CASE REPORTS

Abnormal water retention and symptomatic hyponatraemia in idiopathic diabetes insipidus during chlorpropamide therapy*

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THE ability of chlorpropamide to reduce urinary volume in patients with neurogenic diabetes insipidus has been recently described by Arduino, Ferraz & Rodriguez (1966), Meinders, Touber & De Vries (1967), Reforzo-Membrives *et al.* (1968), Hocken & Longson (1968), and Andreani, Cinotti & Stirati (1969).

This therapy is potentially of great importance in the treatment of neurogenic diabetes insipidus; therapy with chlorpropamide, however, is not always without complications both in the short or long-term management of these patients.

Initially there were no reports that patients with diabetes insipidus undergoing therapy with chlorpropamide were prone to hypoglycaemic episodes (Meinders, Touber & De Vries, 1967; Reforzo-Membrives *et al.*, 1968), but with increasing use of this type of therapy it soon became apparent that hypoglycaemia was the most frequent and important complication.

We have observed symptomatic hypoglycaemia in the early phases of treatment, but with continued treatment it becomes less frequent (Cinotti *et al.*, 1969).

In this paper we emphasize that these patients, when treated with chlorpropamide, may be also subject to water retention and may present the clinical symptoms of water intoxication.

Observations on a patient with idiopathic neurogenic diabetes insipidus (INDI) who developed water retention and mild symptomatic hyponatraemia during long-term treatment with chlorpropamide are reported. This case may also raise some intriguing questions concerning the mechanism of action of chlorpropamide and the physiopathology of diabetes insipidus.

Methods

During both hospital admissions the patient was kept on a standard diet, sufficient to cover caloric requirements; to control sodium intake, a low sodium diet (40 mEq of sodium) was utilized supplemented with 5 g of NaCl (85 mEq of sodium).

Fluid intake was not limited except during standardized periods of water deprivation; urine was collected and measured every 24 hr and more frequently, if necessary.

The measurements of sodium and potassium in blood and urine were carried out with Beckmann DU flame photometer; blood urea nitrogen, blood sugar and creatinine were measured in a Technicon AutoAnalyser; osmolality was determined by freezing-point depression on the Fiske osmometer.

Standard clearance methods were employed, with the patient in the water-loaded fasting state.

Urinary 17-ketosteroid values were determined by the method of Dreker *et al.* (1952); 17-hydroxycorticosteroid values were obtained using the method of Silber & Porter (1954).

The routine tests were also carried out and are referred to in some details along with the results of special tests.

Case report

The patient, R.L., a 43-year-old woman, was admitted to the Second Medical Clinic of the University of Rome in June 1969, with a diagnosis of diabetes insipidus.

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She gave a history of polyuria and polydipsia dating back 4 years and she was at that time treated with posterior pituitary extracts i.m. and with powdered posterior hypophysis, with improvement in her symptoms (diuresis: 3–4 l/day). In February 1966, she began to have episodes of bronchial asthma following nasal use of the posterior hypophysis powder. Her history also included a post-abortion meningitis at 26 years of age. At age 28, she developed a non-toxic goitre with compression symptoms and, because of this, she underwent a partial thyroidectomy. At that time her weight was 58 kg and during the following 10 years her weight increased to 87 kg. She then underwent therapy for weight reduction with anorectic drugs and she lost about 13–14 kg in 4 months.

On admission the patient had a diuresis of 10 l/day and had not received any therapy for 1 week. Physical examination showed a well nourished, hydrated woman weighing 80 kg. The thyroid was uniformly increased in size. Rales and rhonchi were heard over the entire chest. No oedema was observed. Arterial blood pressure was 140/80 mmHg. Initial laboratory values included the following: BUN, 11 mg/100 ml; blood sugar, 92 mg/100 ml; serum creatinine, 0.80 mg/100 ml; creatinine clearance, 108 ml/min; plasma osmolality, 308 mOsm/kg; serum sodium, 150 mEq/l; potassium, 3.90 mEq/l; calcium, 10.6 mg %; phosphate, 3.0 mg %; protein-bound iodine, 6 µg/100 ml. Urinalysis: SG 1002; no protein was present; the sediment contained two WBC/high power field. Urine culture was negative.

Special tests

Water deprivation test. The patient maintained a diuresis of about 400 ml/hr with a specific gravity of 1002–1003. After 7 hr following initiation of the test, the patient became febrile and agitated and the test was stopped. She lost 5.5 kg (3.1% of body weight) during this test.

Nicotine test. The patient, a non-smoker, was given one cigarette to smoke and instructed to inhale deeply for 5 min. The next urine specimen was then collected; the urine did not become hypertonic.

Carter-Robbins test. The patient was submitted to an infusion of hypertonic sodium chloride (3%): no effect was noted.

