Clinical Toxicology

Analgesic nitrous oxide for alcohol withdrawal: a critical appraisal after 10 years' use

Mark A. Gillman and Frederick J. Lichtigfeld

South African Brain Research Institute, 6 Campbell Street, Waverley 2090, Johannesburg, South Africa.

Summary: We describe a method of treating the mild to moderate alcohol withdrawal state which has been used successfully for 10 years in over 7,000 cases. It is now the standard therapy at the largest dedicated alcoholic rehabilitation centre in Southern Africa. The technique uses analgesic (subanaesthetic) concentrations of nitrous oxide, which in most cases is administered on a single occasion for 20 minutes only. This results in the most rapid detoxification presently available, such that within an hour of the commencement of therapy the patient is so improved that they can eat the next ward meal. Provided the correct equipment and simple training is used this non-anaesthetic treatment is completely free of any serious side effects and the patient is at all times conscious and cooperative. Apart from this the amounts of sedative medication, such as benzodiazepines, are drastically reduced during detoxification. Because of the rapidity of the therapeutic response this technique is useful also as a screening test for assessing those patients requiring intensive therapy for the alcohol withdrawal state. There is evidence of the usefulness of analgesic nitrous oxide therapy for treating other addictive withdrawal states including opioid and nicotine.

Introduction

Recently, in a review article on the clinical management of the alcohol withdrawal state (AWS) under the heading 'swift detoxification' the use of diazepam is mentioned.¹ This is certainly not the only, or most rapid detoxification method available. We have developed a technique utilizing analgesic concentrations of nitrous oxide (AN), which provides a rapid, safe and effective treatment of the mild to moderate withdrawal state. This is now standard therapy at the largest dedicated alcoholic facility in Southern Africa and has been used successfully here and elsewhere in over 7,000 cases of chronic alcoholism since 1980.² This is *not* an anaesthetic technique, since the patient is at all times conscious. Anaesthesia and/or anoxia is prevented by the use of a standard dental relative analgesia machine, which is and has been used routinely in dental offices for many millions of cases worldwide without a serious side effect ever being reported following such treatment.³

The gases are given once only on admission (in over 95% of cases) and improvement is so rapid that most patients are able to enjoy the next scheduled ward meal.² The use of sedative medication is reduced to night sedation only (15–60 mg oxazepam) for one or two nights, resulting in a

reduction of the use of these addictive agents by 80%³ or more.² The hospital stay is reduced by up to 20%² and the technique has been used successfully on an out-patient basis in private medical practice. The addictive potential is extremely low^{2,4} and has been dismissed as follows: 'It seems unlikely that as a drug of abuse, nitrous oxide ever will compete seriously with the array of potent mind-altering drugs that are available in much more convenient forms . . .'.⁵ This lack of addictive potential may also be related to its evanescent effects and partial agonistic profile.⁵ This is attested to by not a single case of addictive or gas-seeking behaviour being found in the over 7,000 cases so far successfully treated with this method.² Dyshaemopoiesis due to nitrous oxide, even in severely debilitated intensive care patients, requires at least one hour of exposure.⁶ The overall safety and rapid efficacy of the technique is demonstrated by the successful therapy of more than 7,000 withdrawals since 1980, without a single case of toxicity and/or gas-seeking behaviour being found amongst this cohort.²

The ease of application of this analgesic non-anaesthetic method is underlined by the fact that it has been used safely by nursing sisters after they have received a brief training course.⁷

A major advantage of the technique is that within an hour the physician is able to screen those cases requiring intensive therapy from those who

do not. This is possible since it has been found that only those (a small minority of patients) who do not respond positively to the gas administration appear to need such intensive treatment.

Method

Before giving a detailed description of this method it is essential to understand that this is not an anaesthetic technique. The gas is applied in analgesic concentrations with the patient fully conscious and co-operative at all times, with no impairment of vital reflexes. For these reasons it is totally unnecessary to take the precautions usually associated with the administration of a general anaesthetic. This distinction between anaesthetic and analgesic nitrous oxide is crucial and is related to the fact that at the lower concentrations at which nitrous oxide is analgesic, it is a specific opioid agonist.^{4,8-11}

