HYPOTHERMIA AFTER CHLORPROMAZINE IN MYXOEDEMATOUS PSYCHOSIS

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We report here the case of a patient who developed myxoedematous psychosis and then lapsed into hypothermic coma after an injection of chlorpromazine.

Case Report

The patient, a housewife aged 54, was born in Italy, and came to England at the age of 21. In 1943 she developed thyrotoxicosis and was found to have a nodular goitre, so a partial thyroidectomy was done. She was well thereafter until a year ago, when she began to complain of feeling cold. Two weeks before admission she told her family that the neighbours had turned against her, and that people she met in the street would not look at her or speak to her. Three days before admission she took to her bed, saying that she had split into two pieces, and was living in the left half only. Next day her mental state was worse, and on the day before admission she said that she was now the Queen of Heaven, and that her subjects were telling her to scratch herself. When her family doctor saw her she screamed at him and told him that he was a thief. She was admitted to a mental hospital that night.

When examined there she was found to be maniacal and violent, and was screaming persistently. She was given 100 mg. of chlorpromazine by intramuscular injection; next morning she was quiet but was unable to answer questions, and kept mumbling that she was cold. Methedrine was given (30 mg. intramuscularly) and she became a little more alert, but later in the day she could not be roused. As she was thought to have had a cerebral vascular accident one of us (R. G. W.) was asked to see her, and she was then transferred to the Radcliffe Infirmary.

On examination she was fat and pale, with a cold dry skin. The rectal temperature was 92° F. (33.2° C.). Her hair was coarse and sparse, but the body hair was normal. No peripheral pulses could be felt and the blood pressure was unrecordable, but heart sounds could be heard, the rate being 40/minute.

She would respond to questions by making a croaking, unintelligible noise. The pupils were widely dilated and did not react to light. The limbs were flaccid, the tendon reflexes were just present, and there was a very slow relaxation phase. The plantar responses were extensor.

Initial Investigations.—Blood sugar, 118 mg./100 ml. Serum cholesterol, 400 mg./100 ml. Electrolytes (mEq/l.), Cl, 100; HCO_3, 17; Na, 130; K, 3.5. Chest and skull *x*-rays normal. Blood urea, 65 mg./100 ml. E.C.G.—sinus bradycardia; low-voltage complexes and flat T waves. E.E.G.—sleep pattern. Blood count: Hb, 80%; W.B.C., 10,000/c.mm. W.R. negative.

Management

She was given 40 μg. of triiodothyronine intravenously, and was then immersed up to the neck in a bath of water at 98° F. (36.7° C.). Four hours later her rectal temperature was 100° F. (37.8° C), so she was taken out of the bath and put into a warmed bed. Half an hour later her temperature was 98° F. (36.7° C.), and although she was confused she was able to answer questions and take food and fluid by mouth. Tendon reflexes were brisk, pulse rate 90/min., blood pressure 85/60, and pupils reacted briskly to light. A second intravenous injection of 40 μg. triiodothyronine was given.

The blood pressure steadily rose, and 12 hours from the start of treatment she was alert and cheerful, although still slightly confused. The plantar responses were now flexor, the serum cholesterol was 200 mg./100 ml., and there was no change in blood-sugar or electrolyte levels. She was given triiodothyronine, 20 μg. orally, three times a day, thereafter, but after 48 hours her mental state had deteriorated; she was very confused and apathetic, and could not take fluids by mouth. The blood-pressure fell from 130/90 to 85/60, and the plantar responses became extensor. An E.E.G. at this time showed frequent stretches of sleep pattern. Hydrocortisone 40 mg. was given intravenously; 24 hours later the blood-pressure was 140/90, the plantar responses were flexor, and she was able to eat, drink, and answer questions. Forty-eight hours later, however, the blood pressure had again fallen to 90/60 and she had reverted to her former mental state. A further 40 mg. of hydrocortisone was given intravenously, and in 24 hours the blood-pressure rose to 140/90. She became alert, cheerful, and rational, and remained perfectly well, with no abnormal physical findings thereafter.

Throughout this period the blood sugar had been normal, but the blood urea had risen to 83 mg./100 ml. In the second week of her admission her plasma chloride level had fallen to 83 mEq/l., and the serum sodium was 127 mEq/l., the blood urea being 90 mg./100 ml. She was given sodium chloride supplements (6 g. a day by mouth); a week later the plasma chloride level was 103 mEq/l., and the blood urea was 40 mg./100 ml. There was, it seemed, some element of adrenal insufficiency, so in the fourth week of her admission the following tests were done:

1. *Modified Thorn Test.*—25 units of corticotrophin was infused intravenously over an 8-hour period. On the day of the test the blood urea was 34 mg./100 ml., and the electrolyte levels (mEq/l.) were Cl 108, Na 133, K 4.4, HCO_3 27. The result of the test is set out in the accompanying Table, and shows that the adrenals were capable of responding normally to stimulation with corticotrophin.

Effect of Infusing 25 Units of Corticotrophin Intravenously

Day	Eosinophils/c.mm.		24-Hour Urinary Excretion		
	10 a.m.	4 p.m.	17-Ketosteroids (mg.)	Na (mEq)	K (mEq)
1	30	47	1·8	110	30
2*	34	6	4·0	70	35
3	15	25	1·4	260	27

* Corticotrophin 25 u. i.v. 10 a.m.–6 p.m.

