Management of Alcohol Withdrawal in the Critically Ill Patient: A Selected Review

Rebecca B. Kantz

H. Mathilda Horst

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Proper management of alcohol withdrawal represents a therapeutic challenge in the critically ill patient. The severity of the withdrawal syndrome varies with both the intensity and duration of the preceding alcohol exposure and may be complicated by other diseases such as traumatic injury, alcoholic gastritis, pancreatitis, liver failure, respiratory insufficiency, and/or malnutrition. These patients often cannot use the oral route for therapy, and demonstrate considerable variability in response to treatment modalities.

Diagnosis

Alcohol withdrawal may present a wide variety of clinical patterns ranging from mild self-limiting hyperadrenergic state, termed the common abstinence syndrome (CAS), to full-blown hallucinosis, grand mal seizures, and delirium tremens (DT's). CAS is characterized by tremor, anxiety, and diaphoresis and may occur as soon as six to eight hours after cessation of drinking. Symptoms may occur alone or with auditory hallucinations and/or convulsions. Peak symptoms are seen within ten to 30 hours and generally subside in 40 to 50 hours (1,2). Progression to DT's occurs in 1% to 10% of patients (1). Some authors feel that aggressive treatment of early symptoms will minimize progression to DT's; however, occasionally a patient will develop DT's despite every preventive effort.

DT's consist of profound disorientation associated with visual hallucinations and motor hyperactivity. The onset of DT's is 60 to 80 hours after the last drink. The average duration of DT's is two and one-half days, but symptoms may persist for a week or more (1-3).

Overlap in symptomatology may preclude a precise diagnosis in the critically ill patient (CAS versus DT's), although most authors concur that symptoms are more easily controlled when agressively treated in the early stages (1).

Tolerance

Alcohol, unlike other central nervous system (CNS) depressants, is metabolized primarily by the cytosolic liver enzyme alcohol dehydrogenase. Increased activity of this enzyme contributes to the "tolerance" to alcohol displayed by heavy drinkers (2). In theory, tolerance and physical dependence on ethanol is a manifestation of compensatory neurophysiologic changes which offset the depressant effect of alcohol on neuronal excitability, impulse conduction, and neurotransmitter release (4).

Two methods have been suggested to aid the clinician in identifying the patient at risk of withdrawal (in addition to a positive history for withdrawal or DT's, which may not be elicited from the critically ill patient) (1). Although withdrawal is thought to be a dose-dependent phenomenon, there is considerable individual variation in the amount of alcohol consumption necessary to produce withdrawal. Furthermore, alcoholics are generally unreliable in reporting their true alcohol intake. Blood alcohol concentrations may be used to detect tolerance; heavy imbibers may show no symptoms of intoxication with blood alcohol levels which would render a nontolerant person intoxicated (100 to 250 mg%) or unconscious (350 to 500 mg%).

Since tolerance to other CNS depressant drugs (barbiturates, benzodiazepines, and other sedatives) occurs concurrently with tolerance to alcohol (3), administration of a normally sedating dose of medication (50 mg secobarbital or chlordiazepoxide) to a tolerant individual may produce no sedation whatsoever. This method may provide the clinician with another clue as to which patient is at risk for withdrawal.

The theory behind pharmacologic treatment of alcohol withdrawal syndrome is that of substituting a sedative agent which is cross-tolerant with alcohol, and then slowly weaning the patient from that agent to prevent precipitation of symptoms. Numerous pharmacologic agents have been used to treat alcohol withdrawal syndrome, including phenothiazines, paraldehyde, benzodiazepines, barbiturates, antihistamines, butyrophenones, beta-blockers, and ethanol (Table). Several studies have compared the efficacy of the first four drugs in this list (5-10). In combining the results of five of these studies, Thompson (3) found that patients treated with paraldehyde or benzodiazepines had the lowest incidence of DT's and seizures, while the use of phenothiazines was associated with a greater incidence of seizures. (Of ten deaths reported in the entire study population of 978 patients, nine patients had been treated with phenothiazines.)

These studies were not controlled, and the drug dosages employed varied widely. As there is no conclusive evidence as to which regimen is best, the choice of agent to control alcohol withdrawal syndrome must therefore be based on efficacy, availability, and lowest incidence of toxicity. Furthermore, the most appropriate regimen in the critically ill patient may be different from that used to treat a patient with uncomplicated withdrawal symptoms.

