for it was largely intra-thoracic and yet the tear was limited to the oesophago-gastric junction. It is suggested here that there is occasionally a failure of relaxation of the lower oesophagus which raises the pressure gradient to a sufficient degree to cause a tear, for the lower oesophagus normally relaxes during vomiting and in this patient the gastrografin swallow showed evidence of abnormal neuromuscular activity. It is probable that these tears result from the increased pressure gradient acting on the cardio-oesophageal junction that is displaced above the diaphragm, following a sudden rise in intra-abdominal pressure, and it is postulated that these only occur when a pressure wave is directed against an incompletely relaxed lower oesophagus.

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Recovery in severe glutethimide poisoning

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ALTHOUGH similar in chemical structure to phenobarbital, the sedative drug glutethimide ('Doriden') has a considerably higher mortality in cases of acute intoxication (Maher, Schreiner & Westervelt, 1962). Since the first report of the use of haemodialysis in acute glutethimide intoxication (Schreiner *et al.*, 1958) the procedure has come to have a generally accepted place in the management of this condition. The following case is reported not only to re-emphasize the features of acute glutethimide intoxication, but also because the remarkable clinical course shows that recovery is possible in cases of greater clinical and biochemical severity than those previously reported.

Case report

The patient, a 38-year-old housewife, had been prone to recurrent bouts of depression since her concentration camp experiences in her early teens. Two weeks prior to admission these depressive symptoms became more severe and on 18 August

1965 she was admitted to the Royal Melbourne Hospital following the ingestion of approximately forty glutethimide tablets (10 g).

On examination she was unconscious, but reacted in a semi-purposeful manner to painful stimuli. She had a temperature of 33.5°C, dilated and equal pupils, reacting sluggishly to light, pulse rate of 88/min, respiratory rate of 24/min and BP of 98 mmHg systolic. She was flaccid and areflexic, but would not tolerate an endotracheal tube. There was no other abnormality.

The usual regime for management of patients unconscious due to barbiturate intoxication was followed but within 36 hr her blood pressure had fallen despite intravenous metaraminol ('Aramine') in a dosage of up to 5 mg half-hourly. The pupils were fixed and dilated and she was unresponsive to painful stimuli although respiration was spontaneous and adequate. The serum glutethimide level was estimated by the method of Goldbaum, Williams & Koppányi (1960) to be 11.9 mg/100 ml

and, despite pharmacological advice that the procedure was unlikely to be effective because the drug was predominantly bound to tissues, haemodialysis was started. She was given intramuscular digitalis and an attempt was made to maintain her blood pressure with intravenous noradrenaline ('Levophed') in a dose of 8 mg/500 ml of infusion.

The clinical signs of left sided bronchopneumonia were confirmed by chest X-ray. Three days after admission, during a tracheostomy, cardiac arrest occurred, but was terminated within 60 sec by external cardiac massage. Her respiration was subsequently assisted by means of an intermittent positive pressure respirator (Bird, Mark 7).

Over the ensuing 7 days four further haemodialyses were carried out and resulted in a progressive fall in her serum glutethimide (see Fig. 1). During the first dialysis, 560 mg of glutethimide was removed and 820 mg during the second. Ten days after admission spontaneous respiration and deep reflexes returned and the next day she responded to verbal stimuli.

FIG. 1. Fall in serum glutethimide with haemodialyses.

During the remainder of her stay in hospital her pneumonia resolved. Depressive symptoms became increasingly apparent and 6 weeks after admission she was commenced on imipramine hydrochloride ('Tofranil'), which caused a gradual improvement in her affect. A thoracotomy was performed for repair of tracheal stenosis which became evident after closure of the tracheostomy and several split skin grafts were applied to a necrotic ulcer of the right leg caused by extravasation of noradrenaline.

Outpatient review on one occasion suggested the possibility of organic brain damage, but this was not confirmed by psychometric testing. She failed to attend further out-patient appointments.

On 26 May 1966, 6 months after discharge, she was re-admitted following ingestion of an unknown quantity of glutethimide. Depressive symptoms with suicidal thoughts had recurred about 2 weeks previously.

On examination she was unconscious and cyanosed, with a pulse rate of 80/min, a respiratory rate of 16/min, BP 90/70, and temperature of 37.2°C. She did not respond to painful stimuli and the pupils were widely dilated and reacted to light. Chest movement and air entry were poor, but no adventitious sounds were heard and, although she was completely flaccid, her reflexes were present and equal.

