SIDE EFFECTS OF DRUGS

Cardiac arrhythmias caused by chloral hydrate

In 12 months only two patients were admitted to an acute medical unit after taking an overdose of chloral hydrate. Both developed serious cardiac arrhythmias.

Case 1

A 29-year-old woman swallowed about 15 g of chloral hydrate with sherry. On admission two hours later she responded only to painful stimuli, and, although breathing spontaneously, she was cyanosed. Her systolic blood pressure was 50 mm Hg. She had an irregular pulse and an electrocardiogram was recorded (fig 1). After 10 mg of intravenous practolol atrial fibrillation developed but reverted to sinus rhythm within five minutes. With the restoration of normal rhythm the blood pressure rose to 110/70 mm Hg. She regained consciousness seven hours later. Clinical and electrocardiographic examination confirmed the absence of any cardiac abnormality.

FIG 1—Case 1. Electrocardiogram showing arrhythmias.

FIG 2—Case 2. Electrocardiogram showing arrhythmias.

Case 2

Ninety minutes after taking 10 to 20 g of chloral hydrate with alcohol a 64-year-old woman was admitted deeply unconscious with an irregular pulse. Her blood pressure was 70/50 mm Hg. Electrocardiographic monitoring showed arrhythmias, which persisted for seven hours (fig 2). She was given no anti-arrhythmic drugs and reverted spontaneously to sinus rhythm. Her blood pressure rose at once to 160/100 mm Hg. She gradually regained consciousness and was discharged from hospital two days later. Clinical examination, an electrocardiogram, and chest radiograph showed nothing abnormal.

Comment

Arrhythmias after poisoning with both tricyclic antidepressants and phenothiazines are now well recognised.^{1 2} Chloral hydrate is generally considered a safe hypnotic and is often recommended for children or elderly patients. Its chief disadvantages are an unpleasant taste and an irritant effect on the stomach, which are minimised by prescribing it diluted and mixed with syrup—the chloral mixture taken by both these patients. Acute poisoning causes stupor and vasodilation, and death may result from respiratory depression. The combination of chloral hydrate and alcohol is known to be additive, resulting in higher plasma concentrations—an interaction which, when popularly realised, resulted in the "Mickey Finn" cocktail for rapidly inducing unconsciousness.

Arrhythmias are not well documented as an adverse reaction, although a therapeutic dose of chloral taken with alcohol may cause tachycardia and hypotension.³ After an overdose the first patient

showed a principally uniform ventricular tachycardia, though some beats had a totally contrary direction. There were junctional escape beats with capture of the ventricles, suggesting the possibility of depressed sinus function perhaps associated with the subsequent development of atrial fibrillation. The second patient developed an essentially similar arrhythmia.

Levy, who in 1911 reported death during light chloroform anaesthesia,⁴ recognised that the ventricles fibrillated and that the myocardium was sensitised to circulating catecholamines. These chloral-induced arrhythmias suggest a condition not dissimilar to that seen with chloroform. Both chloral hydrate and chloroform are hydrocarbon anaesthetics, and the successful reversal of the arrhythmia with practolol in case 1 supports the theory that chloral hydrate sensitised the myocardium to catecholamines and that the effect was reduced or abolished by beta-blockade. One other report has described a patient who developed ventricular arrhythmias complicated by cardiac arrest after chloral hydrate.⁵ Alprenolol reversed the arrhythmia.

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² Schoonmaker, F W, Osteon, R T, and Greenfield, J C, *Annals of Internal Medicine*, 1966, **65**, 1076.

³ Chapman, A H, *Journal of the American Medical Association*, 1958, **167**, 273.

⁴ Levy, A G, *Journal of Physiology*, 1911, **43**, 18.

⁵ DiGiovanni, A J, *Anesthesiology*, 1969, **31**, 93.

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Paranoid psychosis with indomethacin

Psychosis associated with indomethacin treatment has not been previously reported.

Case report

A 65-year-old married woman developed rheumatoid arthritis in mid-1970, and two years later began treatment with indomethacin, 100-150 mg by mouth daily. Over the next four years salicylates, steroids, gold, and intra-articular yttrium were also given but without success, and in February 1976 arthrodesis of the left knee was performed. She made an uneventful recovery and was discharged taking indomethacin as maintenance treatment. No other drugs were prescribed.

Soon after returning home she began to have mental symptoms, with morbid jealousy of her husband, paranoid delusions about her family, visual and olfactory hallucinations, and loss of weight (5 kg; normal weight 60 kg). In November 1976 she claimed that loudspeakers emitted poisonous gases, the television was maliciously influenced to produce bright colours, and a mist covered her windows each morning. She stated that she was first convinced of her husband's infidelity when, on fetching her from the hospital, he had replied "no" to her question, "Did you miss me?"

On examination of her mental state she was inattentive but her consciousness was clear and there were no other noticeable affective or cognitive changes. There was no evidence of other physical disease nor any previous history of serious physical, psychiatric, or marital disorder or allergy or hypersensitivity to drugs. She denied abusing drugs or alcohol. Her family described her as normally stable, hard-working, conscientious, and slightly introverted. There was no family history of adverse drug effects.

Indomethacin was withdrawn over the next four weeks, and until March 1977 she received chlorpromazine 100 mg daily for the psychiatric symptoms. She made a rapid, sustained improvement, becoming free of mental symp-

toms within four weeks. She returned to work, and in May 1977 her husband stated that cordial relations with himself and the family had been restored.