In order to achieve optimal results it is important to individualize this treatment for every patient since the concentration of AN required varies widely between cases¹² and can range from as low as 15% to as high as 70%. In the very rare cases where 70% AN is required it is our experience that the alcohol abuse has caused increased tolerance to the effects of AN so that even at this high concentration the patient is not in any way sedated or obtunded. Initially the subject is given 100% oxygen or medical air for 20 minutes (consistent with tidal volume, usually approximately 6 litres/min) both to familiarize the patient with the procedure and also because we have found that this exposure has marked placebo effects; often being sufficient to ameliorate the condition without requiring the use of AN. This placebo effect is considered satisfactory if the patient becomes more comfortable and the symptoms have been largely reversed. We have found in practice that it is not necessary for all the symptoms to be totally ameliorated for the treatment to be effective. Once the symptoms have been attenuated by at least 50% from baseline scores (as measured on a modified Gross scale¹²⁻¹⁴) the patient is sufficiently comfortable to manage without further inhalation therapy. With practice it is possible to determine this level clinically without having recourse to the Gross scale.

When AN administration is necessary after a failure to respond to placebo, careful attention to the technique to be described below is absolutely essential to achieve maximum efficacy. The patient is recumbent and the gases are given with a Quantiflex Dental Relative Analgesia machine (Matrx Medical) or similar apparatus having a fail-safe device. The latter halts the flow of AN when the oxygen concentration delivered to the

patient falls below 30%.¹²⁻¹⁴ This prevents any danger of hypoxia occurring. In addition, since a nasal (never a facial) mask is employed in this open circuit, the possibility of anaesthesia is eliminated.

Three litres of oxygen are given and 0.5 litres nitrous oxide is then added. At least 2 minutes elapse before the effects of this initial concentration are assessed. If this concentration is not effective the amount of AN is increased to 1 litre/min for a further 2 minutes. Additional increments of 0.5 litres/min are given every 2 minutes until an effective dosage is found, namely, when the symptoms are reversed and the patient appears comfortable both subjectively and objectively. This comfort zone or end-point is easily established clinically (and occurs either during placebo or AN administration) since at this point the patient appears relaxed without any signs of sedation. The secret of this technique is careful titration to avoid exceeding the end-point which can result in sedation or excitation. Such an overshoot is readily and swiftly remedied by increasing the oxygen and decreasing the AN. The effective dosage is then continued until the total exposure to AN reaches 20 minutes. It is important to emphasize that the hall mark of this rapid effect is that it occurs either during placebo or AN administration, that is, literally within minutes of and during gas inhalation.

In order to prevent any possibility of diffusion hypoxia, at least 5 minutes of 100% oxygen is given after AN.¹⁵ When this treatment is used on an out-patient basis further oxygen is recommended for another 15 minutes and the patient must not drive for a further 30 minutes thereafter.

The cases of alcohol withdrawal state treated by this method have been mild to moderate in severity with all or some of the following signs and symptoms: tremor, restlessness, irritability, agitation, nausea, autonomic hyperactivity (tachycardia and hypertension), remorse and depression. In the early stage of withdrawal, orientation and alertness are preserved; however, later on disorientation occurs which may be accompanied by misperceptions and illusions, with some measure of preserved insight. Once these early premonitory signs and symptoms had progressed into a full blown withdrawal delirium other methods of therapy were used.

The initial patients used in this study consisted of caucasian male alcoholic patients with a long history of chronic alcoholism, aged between 28 and 60 years. Since then this treatment has also been successfully applied in an African population of both sexes.⁷

The AN treatment is contraindicated in only 2 conditions; delirium tremens (alcohol withdrawal delirium) and chronic obstructive airways disease. Although these conditions are not absolute contra-

indications, great caution must be exercised if it is used here.

Blood pressure and pulse rate are monitored before and after each gas inhalation. Attention was routinely given to vitamins, fluid and electrolyte balance. Anticonvulsants were also given routinely.

Results

Over the last 10 years more than 7,000 cases of mild to moderate AWS were treated of which over 95% were successfully managed with this method. More than 5,500 of these were treated at the Wedge Gardens alcohol detoxification centre (Rand Aid, Johannesburg), the largest dedicated alcoholic rehabilitation centre in Southern Africa. The majority of the balance have been handled at other institutions such as Madadeni Hospital in Natal and Themba Centre in Transvaal, South Africa.

A small percentage of cases responding positively to the treatment have a relapse within the first 24 hours. However, with very few exceptions, these relapsing patients respond positively to a second administration.

In those few patients who are unresponsive to this method of treatment sedative medications such as benzodiazepines, chlormethiazole and/ barbiturates are used.

