The treatment of alcoholic withdrawal states with oxygen and nitrous oxide

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Summary

Chronic alcoholic subjects suffering withdrawal symptoms were treated with 100% oxygen or with oxygen/nitrous oxide. In most cases oxygen alone reversed withdrawal symptoms except, in a few instances, depression. The residual depressive symptoms not reversed by oxygen were completely reversed by nitrous oxide/oxygen. The pathogenesis of alcoholic withdrawal states in the light of the overactivity of the adrenergic system which leads to tissue acidosis is discussed.

The importance of correct psychological management is stressed. Our therapy reduced both the period of hospitalization and the amount of sedation required. The similarity between opiate and alcohol withdrawal and treatment is mentioned.

We have suggested that nitrous oxide (N₂O) inhalation might be beneficial in treating alcohol and opiate withdrawal symptoms.¹ This idea is supported by work showing that there is cross-tolerance between N₂O and alcohol.² It has been shown that alcohol ingestion produces endorphin release,³ a factor which relates alcohol to opiate addiction. This is further supported by the fact that nalofoxone antagonizes severe alcohol-induced coma.⁴ Thus N₂O, an opiate-receptor stimulant,⁵ possibly acting at the morphine receptor,⁶ could be used to treat alcohol withdrawal states. Ross et al.⁷ have shown that both ethanol and morphine can cause a decrease in regional calcium, an effect antagonized by naloxone. Blum et al.⁸ showed that morphine could attenuate the ethanol withdrawal syndrome and that naloxone decreased the development of alcohol dependence. This effect supports the hypothesis that alcohol dependence is mediated by the opiate system.⁹ In addition, a vasopressin fragment has been shown to enhance the development of tolerance to and physical dependence on morphine and ethanol in rodents.¹⁰

Depression is a well-known symptom of withdrawal states.¹¹ The endorphins have been shown to improve the mood of depressed patients,¹² and we felt that the same effect might be achieved with N₂O. In addition, it has been shown that there are decreased serotonin metabolites in the CSF of alcohol withdrawal subjects as well as in patients suffering from depression and/or mania.¹³ Hosobuchi et al.¹⁴ have shown that there is a link between serotonin and the opiates.

Alcohol is known to produce a reductive state,¹⁵,¹⁶ including a hyperlactacidaemia linked to the conversion of NAD to NADH. This being the case, it occurred to us that pure oxygen (O₂) at high enough concentrations might be helpful in reversing this altered reduct state. McFarland and Barach¹⁷ showed that 50% O₂ inhalation for 2 hours in the presence of different concentrations of carbon dioxide (CO₂) reduced both alcohol and lactic acid concentrations in venous blood in subjects after acute alcohol ingestion. This was accompanied by a concomitant improvement of both mental and motor behaviour in most subjects.¹⁷ These workers also noticed 'a striking resemblance between alcohol intoxication and other states of anoxia'.¹⁷ Van Wulffen Palthe¹⁸ demonstrated that O₂ administration could reverse alcohol intoxication in animals and man. He postulated that this effect could possibly reverse the late effect of alcohol on the metabolic system in alcohol withdrawal states. In fact, in two cases of delirium tremens he showed that 95% O₂ with 5% CO₂ (to enhance ventilatory response) did in fact reverse the symptoms.¹⁹ Victor²⁰ found that intermittent ventilation with 5% CO₂ (presumably mixed with O₂) during initial alcoholic withdrawal decreased the undesirable symptoms. Dephosphorylation is a major step in the removal of toxic metabolites of alcohol and O'Hollaren²¹ therefore administered diphosphopyridine nucleotide (DPN) in the oxidized form intravenously to patients suffering from various states of alcohol withdrawal, including delirium tremens, with encouraging results. In addition, he showed that this treatment attenuated drug addiction withdrawal states.²¹ This work further emphasizes the importance of tissue anoxia in the production of symptoms in alcohol withdrawal states.

