Cardiac arrest following chlormethiazole infusion in chronic alcoholics

*G. T. McINNES

B.Sc., M.B., Ch.B., M.R.C.P. (U.K.)

*R. E. YOUNG

M.B., Ch.B., M.R.C.P. (U.K.)

†B. S. AVERY

M.B. B.S., F.D.S.R.C.S. (Eng.)

*Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow G11 6NT, and

†Department of Oral Surgery, Canniesburn Hospital, Glasgow G4 0NA

Summary

Two chronic alcoholics who had cardiac arrests (one fatal) while receiving chlormethiazole by infusion are reported. Although a causal relationship has not been indisputably established, caution is advised when administering this drug to chronic alcoholics during withdrawal.

Introduction

Chlormethiazole is a sedative and hypnotic with marked anti-convulsant properties. It is widely used in the treatment of states characterized by convulsions and agitation, including delirium tremens. Although rarely causing side effects, the drug has been shown to depress the respiratory centre (Lechat, 1966) and toxic interactions with alcohol have been found in animals (Vapaatalo and Karppanen, 1969). Sudden deaths ascribed to chlormethiazole therapy have been attributed to respiratory depression, and alcohol abuse seems to be a predisposing factor (Pentikainen, Valtonen and Miettinen, 1976). Two cases are reported where cardiac arrest, without evidence of preceding respiratory depression, followed chlormethiazole infusion in the treatment of delirium tremens.

Case 1

A 65-year-old Caucasian with a long history of alcohol abuse was admitted following a haematemesis. He had been drinking heavily for one month until 24 hr before admission. Concurrent therapy was atenolol for hypertension. He was confused and disorientated. Blood pressure (BP) was 160/110 mmHg. Electrocardiography showed sinus tachycardia and left ventricular hypertrophy but no ischaemic features. Chest X-ray was normal. Hb and haematocrit were normal but platelets were $55 \times 10^9/l$;

blood film showed target cells. Electrolytes and urea were normal, serum bilirubin $35 \mu\text{mol/l}$, aspartate transaminase (AST) 64 u./l , γ -glutamyl transpeptidase 58 u./l , lactic dehydrogenase 800 u./l and creatinine kinase 880 u./l . Endoscopy was technically unsatisfactory and cimetidine by infusion was commenced.

Initial restlessness progressed to delirium tremens after 24 hr. He was given parenteral diazepam, chlorpromazine and chlormethiazole and, after 24 hr, satisfactory control of symptoms was achieved by chlormethiazole 0.8% infusion alone. Sixteen hr later he developed ventricular tachycardia. He was resuscitated and recovered uneventfully. Investigations excluded myocardial infarction. Total dose of chlormethiazole was 11.2 g.

Case 2

A 54-year-old Asian was assaulted after leaving a bar. X-ray showed severe facial bone fractures. He was conscious although drowsy, disorientated and amnesic. Pulse was normal and BP 190/110 mmHg. Serum sodium was 132 mmol/l , other electrolytes and urea normal, albumin 32 g/l , AST 206 u./l and alanine transaminase 56 u./l . Treatment was with i.v. fluids and prophylactic antibiotics.

After 12 hr, his restlessness required increasingly frequent parenteral diazepam and chlorpromazine with little effect. Whisky proved more successful. Before facio-maxillary surgery he was given oral chlormethiazole and, postoperatively, this was infused intermittently, controlling his symptoms. Three days after surgery, he developed cardiac asystole following a one-hr infusion of $100 \text{ ml } 0.8\%$ chlormethiazole, its only administration in the previous 24 hr. Resuscitation was unsuccessful. The only other drug treatment was 10 mg of diazepam in divided doses in the 6 hr before death. At post-mortem, the findings were an insignificant pulmonary

embolus and focal fatty hepatic degeneration consistent with chronic alcoholism. Total dose of chlormethiazole was 9.4 g, 6.9 g by infusion; tissue concentration was 0.65 mg/100 g liver.

Discussion

The association between chlormethiazole therapy and cardiac arrest is impressive. The only other drugs given for several hours were antibiotics and diazepam in small doses to the second patient. The combination of chlormethiazole and other sedatives has been implicated in the development of respiratory depression (Pentikainen *et al.*, 1976). There was no evidence of this in either case.

The manufacturer's recommended maintenance dose of chlormethiazole is 333–1333 mg/hr. At the times of arrest in the 2 patients, the infusion rates were 667 mg/hr and 600 mg/hr respectively. At these rates, significant accumulation should not occur on long term administration since the elimination half-life is short (Moore *et al.*, 1975). However, chlormethiazole pharmacokinetics are age-dependent and the drug undergoes hepatic clearance (Nation *et al.*, 1976). Thus, in older patients with hepatic insufficiency, as in these 2 cases, lower doses may be desirable. Nonetheless, the tissue concentration in the fatal case suggests that the infusion rate was appropriate. Quality control studies on the chlormethiazole used in that patient failed to identify any adulterants which might have contributed to his death.