Table
Treatment of Alcohol Withdrawal in the Critically Ill

Drug	Route*	Recommended Dose	Dose Frequency	Maximal Reported Dose	Reference
Chlordiazepoxide	PO,IM,IVP	50 to 100 mg	Every 6 hrs	1600 mg/day	1
Diazepam	PO,IM,IVP	5 to 10 mg IV	Every 5 min until calm then		
		5 to 15 mg	every 2 to 6 hrs	1536 mg/48 hrs	13
Lorazepam	PO,IM,IVP	2 to 8 mg	Every 2 to 4 hrs	Not available	
Haloperidol	PO,IM,IVP	0.5 to 5 mg	Every 2 to 6 hrs	Not available	4,9,11,12
Paraldehyde	PO,IV, rectal	10 to 170 mL rectally	Every 6 hrs	436 mL/24 hrs	13
Secobarbital	IM	200 mg initially then 100 to 200 mg	Every 6 hrs	Not available	4,18,19
Propranolol	PO	40 mg	Every 6 hrs	Not available	16,17
	IV	0.5 mg	Every 6 hrs		

*PO = orally, IM = intramuscular, IV = intravenous, and IVP = intravenous push.

Phenothiazines are not widely recommended in the treatment of alcohol withdrawal syndrome since they have not been shown to be superior to other agents. In addition, phenothiazines lower seizure threshold, cause sedation, and may potentiate the hyperthermia seen in withdrawal (4,5,7-9). Antihistamines are contraindicated for this purpose and have anticholinergic effects that can cause tachycardia, somnolence, and hallucinations (4,9,11).

Haloperidol, a butyrophenone and major tranquilizer, has been shown to be effective in controlling agitation, hallucinations, and DT's with minimal side-effects (12). However, the ability of this drug to lower seizure threshold is worrisome. For the treatment of withdrawal, haloperidol is recommended in intramuscular (IM) doses of 0.5 to 2 mg every one to two hours until satisfactory response is achieved, then 2 to 5 mg IM every four to six hours (4,9,11,12).

Paraldehyde is one of the classic drugs used for alcohol withdrawal. Paraldehyde is a short-acting sedative-hypnotic that has cross-tolerance with alcohol. It also has anticonvulsant activity which prevents progression to seizures or DT's when used early in withdrawal (3,5,8). Paraldehyde is not without its attendant problems, such as being erratically absorbed from the oral and rectal routes and causing sterile abscess formation with repeated IM injections. In a controlled comparison of rectally administered paraldehyde and intravenous diazepam to treat DT's, the diazepam-treated patients were calmed in one-half the time needed to calm the paraldehyde-treated patients. No adverse effects were noted with diazepam. One-half of the paraldehyde-treated patients suffered adverse effects (13). Intravenous (IV) administration of paraldehyde has been associated with hypotension, pulmonary edema, metabolic acidosis, and liver toxicity (13-15). Paraldehyde is contraindicated in bronchopulmonary disease and hepatic insufficiency and would be of limited value in the critically ill.

Alcohol withdrawal is associated with an increase in urine and plasma catecholamines, and clinical features suggest a hyperadrenergic state. Beta-blockers such as propranolol have been effective in reducing tremor, blood pressure, heart rate, and catecholamine levels in doses of 40 mg every six hours or 0.5 mg slow IV push (16,17). Propranolol is contraindicated in patients with bronchospastic disease, heart failure, and insulin-dependent diabetes. Efficacy studies of these agents in critically ill patients are lacking.

Barbiturates are effective, inexpensive agents for alcohol withdrawal, provide sedation and anticonvulsant activity, and can be given intravenously (4,18,19). Pentobarbital and secobarbital have been used in doses of 200 mg IM initially, then 100 to 200 mg IM every six hours. Despite favorable effects in controlling withdrawal, barbiturates have largely been replaced by newer agents. Phenobarbital (normal half-life two to five days) metabolism may be impaired in hepatic disease. Furthermore, combining phenobarbital with narcotic analgesics can potentially cause oversedation in the critically ill patient (20,21).