Comment

This patient had a psychotic episode characterised by prominent paranoid delusions and perceptual abnormalities—namely, visual, auditory, and olfactory—occurring in clear consciousness. That the psychosis was symptomatic rather than functional is suggested by the florid hallucinations and the absence of specific evidence of schizophrenia or manic depression. The mental symptoms were linked in time to the indomethacin treatment rather than to the rheumatoid arthritis or operation and cleared up completely soon after this treatment was stopped. There was no suggestion of other possible aetiological factors such as other physical disease, other drugs, alcohol, or drug and food interactions. Side effects from indomethacin are probably dose-related,¹ but the patient's family thought it unlikely that she had exceeded the prescribed amounts. The delay of four years before the onset of symptoms is, however, curious.

Thompson and Percy¹ described hallucinations, depression, and neurological sequelae after indomethacin treatment, and Rothermich² depersonalisation, but I can find no report of paranoid psychosis. There seems to be a risk, however, that patients receiving the drug will develop mental symptoms. Borgkvist and Samuelsson³ advised caution in prescribing it to elderly patients, and I recommend similar care for any patient with a history of psychiatric illness.

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SHORT REPORTS

Responses to angiotensin II antagonist before and after treatment with indomethacin in Bartter's syndrome

A patient with Bartter's syndrome showed the opposite responses to angiotensin II antagonist (1-Sar-8-Ile-angiotensin II) before and after indomethacin treatment. These results indicate that intrinsic angiotensin II plays a part in blood pressure control and that the receptor sites in both arteriolar smooth muscle and adrenal cortex are not impaired in Bartter's syndrome.

Case report

A 25-year-old woman (42 kg, 147 cm) was admitted to hospital for recurrent episodes of tetany and muscle weakness, which she had had for five years. Her blood pressure was 110/60 mm Hg. The serum potassium concentration was 1.9 mmol (mEq)/l, sodium 136 mmol (mEq)/l, and chloride 86 mmol (mEq)/l. Arterial blood gas analysis showed metabolic alkalosis. Plasma renin activity (PRA), determined by bioassay, was extremely high—415 μ g/l in the supine position. Urinary and plasma aldosterone concentrations were moderately increased, with values of 74.6 nmol/day (26.9 μ g/day) (radioimmunoassay: normal 27.7 nmol/day (10 $\pm$ 3.8 μ g/day)) and 852 pmol/l (30.7 ng/100 ml) (normal 228 $\pm$ 88.8 pmol/l (8.2 $\pm$ 3.2 ng/100 ml)) respectively. The blood pressure response to synthetic angiotensin II (Hypertensin—Ciba) was less than that of normal subjects. Histological findings showed hyperplasia of juxtaglomerular complex.

She was placed on a constant regular diet and oral indomethacin was given for 15 days (75 mg/day for 7 days and 150 mg/day for the next 8 days). The treatment with indomethacin caused a gradual increase in body weight (2.2 kg), a fall in the serum total protein concentration from 82 to 60 g/l, and an increase in serum potassium level from 2.0 to 3.1 mmol/l. On the other hand, when treatment was stopped the body weight rapidly decreased, the serum total protein concentration increased again toward the values of the pretreatment period, and the serum potassium concentration dropped to 2.2 mmol/l.

Urinary sodium and potassium excretion tended to decline during the treatment, and PRA and aldosterone concentrations all returned to normal during treatment. Remarkably high serum prostaglandin E_1 and F_{2x} concentrations, which were 41.9 μ g/l (radioimmunoassay: normal 1.38 $\pm$ 0.77 μ g/l) and 20.2 μ g/l (normal 0.90 $\pm$ 0.55 μ g/l) respectively before treatment, decreased to 13.9 and 9.0 μ g/l on the last day of treatment. Her clinical symptoms also improved dramatically on treatment and angiotensin insensitivity was restored.

The angiotensin II antagonist was infused intravenously at a rate of 500 ng/kg/min for 60 minutes, before and after indomethacin treatment (see figure). During the infusion blood pressure was measured with an automatic continuous sphygmomanometer (Ueda Seisakusho Co, Japan) every one minute. During the infusion before treatment the blood pressure fell from 105/48 to 78/35 mm Hg and PRA increased from 485 to 1600 μ g/l,

Effects of 1-Sar-8-Ile-angiotensin II on blood pressure, PRA, and plasma aldosterone before and during treatment with indomethacin.

Normal value for PRA is $28 \pm$ (SD) 7.2 μ g/l/18 h.

Conversion: SI to traditional units: Aldosterone: 1 pmol/l = 0.04 ng/100 ml.

while plasma aldosterone decreased from 668 to 522 pmol/l (24.8 to 18.8 ng/100 ml). After treatment, however, the infusion produced a paradoxical increase in blood pressure from 98/25 to 136/50 mm Hg without any significant change in PRA and plasma aldosterone.

Comment

Fichman *et al*¹ reported the first abnormally high plasma prostaglandin A concentration in Bartter's syndrome. Gill *et al*² also described increased urinary prostaglandin E_2 and F_{2x} concentrations. In their patients indomethacin caused significant falls in plasma or urinary prostaglandins, or both, in PRA, and in plasma aldosterone and the improvement of potassium balance. We have provided additional evidence to support the view that an essential cause of Bartter's syndrome is an excessive production of prostaglandins, with