- O'BRIEN, J.S. (1967) Cell membranes—composition; structure; function. *Journal of Theoretical Biology*, **15**, 307.
- SCHWARTZ, J.F., ROWLAND, L.P., EDER, H., MARKS, P.A., OSSERMAN, E.F., HIRSCHBERG, E. & ANDERSON, H. (1963) Bassen-Kornzweig syndrome: deficiency of serum beta-lipoprotein. A neuromuscular disorder resembling Friedreich's ataxia associated with steatorrhea, acanthocytosis, retinitis pigmentosa and a disorder of lipid metabolism. *Archives of Neurology* (Chicago), **8**, 438.
- SOBREVILLA, L.A., GOODMAN, M.L. & KANE, C.A. (1964) Demyelinating central nervous system disease macular atrophy and acanthocytosis (Bassen-Kornzweig syndrome). *American Journal of Medicine*, **37**, 821.

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Drug-induced hyponatraemia in psychogenic polydipsia

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Summary

Two patients with psychogenic polydipsia developed hyponatraemia, one in association with administration of hydrochlorothiazide and the other with that of tolbutamide. It is suggested that the increased fluid intake in such patients may make them more susceptible to the development of hyponatraemia from thiazide or sulphonylurea compounds.

Introduction

Development of clinical hyponatraemia in patients with psychogenic polydipsia is a rare occurrence (Langgard and Smith, 1967; Hobson and English, 1963). Sulphonylurea compounds (Garcia, Miller and Moses, 1971; Hagen and Frawley, 1970) or thiazides (Fuisz, Laufer and Cohen, 1962; Fichman *et al.*, 1971) have been observed to produce hyponatraemia in patients with normal or excessive water intake. Although patients with psychogenic polydipsia might be expected to develop dilutional hyponatraemia more frequently in association with these drugs, it has seldom been reported (Beresford, 1970; Kennedy and Earley, 1970). Two patients with psychogenic polydipsia are described who presented with acute dilutional hyponatraemia, one in association

with hydrochlorothiazide, and the other with tolbutamide.

Case report

Case 1

A 54-year-old white male with chronic schizophrenia and essential hypertension was first seen by G.A.H. in 1972 on the Psychiatric Service of the St Louis Veterans Administration Hospital (Jefferson Barracks Division) after treatment with hydrochlorothiazide 50 mg daily for 5 days. The patient was extremely weak and mentally obtunded, although able to respond to questions. Blood pressure was 110/70 mmHg, and pulse 84/min. There was no evidence of dehydration. The serum Na level was 106, K 1.7, Cl 57, and CO₂ 34 mEq/l. Serum and urine osmolality were 240 and 115 mmol/kg respectively. Hydrochlorothiazide was discontinued and with fluid restriction serum electrolyte levels gradually returned to normal and urine osmolality increased to 648 mmol/kg. It was also observed that the patient's daily fluid intake averaged 6–8 litres and a diagnosis of compulsive polydipsia was made. The blood pressure returned to its previous level of 190/110 mmHg which was controlled by administration of methyldopa 250 mg q.i.d. and the patient was discharged. He continued to take methyldopa and did well until December 1974, when he was readmitted to the Medical Service because of blood

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pressure of 210/150 mmHg. Funduscopic examination revealed arterial narrowing but no exudates or haemorrhages. The remainder of the physical examination revealed no additional abnormality. The haemoglobin was 12.0 g, haematocrit 35%, and WBC 6500/mm³ with a normal differential count. Urinalysis revealed a specific gravity of 1.005 and was otherwise normal. Serum Na was 138, K 2.1, Cl 87, and CO₂ 34 mEq/l. The blood urea nitrogen was 28, and serum creatinine 2.0 mg/100 ml. The patient was initially given i.v. diazoxide, and subsequently was treated with hydralazine and methyl-dopa. As his blood pressure was not adequately controlled by the latter drugs, hydrochlorothiazide 50 mg daily was added. On the following day, serum Na decreased to 125 mEq/l, and then dropped to 115 mEq/l at which time the patient became stuporous and had a convulsive seizure. Hydrochlorothiazide was discontinued and fluid restriction was instituted. With these measures serum Na returned to normal. Water intake and serum levels of Na and K are shown in Fig. 1. With *ad libitum* fluid intake serum Na varied between 132 and 137 mEq/l. When hydrochlorothiazide was reinstituted, both serum Na and K levels decreased. With administration of KCl 60 mEq/day a temporary improvement resulted in serum Na and K levels. Serum Na returned again to 132 mEq/l when hydrochlorothiazide was discontinued.

