-14)
Antibiotics, n	15
Patients diagnosed with pneumonia, radiologically verified, n	7

a) 1 patient was switched between sufentanil and remifentanil.

propofol infusion rate exceeding 5 mg/kg/h for the full duration of the treatment. Two of these patients received concomitant vasopressor therapy. No patients developed symptoms of PRIS.

GABA and NMDA receptors are involved in the kindling phenomenon; repeated instances of substance withdrawal lead to increasingly severe withdrawal symptoms [19]. In affecting these receptors, propofol may, in theory, affect kindling. Propofol may cause discoloration of the urine due to production of phenolic metabolites. This, typically green, discoloration is not associated with complications, nor does it affect renal function [9]. Discontinuation of infusion leads to resolution of the discolouration within hours. Being aware of this rare, benign side effect can reduce unnecessary urine testing. We observed green discolouration of urine in two patients who received an average propofol infusion rate of 4.11 and 6.17 mg/kg/h, as well as the highest infusion rate at any point (not bolus) of 10.0 and 12.0 mg/kg/h, respectively. Discolouring disappeared with reduction/discontinuation of propofol infusion.

Thirteen of the 15 patients experienced a period of prolonged, gradually receding sedation after propofol was discontinued, which prolonged the total length of their ICU stay. Other causes of delayed emergence (e.g. hypercapnia, hypoxemia, dysglycaemia, hypothermia, metabolic disturbances, organ dysfunction and neurologic insults) were ruled out prior to attributing it to residual drug effects. Recovery from long-term propofol sedation is rapid, but proportional to the rate and duration of the infusion [8]. Higher infusion rates for long periods of time may therefore result in delayed recovery. A total of 13 patients received concomitant opioid infusion (remifentanil or sufentanil) to reduce the propofol infusion rate; the opioid dose was kept as low as possible to ensure a propofol-weighted sedation. Prior to protocolled propofol treatment, our patients received treatment with the long-acting benzodiazepines diazepam ($T_{1/2}$ = 2-3 days) and chlordiazepoxide ($T_{1/2}$ = 10-48 h to several days for active metabolites), as well as phenobarbital ($T_{1/2}$ = 3-5 days). This affected the duration of awakening through own action as well as potentiation. Thus, several factors contribute to the prolonged awakening seen in our patient population.

Evaluation of when patients were free of delirium relied on CAM-ICU assessment twice daily as well as on clinical judgement. Assessing the patient with the CAM-ICU requires the patient to be responsive to verbal stimulation (minimum RASS -3). Thus, CAM-ICU assessment was not possible the first 3.1 (1-6) days of admission. The following days, 13 patients were varyingly evaluated as being CAM-ICU positive or unable to assess over a period of 3.3 days; thus, judged to be unresponsive with fluctuations. Clinically, they were judged to be experiencing prolonged sedation. Comatose patients often experience a period of delirium before recovering to their baseline mental status [20], and their CAM-ICU scores may be indicative of this. In most cases, our patients were transferred from the ICU to a medical ward before they were judged to be completely awake and they were thus not CAM-ICU assessed after transfer.

There are several limitations in our study. Principally, this was not a randomised trial and though it was not protocolised, it follows a locally approved guideline for propofol treatment in the ICU setting. The retrospective nature of our study invariably carries the risk of information and selection bias. As the pre-ICU medication suggests, not all our patients were treated in strict accordance with this guideline. This is a confounding factor as we suspect several interactions between sedative medications administered to the patients. Therefore, not all patients will have been treated uniformly, possibly affecting post-infusion prolonged sedation and ICU stay.

CONCLUSION

Our study suggests that treatment of refractory DT with propofol infusion for 48 h is viable and has good clinical effect as 12 of 15 patients with refractory DT were treated successfully.

Due to the retrospective nature of our investigation, our findings will need to be validated by future pro-

spective randomised studies. Our study raises questions regarding the indication, dose, duration and the long-term effect of propofol treatment of DT compared with treatment with large doses of benzodiazepines or phenobarbital. Until such studies can be undertaken, propofol should only be considered for cases refractory to high doses of benzodiazepines as an alternative to phenobarbital, especially in cases in which admission to ICU and intubation are necessary to ensure a patent airway.

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