Pitressin test. Powdered posterior pituitary extract was administered by nose and the following two 30-min urine samples were taken: there was a good response, but the patient developed an asthmatic crisis.

The acute water load (20 ml/kg of water in 30 min) was entirely eliminated in 5 hr.

Because of her bronchial asthma, the patient was initially treated with aminophyllin i.v. (250 mg/

twice daily); this resulted in an increased diuresis amounting to about 15 l/day.

Treatment was started with chlorpropamide, 500 mg in two divided doses, and diuresis fell from 11 to about 5 l/day.

Chlorpropamide was increased up to 750 mg and the patient experienced a hypoglycaemic attack (blood sugar, 30 mg/100 ml) and a slight increase in diuresis. Chlorpropamide was then reduced to 500 mg and diuresis stabilized at 3 l/day. The patient was again submitted to water loading and was found to be incapable of normally eliminating the acute water load (Fig. 1).

The patient was discharged on a daily dose of 500 mg of chlorpropamide and was told to undergo periodic checks of her blood glucose levels.

This therapeutic regimen was maintained by the patient at home during the period August to December 1969 without complaints and with a daily diuresis varying between 1500–2000 ml. In mid-December 1969 the patient noted a weight increase of about 6–7 kg, without any apparent reason, with an accompanying decrease in diuresis to about 500–600 ml/day. She complained of a feeling of anxiety and a sense of swelling and distension of her body, especially in the chest. This was accompanied by dyspnea, nausea and vomiting and generalized paresthesiae.

The patient was again admitted to our Clinic. On admission she was confused and anxious with nausea, vomiting, muscular cramps and asthenia and refused to eat her standardized diet; her daily diuresis ranged between 500–600 ml; weight 91 kg; blood glucose, 90 mg/100 ml; serum Na, 128 mEq/l; serum osmolality 268 mOsm/kg; urinary 17-ketosteroids, 9.3 mg/24 hr; urinary 17-hydroxycorticoids 4.3 mg/24 hr; GFR 110 ml/min;

FIG. 1. Patient R.L. during chlorpropamide treatment. On the left: urine output and urinary osmolality during water load (20 ml/kg=1600 ml). On the right: water deprivation test.

urinalysis was negative for protein and showed a normal sediment.

Chlorpropamide was reduced to 250 mg in two divided doses and her diuresis increased to 4 l/day; her body weight decreased to 84 kg. Serum Na rose to 142 mEq/l; serum osmolality to 300 mOsm/kg and the patient markedly improved over the next 48 hr.

After 8 days her daily chlorpropamide was again increased to 500 mg and diuresis dropped to 1500–2000 ml/day (Fig. 2), and the patient did not experience any symptoms.

She was discharged 3 weeks following admission, without any of the presenting symptoms and was instructed to maintain a lower fluid intake.

The patient was again examined in June 1970; her condition had remained stable since her discharge from our Clinic; diuresis was maintained at about 1500 ml/day.

Discussion

The syndrome of excessive water retention and

water intoxication that this patient developed, during long-term chlorpropamide therapy, and its remission following reduction in dosage, demonstrates that this drug can cause water intoxication even in subjects with defective ADH secretion.

The reason for the appearance of this syndrome after several months of well tolerated chlorpropamide therapy and for its reversible nature is not clearly apparent. The possibility exists that the anti-diuretic response to the drug has been increased with increasing duration of treatment, or that the patient took in an excessive amount of water in the period immediately before the appearance of the symptoms. However, the dose of chlorpropamide (500 mg) was apparently not excessive for the patient in that this dose was subsequently resumed without symptoms and a diuresis of 1500–2000 ml/day resumed and was maintained with this dose.

It is therefore of the utmost importance for patients treated with chlorpropamide to be warned as to the danger of excessive water intake, since patients

FIG. 2. Patient R.L. Abnormal water retention and hyponatremia during long-term chlorpropamide treatment.

having this disease for some time become accustomed to a large water intake; in fact our patient did not have polydipsia.

In a previous study we were able to demonstrate that following chlorpropamide administration, urine became more concentrated than plasma, that negative values were obtained for CH_2O and that during water loading the kidney was incapable of producing normally diluted urine (Andreani *et al.*, 1969).

Recently, a syndrome resembling inappropriate ADH secretion was described by Fine & Shedrovilzky (1970) in a 28-year-old woman with diabetes mellitus on chlorpropamide therapy. While this present work was in preparation, two relevant reports appeared. Webster & Bain (1970) reported a girl with both diabetes insipidus and diabetes mellitus, the first developing after pituitary stalk section for diabetic retinopathy; panhypopituitarism was also present with evidence of impaired renal function; in this patient therapy with chlorpropamide caused the appearance of symptoms due to water intoxication; another patient in Webster's series presumably experienced an acute episode of water intoxication after being discharged from the hospital. Weissman, Shenkman & Gregerman (1971) reported symptomatic hyponatremia, developed in five patients affected by diabetes mellitus during treatment with chlorpropamide.