Case 2

A 52-year-old man was admitted to the Medical Service of the St Louis Veterans Administration Hospital (Jefferson Barracks Division) in December

1973, because of extreme weakness, mental confusion, and vomiting of 1 day's duration. The patient had chronic schizophrenia and diabetes mellitus of 20 years' duration. He had been receiving tolbutamide 0.5 g t.i.d. since 1962. About a week before admission the patient had been drinking large quantities of water because of increased anxiety. On examination the patient was unable to stand without assistance. Pulse was 100/min and BP 190/90 mmHg. Skin turgor was normal. Physical examination was otherwise unremarkable. The haemoglobin was 14.2 g and haematocrit 42%. White blood cell count was 10,400/mm³ with normal differential count. The serum Na level was 108, K 3.4, Cl 81, and CO₂ 24 mEq/l. The blood urea nitrogen was 7 mg/100 ml and blood glucose level was 308 mg/100 ml. On catheterization of the bladder 1900 cc of urine was obtained. The urinalysis revealed a specific gravity of 1.008 and 4+ glucose, but no albumin or ketones. X-ray of the chest was within normal limits. Electrocardiogram revealed complete right bundle branch block and an old inferior myocardial infarction.

Following admission tolbutamide was discontinued and blood sugar was controlled with 10 units of NPH (neutral protamine Hagedorn) insulin administered daily. The patient continued to have a high urine flow which totalled 18 litres during the first 24 hr, being partly replaced by 13 litres administered parenterally. The serum Na had increased to 135 mEq/l by 24 hr after admission. Intravenous fluids were discontinued and patient was allowed to drink fluids *ad libitum*. Daily average fluid intake was 7 litres. A dehydration test was attempted, but the patient did not co-operate adequately. Nevertheless

FIG. 1. Development of hyponatraemia following administration of hydrochlorothiazide in a patient with psychogenic polydipsia. Patient was on an *ad libitum* fluid intake throughout the study except on days 8–12 when fluid intake was restricted because of hyponatraemia. ▨, Water intake; □, urine output; ●—●, serum Na; ▲—▲, serum K.

after only 8 hr of attempted dehydration urine osmolality increased from 151 mmol to 603 mmol/kg. Randomly obtained serum osmolalities varied between 282 and 292 mmol/kg on an *ad libitum* fluid intake. A hypertonic saline test to evaluate (antidiuretic hormone) ADH response was also performed (Carter and Robbins, 1947). Following i.v. administration of 3% saline, urine flow decreased from 22 ml/min to 6 ml/min, a normal response. During the last year the patient has been followed as an out-patient. The diabetes has remained under good control and serum electrolytes obtained on several occasions have been within normal limits.

Discussion

Both patients described had psychiatric illness (compulsive water drinking) and presented with acute hyponatraemia which was apparently drug-induced. Both had normal pituitary ADH release as demonstrated by a rise in urine osmolality when fluid intake was restricted. A hypertonic saline test in the second patient confirmed his ability to release ADH in response to serum hyperosmolality.