As far as we are aware this method of treatment is the most rapidly acting of the current therapies available for treating mild to moderate AWS. In addition it has proved to be extremely safe with no evidence of toxicity or drug-seeking behaviour being found in any of the patients so far treated. It has excellent patient and staff acceptability. Since the patient's consciousness is not obtunded either during or after gas administration, and in view of the rapid amelioration achieved, the management of the patient is very much improved. This enables rehabilitation methods to begin immediately gas inhalation is ended. For this reason the period of hospital stay is reduced by up to 20%.^{2,3,12}

The use of this inhalation method also drastically reduces the benzodiazepine and other sedative medications^{2,12} by approximately 80%.³ However, we have found since then that it has been possible to reduce the amount of sedation used even further, so that even night sedation is found unnecessary in some cases. Where night sedation is used this is extremely limited and for one or two nights only using between 15 and 60 mg oxazepam.³

Initially, oxygen was used as a placebo and was found to reduce the symptoms by approximately 60%.¹² Since then oxygen has been compared against medical air, both agents being equally effective with just over 50% showing positive placebo responses. Of those patients not respond-

ing to placebo, 87.5% responded satisfactorily to an ensuing AN administration.^{13,14} Autonomic signs such as blood pressure and pulse rate were reduced in most cases.¹²

Studies done on patients receiving this treatment show no evidence of any untoward haematological changes as found in peripheral blood.^{6,11} This is perhaps not surprising since it has been shown that at least one hour's exposure to AN is required even in severely debilitated intensive care patients for haematological changes to occur.⁶ In addition to its other positive attributes, AN appears to have a marked anti-depressant effect both during and after its use in the therapy of the AWS.^{11,12} Clinically we have also found that AN has excellent anti-craving effects both during and after the treatment of AWS. This finding has been supported by other work.⁷

Discussion

How close is AN to the ideal AWS therapy? Its effects are, of course, not instantaneous, although a therapeutic response occurs within minutes of starting the gas administration and a maximal response is found during the inhalation period. Usually the placebo precedes AN for 20 minutes, making the total period for a placebo non-responder 40 minutes. This time interval could conceivably be shortened to 20 minutes by using AN only and eliminating the placebo period.

In our hands approximately 5% of patients failed to respond to AN^{13,14} while in another study, in a rural setting, there was a 15% failure rate, all of whom were male subjects ($n = 139$), with no failure recorded amongst the females ($n = 11$).⁷

The AN therapy is of minimal addictive potential^{2,5,11} and is therefore preferable to the customary methods, relying as they do on the addictive sedatives such as benzodiazepines.^{3,11}

The technique is extremely simple to master, provided strict attention to the method described above is adhered to. This is well illustrated by the fact that most of the treatments have been given by trained nursing staff under medical supervision. This supervision did not require the physicians to be routinely present during gas administration, which has enabled it to be applied successfully in a rural African setting.⁷

Although the patient must be closely supervised during AN administration, which is initially staff intensive, this is more than offset by the reduced drug and staff requirements following the rapid amelioration of the AWS by the gas method.

Apart from the therapeutic advantages mentioned above, use of this treatment has given some further insights into the possible underlying mechanism of AWS, and has enabled us to attempt

an integration between the opioid and other neurotransmitter systems active in this process.¹⁶ These insights into the AWS illustrate the possible usefulness of AN in investigating and treating disorders where a disturbance of the endogenous opioid system might be involved.^{11,16} We have also found that AN is useful in the treatment of other addictive withdrawal states, including opioids and nicotine.^{2,11} It would appear that the only disadvantages relating to this method are that specialized equipment is needed requiring an initial financial outlay, initial but limited training is required for the nurses applying the therapy and, for a maximum of 40 minutes on admission, the treatment is staff intensive. Despite these apparent disadvantages, the use of AN for treating the AWS is extremely beneficial and cost effective, being considerably cheaper than the currently available sedative therapies.

In view of the current intention to treat mild to moderate AWS on an out-patient basis¹⁷ it would seem essential to find a suitable rapid screening

method to pin-point those patients who might require intensive in-patient therapy. We consider that the use of AN in this setting has clear-cut advantages over any other currently available test. It will rapidly distinguish between those who respond positively and the small minority requiring in-patient therapy. This proposition requires further investigation before one can recommend routine out-patient care for the mild to moderate AWS. For those interested in further details a teaching manual for this technique is being prepared.

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