Review Article

The drug management of severe alcohol withdrawal syndrome

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Summary: We describe the various phases of the alcohol withdrawal syndrome with special reference to the pitfalls of using neuroleptics. We outline the importance of adequate sedation using either benzodiazepines or chlormethiazole. We provide a critical appraisal of the currently employed anti-epileptic medication in the alcohol withdrawal syndrome. We also indicate the usefulness of analgesic nitrous oxide as a screening test in differentiating the cases of alcohol withdrawal syndrome needing further intensive therapy to prevent progression to delirium tremens.

The presentation of alcohol withdrawal states

The alcohol withdrawal state (AWS) is a progressive pathophysiological condition.^{1,2} The initial signs and symptoms begin some hours after the last drink, but in some cases occur while the patient is still drinking; particularly if accompanied by a physical insult or illness.^{3,4} This early stage presents as a classical hyperadrenergic state including tremor, tachycardia, sweating and hypertension. Sometimes this is accompanied by mild disorientation, anxiety, impaired concentration, depression, agitation, tremor, as well as gastro-intestinal symptoms (nausea, vomiting and diarrhoea). Insomnia, nightmares and transient hallucinations can also be present. The intensity of the condition at this stage can be mild or moderate in nature and last for approximately 48 hours after cessation of drinking. This condition is sometimes self-limiting without any therapeutic intervention required.⁵ However therapy is essential to prevent progress to the more severe and potentially fatal condition of delirium tremens (DTs), that is, severe AWS. It has been almost impossible, up to now, to predict with any degree of certainty which patients will worsen.⁶ Usually, within the initial 24 hours, withdrawal fits may occur,^{1,2} and for this reason also, early therapy is essential.⁶ These early onset fits must be distinguished from those that occur during the more severe later stages of the AWS. The latter may be due not to the withdrawal state alone, but to secondary complications, such as hypoglycaemia,⁶ hypomagnesaemia^{1,2} and hypernatraemia.⁷ Furthermore the depression found in the AWS is some-

times associated with suicidal ideation and even suicide attempts.⁸ This is another important reason for keeping such patients under observation, until the depression lifts.

If the condition progresses further into frank DTs, there is a marked increase in motor and autonomic activity. In addition, gross disorientation and sensory perception disorders occur with misidentification, delusions, persistent hallucinations and impaired level of consciousness and hyperpyrexia. The patient becomes very restless with marked tremor and can become violent and assaultive. This presentation usually climaxes during the third or fourth day after cessation of drinking.¹⁻⁵

Although the above description gives the impression that the stages occur by gradual progression this is not always the case. Sometimes the stages become telescoped into one another.^{6,9,10} It has also been noted that DTs can occur even while the patient is still drinking.¹⁰

It is very important that the organic complications sometimes associated with the AWS are recognized early and treated promptly since their presence during DTs is associated with an increased mortality.^{5,11} The most common physical complications found are pulmonary infection, pancreatitis hepatic pathology and subdural haematoma.^{8,11} Concomitant pathology can confuse diagnosis and treatment. For instance, it is sometimes difficult to distinguish between incipient hepatic encephalopathy and DTs.¹² Such double pathology highlights the problems found in treating complicated DTs. All these conditions are compounded by the almost ubiquitous avitaminosis and magnesium deficiency found in these patients.¹⁻⁶

Notwithstanding the importance of monitoring patients during the AWS, their screening prior to possible admission involves risks, particularly in those with severe dependence or medical problems.¹³ Despite this, many alcoholics are routinely withdrawn on an out-patient or day hospital basis with or without the use of pharmacological agents.^{13,14} It has been shown in AWS that the response to any treatment, pharmacological or non-pharmacological, has a substantial placebo component.¹⁵⁻¹⁷ Since the placebo response may be mediated by activation of the endogenous opioid system¹⁸ it is likely that the success of non-pharmacological methods in the AWS may well depend on stimulation of this system as well.¹⁵⁻¹⁷

It is interesting therefore that an opioid agonist, namely analgesic nitrous oxide, would appear to offer a means of screening those patients requiring intensive in-patient treatment from those who do not. In the latter case merely the administration of analgesic nitrous oxide is sufficient to curtail the progression of the condition as well as relieving the symptoms both physical and psychological.¹⁸ It has become apparent that some regimes employed for the AWS have had detrimental effects and should be avoided.

The dangers of neuroleptics in AWS

There appears to be decreased dopamine activity in the AWS,^{19,20} as shown by a decrease in homovanillic acid, the major metabolite of dopamine in the cerebrospinal fluid (CSF). It has therefore been suggested that alcoholic delirium may be directly related to reduced central dopaminergic activity.²⁰ This highlights the dangers of using anti-dopaminergic neuroleptic agents in this condition despite their sedative action.