In our patient diabetes mellitus was not present and she possessed good renal and adrenal function.

Discussion exists as to the mechanism of anti-diuretic action of chlorpropamide. It has been suggested that it acts by means of a central action involving production or release of ADH (Miller & Moses, 1969). This is not in agreement with the *in vitro* studies carried out by Mendoza (1969) and Ingelfinger & Hays (1969); from their works it appears that while chlorpropamide alone has no effect on water movement across the toad bladder, chlorpropamide markedly potentiates the effect of small amounts of vasopressin *per se* ineffective.

Subsequently, Miller & Moses (1970a) accepted this last hypothesis, i.e. that chlorpropamide is capable of potentiating the action of minimal levels of endogenous ADH resulting in an enhanced anti-diuretic effect.

In agreement with this hypothesis it is possible that in patients with INDI there are trace amounts of circulating ADH.

The appearance of the water intoxication syndrome, during chlorpropamide treatment, raises one clinical point of some importance: dilutional hyponatraemia can occur in patients with INDI when they are treated with chlorpropamide; the observation is also of some theoretical interest. Recent experiments performed by Miller & Moses (1970b) found that, in patients with INDI, alcohol and water load-

ing were able to overcome the effect of chlorpropamide resulting in significant diuretic effect, i.e. alcohol and water were able to decrease the release of ADH.

The appearance of a dilutional hyponatraemic state suggests that in some patients with INDI water retention with hyponatraemia and hypo-osmolality is not always able to suppress residual ADH which, therefore, persists even though in minimal but inappropriate quantity.

It is possible that this syndrome, which can also occur in patients with diabetes mellitus when they are treated with chlorpropamide, may be caused by direct action of chlorpropamide on ADH release or may reveal the presence of an alteration in the afferent pathways regulating the production and release of ADH.

Addendum

The patient was again seen on an out-patient basis in December 1970. She had been well and controlled in the months since her last visit; however, in the previous 2 weeks or so she had increased in weight by about 3 kg without any symptoms.

Diuresis remained about 1200 ml/day. The patient stated that her fluid intake was modest. Pertinent laboratory data were: serum sodium, 141 mEq/l, serum osmolality, 301 mOsm/kg.

Therapy with chlorpropamide 500 mg/day in two divided doses was maintained.

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Micro-angiopathic haemolytic anaemia associated with a giant haemangioma of the liver

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MICRO-ANGIOPATHIC haemolytic anaemia is the term introduced by Brain, Dacie & Hourihane (1962) to describe an unusual type of haemolytic anaemia found in association with thrombotic thrombocytopenic purpura, acute glomerulonephritis in infancy and childhood (haemolytic-uraemic syndrome), renal cortical necrosis, microscopic polyarteritis nodosa, some cases of malignant hypertension and carcinomatosis. The characteristic blood changes were the presence of contracted cells, triangular cells, burr cells, crenated cells and red cell fragments.

The association of similar haematological features with benign tumours has not been recorded. The present report records a case of micro-angiopathic haemolytic anaemia found in association with a giant haemangioma of the liver.

Case report

The patient, a 40-year-old Sinhalese housewife, was admitted to a surgical ward of the General Hospital, Kandy, Ceylon, on 19 September 1970, with a history of a painless lump in the abdomen of 13 years' duration, gradually increasing in size. Her bowels were regular. There was no history of having passed blood per rectum. There was no vomiting and no past history of jaundice. Her menstrual periods were regular. She had had seven pregnancies of which the first child is alive. All other pregnancies, except the second, ended in abortions between the third and the seventh months, the second being a premature delivery at 8 months, and the baby died

on the eighth day. The cause of death was not known, but the baby was neither jaundiced nor oedematous. Four of the pregnancies occurred before the present illness. Six years ago, the patient had undergone a laparotomy in another hospital for the same complaint and a large haemangioma of the liver was detected but not excised.

On examination, the patient was afebrile. BP 120/75. Heart and lungs were clinically and radiologically normal.

Her abdomen was grossly enlarged. There were dilated veins on the anterior abdominal wall, which drained from above downwards. There was a lump arising from under the right costal margin and extending about 35 cm down to the right iliac fossa. It was firm and nodular, its dullness on percussion being continuous with the liver dullness. There was a band of resonance across the lower part of the lump which on radiological examination was found to be the transverse colon pushed downwards by the lump. The spleen was 7 cm below the left costal margin, firm and non-tender. There was a little ascites.

Gynaecological examination revealed no abnormality in the uterus or the ovaries.

On radiological examination a large soft tissue tumour arising from the liver was seen. It showed patchy areas of calcification. The right kidney was occupying a position immediately to the left of the midline, while the left kidney was in its normal position. Both kidneys were found to function normally. Barium meal studies showed that the