Madden²² suggests that the pharmacological action of drugs provides a comparatively minor contribution to the relative ease with which this usually self-limiting condition runs its course. He feels that psychological factors such as motivation, reassurance by staff and peers and the placebo effect are far more important factors in enhancing recovery.²² A placebo has been shown by Glatt et al.²³ to have some effect even with no active psychological intervention included in the treatment regimen. Furthermore, there are data supporting the contention that withdrawal symptoms are a conditioned response in former drug addicts returning to their old environment.²⁴

We therefore decided to test the efficacy of O₂ alone and in combination with N₂O in the treatment of alcohol withdrawal states.

Patients and methods

Ninety-eight White male patients between the ages of 22 and 60 years (mean 37 years) admitted to an alcohol treatment centre (Northlea Hospital, Johannesburg) for alcohol withdrawal treatment were investigated. Informed consent was obtained in each case. Patients with chronic lung lesions were excluded. In most cases the only other medication given was routine anti-epileptic drugs. If other medication was used during treatment this consisted of a continuation of any routine maintenance therapy, plus oxazepam at night.

Blood pressure and pulse rate were measured before and after administration of O₂. The gases were administered with a
Quantiles relative analgesia dental machine. This is not a closed circuit system but adequate gas concentrations are obtained. Initially, pure O$_2$ at 8 l/min was given for 20 minutes. This was followed (if necessary) by N$_2$O and O$_2$ (O$_2$ level not less than 3 l/min and the N$_2$O level between 3 and 6 l/min), again for 20 minutes. After receiving N$_2$O the patients were oxygenated for a further 20 minutes. Only just enough N$_2$O was given to reverse the depression; this is possible since the Quantiles system enables one to titrate the N$_2$O required. Some patients reported euphoria, but this was incidental to the study and can be avoided. In 24 patients this procedure was repeated on recurrence of symptoms (within the first 24 hours).

Results

Each patient was given a 'symptom score', assessed by assigning 1 point per symptom. The following symptoms were scored: craving, tremor, head pressure, sweating, restlessness, 'butterflies in the stomach', and delusions, hallucinations, confusion, guilt, depression and remorse. These scores were then added together to form a composite aggregate for the entire group, as follows: (i) before O$_2$ — 51.8; (ii) after O$_2$ — 18.8; and (iii) after N$_2$O/O$_2$ — 5.7. The average decrease in systolic blood pressure was 9% and the average decrease in pulse rate was 13% for the group studied. The diastolic blood pressure was not significantly affected by our treatment.

In the patients treated by this method the following regimen for sedation was followed: (i) first night oxazepam 60 mg; (ii) second night oxazepam 30 - 60 mg; and (iii) on the following nights oxazepam 30 mg if necessary. This regimen is in stark contrast to the standard method of treating such patients — heavy sedative administration is usually relied on.

The detoxification period at Northlea is 7 days using conventional sedative therapy; however, in our sample most patients were fit for discharge 1 - 2 days sooner than this.

Discussion

It is quite clear from our results that O$_2$ alone reverses most of the physical symptoms of alcohol withdrawal states and some of the psychological symptoms as well. The affective symptoms, however, seem to respond maximally to N$_2$O. The O$_2$ primarily exerts its effect by reversing the reductive state, which has been implicated in causing most of the symptoms in alcohol withdrawal. A marker for this reductive phase is the presence of excess lactic acid in the blood (which may persist for up to 10 days after a binge) and which, in addition, has been related to the degree of hangover experience. The degree of lactic acidosis has been highly correlated with the intensity of the hangover symptoms by other workers; in addition, adrenergic overactivity may enhance the lactic acidosis, and may also contribute to many of the hangover symptoms.

Lactate infusions in anxiety states cause a syndrome which mimics that of alcohol withdrawal states in many respects and these symptoms may well arise as a result of stimulation by lactate of adrenergic activity. The anxiety state increases adrenaline production which then increases lactate production by direct action on metabolic receptor sites activating the cellular glycolytic processes. This would initiate a vicious cycle. In experimental findings have indicated that clonidine, the α-adrenergic agonist, can decrease opiate withdrawal symptoms by acting on the noradrenergic neurons in the locus caeruleus. Furthermore, studies have shown that clonidine is helpful in treating opiate and alcohol withdrawal states in man, thereby supporting the concept of a noradrenergic mediation of opiate and alcohol withdrawal symptoms.