The administration of intravenous ethanol has been used as a 5% solution in 5% dextrose at 150 mL/hr to prevent withdrawal symptoms (22). The drug has a narrow therapeutic index, a short half-life, and may perpetuate metabolic disturbances. Its use is not widely recommended (4).

Many clinicians consider the benzodiazepines to be the agents of choice for the treatment of withdrawal due to their efficacy as well as their safety. These drugs produce adequate sedation, anticonvulsant activity, and fewer side-effects than other agents. While control of withdrawal symptoms may be achieved with any benzodiazepine, only three agents are available in the parenteral form, lending themselves to treatment of the critically ill patient: diazepam, chlordiazepoxide, and lorazepam. Rapid onset of action is achieved using the IV route, while IM injections may be absorbed erratically or incompletely. Of these three agents, differences in pharmacokinetic parameters may predispose one agent to be superior in treating alcohol withdrawal syndrome.

Distribution

The capacity of drugs to cross the blood-brain barrier is determined in part by their inherent lipophilicity. While all benzodiazepines are lipophilic, diazepam is more so than either chlordiazepoxide or lorazepam. Presumably owing to its lipophilic nature, diazepam also has a greater propensity for peripheral distribution to nonblood compartments (adipose tissue). Following IV administration, diazepam has a rapid

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onset of action, but CNS levels of the drug fall rapidly, coinciding with peripheral redistribution of the drug. Lorazepam, however, is less lipophilic and has less propensity for peripheral redistribution. Thus, paradoxically, the ''shorter acting'' benzodiazepine (lorazepam T ½ = 10 hours) may have a longer acting clinical effect in the treatment of alcohol withdrawal than the "longer acting" diazepam (T ½ = 36 hours) and may require less frequent dosing (23-25).

Metabolism

Clinical side-effects of benzodiazepines (including respiratory depression) during chronic dosing may be the result of drug accumulation. The longer the half-life of the drug, the more extensive will be its accumulation. Lorazepam has the shortest half-life of the injectable benzodiazepines. This is due in part to diazepam and chlordiazepoxide being hepatically oxidized to active metabolites, whereas lorazepam forms an inactive glucuronide conjugate (23).

Furthermore, these two metabolic pathways are differently influenced by factors altering the individual capacity for drug biotransformation. Oxidation of diazepam and chlordiazepoxide may be impaired by liver disease (ie, cirrhosis), old age, or by coadministration of drugs (ie, cimetidine), further extending the half-life of these agents. Conjugation is not impaired by these same factors; thus inactivation of lorazepam is not influenced by alcoholic cirrhosis (23,24).

In dosing the benzodiazepines to treat alcohol withdrawal, several regimens have been reported to be successful. Chlordiazepoxide may be used in initial doses of 50 to 100 mg every six hours (IM or IV push). Doses of up to 1600 mg/day have been employed (1).

Thompson et al (13) reported that patients with simple DT's required less than half the sedative dose required for calming than patients with associated pneumonia, hepatitis, or pancreatitis. Diazepam doses of 15 to 215 mg were required to initially calm patients, and total doses of 525 to 1355 mg were employed over six to 52 hours without excessive sedation (13). Thompson et al advocate initial treatment with 5 mg diazepam IV push every five minutes until the patient is calm but awake. (If agitation persists after 30 minutes, the dosage can be doubled.) Maintenance doses of 5 to 15 mg should be given every two to six hours until the patient has remained calm for 48 hours; then the doses can be tapered.

Appropriate doses of lorazepam for alcohol withdrawal in the critically ill have not been identified. Conner et al (26) found that 2 mg of lorazepam was as effective as 10 mg of diazepam in relieving anxiety and providing preoperative sedation.

Many therapeutic problems still exist in treating the critically ill patient having alcohol withdrawal. Definitive means of predicting progression to delirium tremens, as well as specific ways of preventing this progression, are unavailable for this patient population. Studies comparing clinical efficacy of lorazepam, chlordiazepoxide, and diazepam in treating alcohol withdrawal in the critically ill are lacking. No statistically significant differences in efficacy among these agents have been demonstrated in outpatients treated for alcohol withdrawal (27,28). Further trials are needed in the critically ill to detect potential differences in clinical efficacy among the benzodiazepines and to further delineate optimal dosing regimens.

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