In severe cases of AWS, patients are often restless, and/or aggressive and hence uncooperative; here additional medication is usually required to prevent deterioration to frank DTs. Unfortunately some of the treatments recommended for this pre-delirium tremens state may do more harm than good. We refer here particularly to the use of neuroleptic agents¹³ such as chlorpromazine. Neuroleptics have been shown to enhance noradrenaline release in the cerebral cortex in animals and may also antagonize the α_2 presynaptic agonistic action of clonidine, indicating a possible additional mechanism for the aggravation of AWS by phenothiazines,²¹ apart from the decrease in dopaminergic activity that is also present,^{19,20} which has been referred to above.

In addition, the use of these agents for AWS has been criticized, since they lower seizure threshold and some well controlled trials have indicated that symptoms of this condition were aggravated by a neuroleptic (chlorpromazine).⁵ A good illustration

of this negative effect was demonstrated in a double-blind study where piracetam was shown to be significantly better than chlorpromazine.²² It was found that whilst none of the patients on piracetam developed DTs, 40% of those receiving the neuroleptic developed this condition.²²

A neuroleptic which may be potentially less dangerous in this condition is promazine. This agent, although a phenothiazine, possesses much lower antipsychotic and toxic properties than does chlorpromazine.²³ One clinical study with promazine demonstrated that none of the complications reported after the use of other phenothiazine derivatives was noted.²⁴

Another danger of using neuroleptics is the possible precipitation of the malignant neuroleptic syndrome. This normally occurs within the first 2 weeks of the administration of a neuroleptic.²⁵ In a postmortem study of 24 patients suffering from DTs, it was found that only 2 cases did not exhibit an organic cause of death. In both, a constantly rising temperature had been observed prior to death.¹¹ It may therefore be significant that both these patients had received a neuroleptic agent, promazine. It is possible that these patients died as a result of a precipitated neuroleptic syndrome; a major symptom of which is hyperpyrexia of unknown origin. This would highlight the possibility that the increased death rate following treatment of DTs with neuroleptics might partly be due to precipitation of an undiagnosed neuroleptic malignant syndrome in such cases. In this respect it is of interest that in outcome studies of patients with DTs the lowest mortality rate was seen in those treated either with chlormethiazole and/or benzodiazepine drugs. In contrast, significantly higher mortality rates were seen with either butyrophenone or phenothiazine neuroleptics.^{26,27}

Phenothiazine treated subjects were also found to manifest more seizures and delirium than even those only receiving placebo.^{28,29} In a series of 786 patients studied, 9 of the 10 deaths recorded were in patients who had been given phenothiazines.²⁸ Since many neuroleptics have epileptogenic properties,²⁹ they should be used with extreme caution, if at all, in the AWS in view of the fact that they may aggravate the situation which they are given to control.³⁰

Thus the practice of using major tranquillizers in AWS can no longer be recommended, since these agents could have serious adverse effects on blood pressure, seizure threshold, temperature regulation and liver function, to all of which the chronic alcoholic is especially vulnerable during AWS.³ We therefore suggest that the use of neuroleptic agents for alcohol withdrawal is contraindicated.

If major tranquillizers are contraindicated in AWS, including delirium tremens, what are the alternatives?

Non-neuroleptic sedatives

Current practice consists in using safe and potent sedative medications such as chlormethiazole^{26,27} and benzodiazepines.^{31,32} It would appear that the use of these agents has tended to prevent progression to seizures and delirium if applied early enough.¹³

The latter two treatments have become the sheet-anchor of all stages of the AWS in many units. Both types of medication, however, have one decided disadvantage; they have addictive potential, although at present there is no study available indicating which is the more addictive. One authority³³ has stated that when chlormethiazole is used in in-patients, as a rule for no longer than 6 or 7 days, the risk of dependence is extremely low. Dependence, mainly psychological but occasionally physical, had been seen in patients who had been prescribed the drug for lengthy periods on an ambulatory basis, all of whom were highly unstable individuals who often in the past had also misused other drugs apart from alcohol.³³ Chlormethiazole has therefore been restricted for use only in the acute in-patient AWS and, used in this way, has been regarded as a safe and effective treatment of the AWS with minimal addictive potential.³⁴

However, the same cannot be said of the benzodiazepines which have been used rather irresponsibly by the medical profession in out-patient treatment of the alcoholic.³⁵ As a result of their addictive potential some alcoholic rehabilitation centres in the United States eschew the use of these agents in treating the AWS.³⁶ In all fairness, however, it may be emphasized that chlormethiazole has never been registered for use in the US.³⁷ Had it been so used it may also have led to problems of addiction there. However, in countries where it has been available, its uses have been deliberately restricted to specific indications, thereby preventing the occurrence of significant dependence in the population.³⁴