It seems unlikely that the incidents reported were due simply to acute withdrawal of alcohol from chronic alcoholics. Unexpected deaths have been reported in such patients but the incidence is extremely low and the absence of preliminary signs makes this unlikely (Shaw, 1978). However, potassium concentrations decline during acute withdrawal from alcohol (Wadstein and Skude, 1978) and low serum potassium may be associated with cardiac arrhythmias (Dyckner, Helmers and Wester, 1975; Duke, 1978). In neither of these patients was serum potassium known at the time of arrests but a low concentration might have contributed to an adverse cardiovascular effect of chlormethiazole.

Sudden withdrawal of β -blockers from patients with coronary artery disease is infrequently followed by acute coronary syndromes (Mizgala and Counsell, 1976; Williams, Turney and Parsons, 1979) although a recent prospective study has questioned this (Myers *et al.*, 1979). Such events are unlikely to follow abrupt cessation in patients receiving these drugs for hypertension (Maling and Dollery, 1979). In the first case reported here, compliance with atenolol given for hypertension may have been incomplete but there is no evidence of sudden discontinuation nor resultant coronary insufficiency.

Cohen *et al.* (1979) have recently reported that cardiac arrhythmias may follow bolus i.v. injections of cimetidine. Case 1 was given cimetidine by this route but by slow infusion and this had been discontinued for more than 2 hr before the cardiac arrest.

The second patient had suffered severe injuries but clinically was recovering satisfactorily. The post-mortem findings did not suggest that his injuries contributed to his death.

Both cases show a clear temporal relationship between chlormethiazole infusion and the development of serious cardiac arrhythmias. Although a causal relationship has not been established, these findings suggest that this therapy should be administered with caution to alcoholics during acute withdrawal.

Acknowledgments

We wish to thank Dr W. D. Alexander and Mr K. F. Moos for permission to report these cases.

References

- COHEN, J., WEETMAN, A.P., DARGIE, H.J. & KRIKLER, D.M. (1979) Life-threatening arrhythmias and intravenous cimetidine. *British Medical Journal*, **2**, 768.
- DUKE, M. (1978) Thiazide induced hypokalemia. Association of myocardial infarction and ventricular fibrillation. *Journal of the American Medical Association*, **239**, 43.
- DYCKNER, S., HELMERS, C. & WESTER, P.G. (1975) Initial serum potassium levels in relation to early complications and prognosis in patients with acute myocardial infarction. *Acta medica Scandinavica*, **197**, 208.
- LECHAT, P. (1966) Toxicology and pharmacological properties of chlormethiazole. *Acta psychiatrica Scandinavica*, **192** (suppl.), 15.
- MALING, T.J.B. & DOLLERY, C.T. (1979) Changes in blood pressure, heart rate and plasma noradrenaline concentration after sudden withdrawal of propranolol. *British Medical Journal*, **2**, 366.
- MIZGALA, H.F. & COUNSELL, J. (1976) Acute coronary syndromes following abrupt cessation of oral propranolol therapy. *Canadian Medical Association Journal*, **114**, 1123.
- MOORE, R.G., TRIGGS, E.J., SHANKS, C.A. & THOMAS, J. (1975) Pharmacokinetics of chlormethiazole in humans. *European Journal of Clinical Pharmacology*, **8**, 353.
- MYERS, M.G., FREEMAN, M.R., JUMA, Z.A. & WISENBERG, G. (1979) Propranolol withdrawal in angina pectoris: a prospective survey. *American Heart Journal*, **97**, 298.
- NATION, R.L., LEAROYD, B., BARBER, J. & TRIGGS, E.J. (1976) The pharmacokinetics of chlormethiazole following intravenous administration in the aged. *European Journal of Clinical Pharmacology*, **10**, 407.
- PENTIKAINEN, P.J., VALTONEN, V.V. & MIETTINEN, S.A. (1976) Deaths in connection with chlormethiazole (Heminevrin®) therapy. *International Journal of Clinical Pharmacology*, **14**, 225.
- SHAW, G.K. (1978) Alcohol and nervous system. *Clinics in Endocrinology and Metabolism*, **7**, 385.
- VAPAATALO, H. & KARPPANEN, H. (1969) Combined toxicity of ethanol with chlorpromazine, diazepam, chlormethiazole or pentobarbital in mice. *Agents and Actions*, **1**, 43.
- WADSTEIN, J. & SKUDE, G. (1978) Does hypokalaemia precede delirium tremens? *Lancet*, **ii**, 549.
- WILLIAMS, L.C., TURNEY, J.H. & PARSONS, V. (1979) Beta-blocker withdrawal syndrome. *Lancet*, **i**, 494.