CLONIDINE IN THE TREATMENT OF ALCOHOL WITHDRAWAL IN THE INTENSIVE CARE UNIT

P. C. IP YAM, A. FORBES AND W. J. KOX

SUMMARY

We present two cases of patients with a past history of alcohol abuse admitted to the Intensive Care Unit (ICU) for treatment of respiratory problems, after multiple trauma and after sub-total colectomy, respectively. In both patients, features of alcohol withdrawal were prominent after sedation had been discontinued. Both were treated successfully with an infusion of clonidine.

KEY WORDS

Intensive care: alcohol withdrawal. Pharmacology: clonidine

The treatment of alcohol withdrawal is difficult when superimposed on the physiological disturbances present in critically ill patients. Drugs given to alleviate withdrawal symptoms should be safe yet effective, ideally without impairing communication between the patient and medical and nursing attendants. The mainstay of treatment in the U.K. has been chlormethiazole infusion, 24—60 mg min"1 until sedation is achieved, then 4—8 mg min"1 for maintenance. This has hypnotic and anticonvulsant properties, but substantial volumes of fluid may be necessary leading to fluid overload associated with pulmonary and peripheral oedema and systemic hypotension [1]. However, elimination is fairly rapid, the drug having a plasma half-life of 4–6 h.

Benzodiazepines have been used also for treating alcohol withdrawal (particularly in North America), as they have anticonvulsant, anxiolytic and sedative properties, with a relatively high therapeutic index, but no effect on withdrawal hallucinations. Furthermore, the active metabolite, desmethyldiazepam, common to the two most frequently used agents (chlordiazepoxide and diazepam) tends to accumulate not only in sepsis (with which hepatic blood flow may be impaired [2]), but also in patients with alcoholic liver disease. Because midazolam and its principal hepatic metabolite (1-(OH)-midazolam) have a relatively short half-life (less than 2 h [3]), this drug is now the most commonly used benzodiazepine for the treatment of withdrawal in ICU. Evidence of impaired clearance in patients with liver disease exists nonetheless, and midazolam is at least a theoretical risk in critically ill patients [4].

Clonidine, an $\alpha_2$-adrenergic agonist, has several properties which may make it suitable for the treatment of alcohol withdrawal in the ICU. Although it prolongs barbiturate sleep time, reduces the MAC of inhalation agents [5] and has anaesthetic-like effects on evoked potential responses [6], oral clonidine 0.3 mg given as premedication has a sedative and anxiolytic effect without loss of responsiveness or side effects [7]. In common with other $\alpha_2$-agonists, clonidine acts at receptor sites in the medulla oblongata and presynaptically at peripheral nerve terminals, to cause reduction in activity of the sympathetic nervous system [8, 9]. It has earned a significant place in the management of opioid withdrawal states [10]. Sympathetic overactivity is a constant feature of alcohol withdrawal states, and a study of clonidine has confirmed that it reduces plasma catecholamine concentrations [11]. Three open trials [12–14] (n = 200) and three double-blind trials [11, 15, 16] (n = 50) in which clonidine 0.3–0.45 mg day"1 was given orally, indicated its effectiveness in relieving both autonomic and psychological manifestations of alcohol withdrawal. In another double-blind study [17] (n = 61), it was concluded that clonidine was better than chlordiazepoxide at controlling alcohol withdrawal symptoms and haemodynamic disturbances. We report here the successful use of clonidine in two patients with problematic alcohol withdrawal states.