Notwithstanding the severe metabolic disorders in certain cases of the alcohol withdrawal syndrome, it has been shown that this condition is amenable to psychological treatment alone. Obviously, selection of cases before admission will result in very different samples of the alcohol withdrawal state being seen at detoxification stations compared with a general hospital. The psychological therapy consists of reassurance, attention and encouragement in abandoning the sick role. Whittleford considers these simple means effective in many cases of alcohol withdrawal.

It would appear from the results of our treatment that the symptoms of the physical and affective disturbances are both adequately dealt with by administration of O$_2$, where necessary followed by N$_2$O/O$_2$. This therapy results in a marked decrease in the use of sedatives, thereby encouraging patient compliance and cooperation. Although we have not treated any severe cases of delirium tremens with this method, 2 patients with mild symptoms responded favourably and it is likely that the more severe cases would be helped as well. Hyperventilation caused by psychogenic factors in these cases would enhance the hyperadrenergic state, thereby aggravating the emotional crisis. Since N$_2$O has been shown to act on opiate receptors, it is possible that it not only controls the affective symptoms but also inhibits the hyperadrenergic state.

In conclusion, it would appear that a rational method of treating alcohol withdrawal states is the use of O$_2$ (with 5% CO$_2$ if necessary), and the addition of O$_2$/N$_2$O treatment for the control of the affective disturbance and also any residual symptoms of hyperadrenergic activity. This combination with the usual supportive therapy (replacement of fluids and electrolytes, especially magnesium, vitamins and glucose) should then suffice without the need for over-sedation of the patient.

This physical treatment can be markedly reinforced by correct attention to the psychological needs of the patient, which in turn might enhance the response of the opiate system. In addition, other neurotransmitter systems, such as the γ-aminobutyric acid (GABA) system in particular, appear to contribute to the pathogenesis of this condition. The use of GABAAergic agents such as benzodiazepines in small amounts is rational treatment as the GABA receptors have been shown to increase in number in the brain of alcoholics.

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REFERENCES

The insulin and glucose response to an oral glucose load in non-insulin-dependent diabetes in the young

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Summary

Non-insulin-dependent diabetes with age of onset under 35 years was studied in 85 Indian patients. Eighty-one per cent of the group were females, the mean age of onset of diabetes was 27 years while the mean duration was 6.3 years. The mean percentage desirable mass of the patients was 122%, obesity being present in 55% of the group. Eighty-two per cent of patients gave a positive family history; closer analysis revealed that 75% of the propositi had a diabetic parent and 41% a diabetic sibling; while three-generation transmission was present in 76%.

Eighty-one patients consented to a 100 g oral glucose load. The insulin and glucose response during a 3-hour period revealed fasting hyperinsulinism with a delayed and attenuated insulin response, a much lower insulin area and a lower modified Seltzer insulinogenic index when compared with 50 non-diabetic reference subjects. There was no difference in insulin and glucose responses in obese and non-obese diabetics. However, subdivision of the group into those with moderate and those with severe diabetes demonstrated that the latter had significantly higher plasma glucose levels and lower insulin levels at all times, except in the fasting state, during which the insulin levels were not significantly different.


Fajans and Conn1 were the first to draw attention to the occurrence of mild diabetes in young people which responded by improvement of glucose tolerance with tolbutamide therapy. Similar studies confirming this entity were subsequently reported from Scandinavia, England and the USA.2-4

About the time Fajans and Conn reported their study, Campbell5 drew attention to the existence of insulin-dependent diabetes in young Natal Indians; more recently, Jackson6 stated in a review that whereas insulin-dependent diabetes is extremely rare in young South African Indians, a maturity-onset type of diabetes in the young (MODY) is fairly common. In a preliminary report certain aspects of non-insulin-dependent diabetes with onset below 35 years in 43 Indian and 9 Black patients were considered.7

In the present study, which is part of an ongoing study of this type of diabetes, we wish to report in greater detail on the clinical features in 85 Indian patients as well as on the glucose and insulin response to a 100 g oral glucose load.

Patients and methods

Non-insulin-dependent diabetes in the young (NIDDY) was categorized according to the following criteria: age of onset

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