Hydrochlorothiazide administration was followed by the appearance of hyponatraemia on three occasions in the first patient, and each time the serum Na returned to normal levels when the drug was discontinued. Diuretic-induced hyponatraemia is characterized by an accompanying hypokalaemia and metabolic alkalosis and can be corrected in part by administration of potassium (Fichman *et al.*, 1971). Such biochemical abnormalities were present and the serum sodium level improved with administration of potassium in patient 1. In the second patient, markedly increased fluid intake a few days before admission along with ingestion of tolbutamide appeared to have precipitated hyponatraemia. The hyponatraemia did not recur on an *ad libitum* fluid intake after tolbutamide was replaced by insulin.

Although most cases of hyponatraemia due to sulphonylurea compounds have resulted from chlorpropamide with relatively few caused by tolbutamide, the mechanism of action of these drugs appears to be similar (Moses and Miller, 1974). The effect of tolbutamide, like chlorpropamide, may be the result of enhancement of the action of ADH already present (Hagen and Frawley, 1970) or stimulation of ADH release (Moses, Numann and Miller, 1973). Hypokalaemia due to urinary potassium loss from hydrochlorothiazide may exaggerate the normal

release of ADH occurring in response to diuretic-induced sodium loss and volume depletion (Fichman *et al.*, 1971). In effect, both sulphonylurea and thiazide compounds may produce an inappropriate ADH-like syndrome although through somewhat different mechanisms. In addition, thiazides may cause a relatively greater excretion of solute than water during polydipsia so that 'free water clearance' is decreased, leading to hyponatraemia (Heinemann, De-Martine and Laragh, 1959).

In view of the large number of patients receiving thiazide and sulphonylurea compounds, hyponatraemia appears to be an infrequent complication of their use. However, patients who have primary polydipsia are probably more susceptible to drug-induced hyponatraemia and require greater caution by physicians administering thiazide or sulphonylurea compounds to them.

References

- BERESFORD, H.R. (1970) Polydipsia, hydrochlorothiazide and water intoxication. *Journal of the American Medical Association*, **214**, 897.
- CARTER, A.C. & ROBBINS, J. (1947) The use of hypertonic saline infusions in the differential diagnosis of diabetes insipidus and psychogenic polydipsia. *Journal of Clinical Endocrinology and Metabolism*, **7**, 753.
- FICHMAN, M.P., VORHERR, H., KLEEMAN, C.R. & TELFER, N. (1971) Diuretic-induced hyponatremia. *Annals of Internal Medicine*, **75**, 853.
- FUISZ, R.F., LAULER, D.P. & COHEN, P. (1962) Diuretic-induced hyponatremia and sustained antidiuresis. *American Journal of Medicine*, **33**, 783.
- GARCIA, J., MILLER, M. & MOSES, A.M. (1971) Chlorpropamide-induced water retention in patients with diabetes mellitus. *Annals of Internal Medicine*, **75**, 549.
- HAGEN, G.A. & FRAWLEY, T.F. (1970) Hyponatremia due to sulfonylurea compounds. *Journal of Clinical Endocrinology and Metabolism*, **31**, 570.
- HEINEMANN, H.O., DE-MARTINE, E.E. & LARAGH, J.H. (1959) The effect of chlorothiazide on renal excretion of electrolytes and free water. *American Journal of Medicine*, **26**, 853.
- HOBSON, J.A. & ENGLISH, J.T. (1963) Self-induced water intoxication. *Annals of Internal Medicine*, **58**, 324.
- KENNEDY, R.M. & EARLEY, L.E. (1970) Profound hyponatremia resulting from a thiazide-induced decrease in urinary diluting capacity in a patient with primary polydipsia. *New England Journal of Medicine*, **282**, 1185.
- LANGGARD, H. & SMITH, W.O. (1962) Self-induced water intoxication without predisposing illness. *New England Journal of Medicine*, **266**, 378.
- MOSES, A.M. & MILLER, M. (1974) Drug induced dilutional hyponatremia. *New England Journal of Medicine*, **291**, 1234.
- MOSES, A.M., NUMANN, P. & MILLER, M. (1973) Mechanism of chlorpropamide antidiuresis in man: evidence of release of ADH and enhancement of peripheral action. *Metabolism*, **22**, 59.