CASE REPORTS

Patient 1

A 49-yr-old man was admitted to the ICU with multiple injuries after a road traffic accident. He had undergone emergency laparotomy at which splenectomy was performed. He underwent artificial ventilation after operation because of severe left sided pulmonary contusion associated with multiple rib fractures. Pain relief was achieved with thoracic extradural infusion of bupivacaine and diamorphine (10 mg h"1 and 1 mg h"1, respectively). Sedation was provided initially with 0.2–0.4% isoflurane. When this was discontinued 36 h after admission, the patient became severely agitated, with apparent visual hallucinations. This was associated with signs of sympathetic overactivity, including perspiration, tachycardia and hypertension. The patient was not hypoxic or hypercapnic, and there were no electrolyte disturbances. From the history, it was known

that previous alcohol intake had been excessive (more than 60 units or 600 g per week). An infusion of clonidine was commenced at 60–120 μg h⁻¹, increasing to a maximum rate of 180 μg h⁻¹. Over 3 h there was a marked improvement in his physiological state: he became responsive to commands, was no longer agitated and was much easier to nurse. There was a corresponding improvement in his physiological state, in particular a reduction in oxygen consumption as derived from the reverse Fick method (table I). After 2 days, clonidine was withdrawn steadily over 36 h, and there was no recurrence of the original signs of sympathetic agitation, or evidence of a clonidine withdrawal state.

Patient 2

A 68-yr-old man was admitted to the ICU after laparotomy for wound dehiscence. He had previously undergone sub-total colectomy for ulcerative colitis which had failed to respond to medical therapy. Problems included fresh bleeding from the ileostomy site, hypoalbuminaemia, hypokalaemia of 3.1 mmol litre⁻¹ and atrial fibrillation, associated with impaired coagulation (International Normalized Ratio 1.9) and thrombocytopenia (platelet count 39 × 10⁴ litre⁻¹). He was treated with replacement blood products, appropriate electrolytes and digoxin. Initial sedation and analgesia were provided with 0.2–0.4% isoflurane and infusion of alfentanil 0.6 μg kg⁻¹ min⁻¹, respectively. When sedation was stopped, the trachea was extubated (48 h after the initial surgery), but then the patient became agitated, anxious, disoriented and confused, with apparent visual hallucinations. He had a resting tremor, was sweating and persistently attempted to remove vascular cannulae and CPAP mask. He had a long history of alcohol abuse, with biochemical evidence of liver disease for at least 2 yr before the colitic presentation. Direct cholangiography had indicated that he also had primary sclerosing cholangitis. Before operation, plasma concentration of bilirubin was 55 μmol litre⁻¹, alkaline phosphatase 355 u. litre⁻¹, aspartate aminotransferase 20 u. litre⁻¹ and serum albumin 28 g litre⁻¹. He was commenced on an infusion of clonidine 60 μg h⁻¹, increasing to 120 μg h⁻¹, which settled his heart rate from 112 to 96 beat min⁻¹ and mean arterial pressure from 109 to 96 mm Hg immediately, and improved his mental state within 2 h. There were no adverse effects. Clonidine infusion was continued for 24 h and then withdrawn over 12 h, with no further problems and no evidence of a clonidine withdrawal state.

**DISCUSSION**

It appears that clonidine may be used safely and effectively in the management of acute alcohol withdrawal symptoms complicating the management of patients already requiring ICU treatment. Our observations are consistent with those of Metz and Nebel [14] who used similar doses in ICU patients. They argued that the total duration of treatment required, the need for parenteral nutrition and the duration of mechanical ventilation may be decreased when clonidine is used. However, it is recognized that additional agents may still be required to manage psychosis and seizures, but this was not so in the two patients presented here. There is general consensus [18, 19] that clonidine is well tolerated and that the principle side effect, hypotension, is minor and easily overcome, especially with attentive ICU monitoring. The one study [20] apparently at odds with this consensus involved 32 patients admitted for detoxification, in whom hallucinations, seizures and hypotension were more common with clonidine than with chlormethiazole. These patients were in good general health, the drugs were given orally in conservative doses, and extrapolation of these results to the ICU situation is almost certainly inappropriate. Prospective clinical trials are required to clarify the optimal regimens to maximize efficacy and minimize side effects.

**REFERENCES**

activity, the renin aldosterone system, and clinical symptoms. 