Sedative medication regimes with benzodiazepines or chlormethiazole

These agents are particularly valuable in preventing an established AWS progressing further to the pre-DTs or DTs state. Chlormethiazole is given orally, a loading dose of 4 capsules (2 grams) followed by a single capsule every half hour until sleep is induced. Thereafter 1 to 4 capsules are given at 3–6 hourly intervals.⁵ In this regimen up to 5–6 grams chlormethiazole may be required orally (daily) for the initial 72 hours of treatment; the drug is then tapered off over a period of a week as the delirium subsides.^{26,27} An alternative approach is to use chlormethiazole or benzodiazepines intra-

venously.⁵ In one method described, an intravenous infusion of chlordiazepoxide is given at the rate of 12.5 mg/min until the patient is calmed.⁵

This sedative approach has been further developed by Leigh-Thompson on the basis of studies of the causes of deaths following DTs.²⁸ He found that the causes of death were poorly defined and varied; some patients dying from over-sedation and others from under-hydration and excessive psychomotor agitation. He advised that patients suffering from DTs should be admitted to an intensive care unit, intravenous diazepam 5 mg/5 min then administered until the patient is calm but not excessively sedated, the peak response to each dose being evaluated prior to succeeding doses. A wide variation in response to dosage has been noted, highlighting the importance of careful titration of sedation.²⁸ It is of course absolutely essential in all cases of AWS, especially in DTs, to correct hypoglycaemia, dehydration, electrolyte disturbances (in particular magnesium) and thiamine and other avitaminoses which are prevalent in this condition.^{3,5,6} In view of the increased water content of the brain in AWS³⁸ the use of urea or dexamethasone and magnesium sulphate has been shown to be of value in assisting the recovery of patients with DTs.³⁹ More recently dexamethasone has been successfully used in the treatment of benzodiazepine-resistant DTs.⁴⁰

Use of anti-epileptic agents in AWS

Raising the seizure threshold during AWS has been regarded as a mainstay of treatment and also for preventing withdrawal fits and DTs.³⁴ The particularly effective agents, carbamazepine, valproic acid, diazepam and chlormethiazole, have equipotent anti-convulsive actions.³⁴ However, phenytoin is commonly advocated for controlling seizures during AWS, but has only been shown to be useful as a prophylactic anti-convulsant in patients with pre-existing epilepsy.¹³ It should be noted that chlordiazepoxide treatment alone, in a series of 2200 AWS, prevented fits in all but 4 cases.⁴¹ In the latter study phenytoin at 300 mg/day produced effective control of fits in adults with a previous history of convulsions. This effect occurred despite the fact that steady state levels of the drug were not obtained. Such levels require a longer time period to be reached, unless an oral loading dose of phenytoin is used.⁴¹ Since the latter agent is not a central nervous system depressant, and has no cross-tolerance with ethanol, it is ineffective in preventing withdrawal seizures or reducing delirium.³ The ineffectiveness of phenytoin in these circumstances has been confirmed in a prospective double-blind study.⁴² This author also refers to the use of a single intravenous loading dose of pheno-

barbitone in a dosage range of 348–736 mg to prevent withdrawal seizures.⁴² It is interesting to note that in Denmark, phenobarbitone is still considered the drug of choice in the treatment of AWS.⁴²

Another anti-epileptic agent that has been used effectively and safely in AWS is carbamazepine.⁴⁴ The latter agent proved to be at least as effective as a barbiturate in a randomized double-blind trial.⁴³ It would therefore be more suitable in the prophylaxis of withdrawal seizures, since it is non-addictive and its metabolism is unaffected by the liver dysfunction often found with alcohol abuse.⁴⁴ Furthermore carbamazepine has proved useful for treating other symptoms of the AWS.⁴⁴ It would appear that if one is to use an anti-convulsant agent routinely for the prophylaxis of AWS fits then a medication other than phenytoin, such as carbamazepine, valproic acid or phenobarbitone, should be used. Furthermore one should remember that the use of chlordiazepoxide alone is very effective in preventing AWS fits⁴¹ as is diazepam.³¹

Beta-blockers as adjunctive agents

These agents have proved useful for treating mild to moderate AWS.⁴⁵ Furthermore propranolol has been used for alcoholic pre-delirium and delirium states when combined with chlormethiazole and compared with placebo chlormethiazole combina-

tion. It was found that the addition of propranolol had no effect on the duration of delirium nor did it enable reductions in the dose of chlormethiazole required.⁴⁶ Because of the above findings it would appear that, for treating the more severe AWS (pre-delirium and delirium), beta-blockers are only suitable as adjunctive agents,⁴⁷ in which role their efficacy still remains unproven.

Conclusion

We mention the use of analgesic nitrous oxide to distinguish those patients requiring intensive inpatient care from those who do not. We also provide evidence for the dangers of using major tranquilizers in the treatment of AWS and highlight the advantages of using adequate doses of suitable anti-epileptic agents (not phenytoin) in the treatment of these conditions. The judicious and adequate use of sedatives such as benzodiazepines or chlormethiazole is indicated for treating AWS, provided the dangers of addiction to these agents are recognized and suitably addressed.

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