Serum glutethimide level was 4.1 mg/100 ml and the P_{CO_2} , as estimated by the rebreathing method of Campbell & Howell (1962), was 55 mmHg. An endotracheal tube was passed and respiration was assisted with a Bird, Mark 7 Respirator. She became areflexic and hypotensive within 4 hr of admission, the very low blood pressure being associated with intense peripheral vasoconstriction and a fall in urinary output. Intravenous isoproterenol ('Isuprel') in a dose of 0.8 mg/500 ml of 4% dextrose was commenced and a haemodialysis was performed for 4 hr using a Kolff twin-coil dialyser. Following the isoproterenol the pulse volume increased with concomitant improvement in the peripheral circulation, although the blood pressure remained difficult to record for some 8 hr after the dialysis. Twenty-four hours after dialysis, isoproterenol was stopped as the blood pressure and urinary output had returned to normal. The serum glutethimide level at this stage was 1.4 mg/100 ml and dialysis was not repeated.

Six days after admission the endotracheal tube was removed, but the patient remained deeply unconscious and developed a severe staphylococcal pneumonia. The pneumonia, in association with the recently repaired tracheal stenosis, necessitated repeated bronchoscopy. After treatment with large doses of intravenous penicillin and chloramphenicol, the pneumonia resolved.

Nine days after admission she recovered consciousness and marked depressive symptoms with suicidal thoughts were noted. She was again treated with imipramine hydrochloride 50 mg t.d.s. Her haemoglobin, which was found to have fallen to 8.4 g/100 ml, was corrected by a blood transfusion.

She was discharged 27 days after admission. A bronchoscopy performed prior to discharge demonstrated an excellent result of her previous tracheal repair. Depressive symptoms had improved, her chest was clinically and radiologically clear and her haemoglobin was 12.4 g/100 ml.

When last seen on 12 September 1966, 12 weeks after discharge, she was in excellent health with no sign of recurrence of depression.

Discussion

This case illustrates most of the clinical features which distinguish acute glutethimide from barbiturate intoxication (Maher *et al.*, 1962). Prolonged coma, hypothermia, profound hypotension and widely dilated pupils with little respiratory depression were all seen, although the cyclical variation in the conscious state noted by Maher *et al.* (1962) and seen in the case reported by Irvine, Montgomerie & Spence (1963) was not apparent.

After intestinal absorption, glutethimide is excreted in the bile. It is mainly reabsorbed and excreted by the kidney as a conjugated metabolite. Due to its poor solubility in water and the large intestinal reservoir, gastric lavage would seem to have limited value, although Schreiner *et al.* (1958) reported the recovery of undissolved glutethimide in the stomach 69 hr after ingestion. Despite occasional reports to the contrary (Barbour, 1960; Ellis, Lea & Drysdale, 1963), it is the opinion of McDonald *et al.* (1963) that peritoneal dialyses is of little use in the treatment of glutethimide overdose. According to Maher & Schreiner (1961), glutethimide has a dialysance and 'time-dose-cytotoxic relationship' which make haemodialysis an effective treatment for cases of acute intoxication. The case reported here, on both occasions, fulfilled most of the criteria for haemodialysis in acute poisoning suggested by Maher & Schreiner (1961) and there is no doubt that the procedure contributed largely to the patient's recovery. The serum glutethimide level on the first admission was much higher than any in the series reported by Maher *et al.* (1962). It is also of interest that the duration of coma was far in excess of previously reported cases (Winters & Grace, 1961; Maher *et al.*, 1962). It is felt that the use of intravenous isoproterenol was decisive in the reversal of the profound shock seen during the second admission, in which the combination of severe peripheral vasoconstriction and diminished urinary output contra-indicated the use of vasopressor agents (MacLean *et al.*, 1965).

Claims have been made that glutethimide is a superior hypnotic to barbiturates. The problems of

resuscitation in cases of acute poisoning, such as those described above, as well as the higher mortality should limit its use, particularly in patients with depressive symptoms.

Summary

Two successful resuscitations of a patient with glutethimide intoxication of greater severity than previously reported are described. The contribution of haemodialysis to recovery on both occasions and of intravenous isoproterenol in the management of peripheral circulatory failure on the second are discussed. The clinical distinction between acute glutethimide and barbiturate intoxication is re-emphasized.

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