2. *Water-Load Test.*—After 1,200 ml. of water by mouth, 81% was excreted in the next four hours, the maximum urine flow being 8 ml./min.

During her convalescence thyroid extract, ½ gr. (33 mg.) three times daily, was gradually substituted for the oral triiodothyronine; at the end of the fourth week she was alert, cheerful, and completely rational, although she felt that the other ward patients were talking about her and were unfriendly. At this stage the sodium chloride supplements were stopped and she was sent home. She was completely unable to recall the happenings in the two weeks before and the week after her admission to hospital.

She has been seen regularly during the six months since she left hospital, and on thyroid ½ gr. (33 mg.) three times a day is normal, mentally and physically. The blood urea, cholesterol, sugar, and electrolyte levels are normal.

Discussion

Two important points arise from this case. Firstly, the relationship of the hypothermic coma to the injection of chlorpromazine; secondly, the fact that the patient survived.

Delay and Deniker (1952) showed that chlorpromazine caused a marked fall in basal metabolic rate, and this was confirmed by Ratschow (1953). Marocco and Brena (1953), working on guinea-pigs, showed that chlorpromazine reduced the uptake of ^{131}I by the thyroid gland; Milcou *et al.* (1957) found that, in the rat, chlorpromazine lowered the basal metabolic rate and produced large colloid-filled thyroid follicles. It seems, therefore, that chlorpromazine depresses thyroid activity, and this may account for the development of hypothermic coma in our patient after an injection of 100 mg. of the drug. As a similar dose given intravenously does not produce hypothermia in clothed patients (Shackman *et al.*, 1954) it is unlikely to be a direct effect of the drug.

Recovery from hypothermic myxoedema coma is unusual. Of the 19 patients reviewed by Macdonald (1958) only three survived, and one of these died a month later. It is hardly surprising, therefore, that there has been considerable discussion on the management of these moribund patients. Our patient, and two out of the other three who recovered from the hypothermic coma, received triiodothyronine intravenously. There is no doubt that it has the most rapid action of any of the available thyroid hormones (Asper *et al.*, 1953), being effective within a few hours. We used relatively small doses (two injections of 40 μg., each equivalent to 2 gr. (130 mg.) of thyroid extract), whereas the patient described by Dyson and Wood (1956) was given 1,200 μg. and did not survive.

Forty-eight hours after the hypothermia had been corrected, our patient's blood-pressure fell, but it returned to normal levels after two injections of hydrocortisone. During the second week the blood-urea level rose and the levels of serum sodium and chloride fell. This tendency was corrected by salt supplements, but by the fourth week the extra sodium chloride was stopped, and there has been no tendency to relapse. There thus seems to be clear evidence of a transient phase of adrenal insufficiency. Myxoedematous patients have been shown to have impaired adrenal function (Statland and Lerman, 1950; Beierwaltes and Bishop, 1954; Hubble, 1955), and it has been suggested that the pituitary may also be involved (Statland and Lerman, 1950). If these patients do have both secondary adrenal and pituitary insufficiency, giving thyroid hormones might precipitate adrenal failure, for Lerman and Stebbins (1942) showed that thyroid medication could provoke an Addisonian crisis in patients with hypopituitarism. It seems likely, therefore, that hydrocortisone has a valuable part to play in the treatment of severely myxoedematous patients.

As our patient responded normally to a water load and to intravenous corticotrophin four weeks after starting thyroid replacement therapy, the depression of other endocrine functions by the myxoedematous process is clearly reversible. Crispell *et al.* (1954) and Paull and Phillips (1954) found that thyroid extract and thyroxine corrected the delayed water diuresis of myxoedematous patients, but only after many months of treatment. As our patient responded normally to a water load after four weeks this is probably another indication of the speed with which triiodothyronine acts compared with thyroid extract and thyroxine.

Summary

Fifteen years after thyroidectomy, a woman of 54 developed myxoedematous psychosis. Chlorpromazine (100 mg. intramuscularly) was given and the patient lapsed into hypothermic coma.

External warmth and intravenous triiodothyronine produced rapid improvement; secondary adrenal insufficiency occurred, and was corrected by intravenous hydrocortisone and sodium chloride supplements orally.

We are grateful to Sir George Pickering for permission to report this case. The triiodothyronine used was supplied by Glaxo Laboratories Ltd.

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Medical Memoranda

Problem of Cooling a Gangrenous Leg

Whether to cool or not to cool a gangrenous leg will be the question confronting the surgeon when called upon to treat such a condition. The routine of exposing and keeping cool a gangrenous limb would seem to have been actually harmful in the following case. The thrombosis appears to have been due to the presence of autohaemagglutinins and perhaps to an added local factor. No vascular disease was present.

Case Report

A married woman aged 59 was admitted to hospital in August, 1957, with a discoloration of the toes of the left foot which had occurred three weeks previously. There was no history of vascular disease, injury, or exposure to cold. Tobacco consumption was 5–15 cigarettes a day. Right radical mastectomy had been performed eight years previously with apparently excellent result. There was no diabetes or familial disease. The patient was of non-Jewish extraction, though married to a Jew, who had died several years ago; there were no children.

General examination revealed no abnormality apart from the blue, cold, gangrenous toes of the left foot. Peripheral