# ANTIDIURETIC PROPERTIES OF HYDROCHLOROTHIAZIDE IN DIABETES INSIPIDUS

BY

C. W. H. HAVARD, M.A., D.M., M.R.C.P.

AND

PHILIP H. N. WOOD, M.B., B.S.

*From the Departments of Medicine and Chemical Pathology, St. Bartholomew's Hospital, London*

Recently it has been stated that when experimental animals with diabetes insipidus are given hydrochlorothiazide the urinary volume is reduced by half (Kennedy and Crawford, 1959). This observation prompted us to assess the therapeutic response in a patient with diabetes insipidus who was loath to accept the prospect of daily injections of vasopressin. Treatment with hydrochlorothiazide reduced the urinary volume from 9.5 to 2.5 litres per 24 hours. The purpose of this paper is to record our investigations into the mechanism of this therapeutic paradox, and to assess the value of this drug in the management of patients with diabetes insipidus.

## Case Report

A married woman of 33 was first seen in July, 1959. Two months previously symptoms of polyuria and polydipsia suddenly appeared and had persisted unabated. She had suffered no serious past illnesses, and her family were healthy. There were no physical signs of disease, and the urine contained no abnormal constituents. Her weight was 98 lb. (44.5 kg.), her height 56 in. (142 cm.), and her blood-pressure 125/80. After 24 hours of fluid deprivation the urinary volume was 4 litres, with a specific gravity of 1006. Vasopressin tannate by injection effected a prompt reduction in the urinary output. A radiograph of the skull and an electroencephalogram were normal, and no cause for the diabetes insipidus was discovered.

### Methods

At first the patient received an ordinary ward diet, but a measured intake of 10 g. of sodium chloride daily was substituted while the effect of salt replacement was studied. Fluid intake was unrestricted and no potassium supplements were given. The patient was weighed daily, and 24-hour urine collections were made throughout. Urine volume, specific gravity, and electrolyte excretion were measured daily; serum electrolytes were estimated twice weekly. On selected representative days plasma volume, glomerular filtration rate, and urine osmolarity were determined.

After a control period, during which no treatment was given, hydrochlorothiazide, 50 mg. twice daily, was administered until the maximum reduction in urinary output occurred. The drug was then discontinued and the patient allowed to return to control conditions. In order to elucidate whether hydrochlorothiazide acted by influencing salt excretion a further study was made; the same dose of hydrochlorothiazide was given, and the ensuing increase in urinary sodium loss in each 24 hours was replaced by oral sodium chloride. During the control period the mean daily sodium excretion was 135 mEq per 24 hours. This figure was subtracted from the urinary sodium content and the balance was replaced by sodium chloride in cachets. After discontinuing salt replacement the patient was discharged from hospital taking 50 mg. of hydrochlorothiazide twice daily on alternate days. Observation as an out-patient was continued, with a brief readmission to obtain a 24-hour urine collection.

*Technical Methods.*—Sodium and potassium were estimated by flame photometry; chlorides by potentiometric titration, using a silver electrode; and carbon dioxide by a manometric method. Glomerular filtration rate was determined by endogenous creatinine clearance, creatinine levels being estimated by the method of Løken (1954). Plasma volume was determined by dilution techniques with $^{131}I$ human serum albumin. Urine osmolarity was approximated from urea and electrolyte excretion.

### Response to Hydrochlorothiazide

On the first day of treatment there was an increased loss of sodium and chloride, without any significant change in urinary volume (Fig. 1). On subsequent days sodium

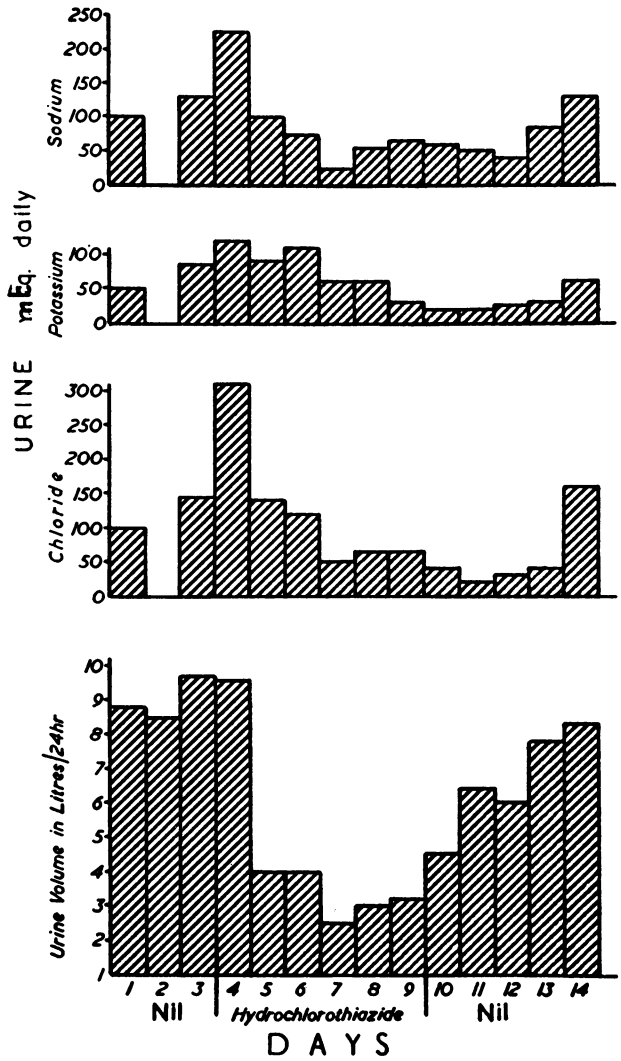


FIG. 1.—Urinary volume and electrolyte excretion during the administration of hydrochlorothiazide.

excretion fell to below the level observed before treatment commenced; this was associated with a reduction in urinary volume from 9.5 to 2.5 litres per 24 hours. Urinary potassium excretion was approximately doubled in the first few days of treatment, but thereafter the loss fell to control levels.

These changes were accompanied by a 20% reduction in plasma volume (from 2.2 to 1.76 litres) and by a 65% decrease in creatinine clearance (from 71 to 22 ml. per minute) (Table I). Over the same period the patient lost 5 lb. (2.3 kg.) in weight. Her diminutive size must be borne in mind, her surface area amounting to 1.3 square metres; to facilitate comparison the creatinine clearances are tabulated additionally corrected to a surface area of 1.73 square metres.

TABLE I.—*Plasma Volume, Glomerular Filtration Rate, Serum Electrolytes, and Urine Concentration After Administration of Hydrochlorothiazide*

| Treatment | Urine Volume (ml./24 hrs.) | Weight lb. | | Plasma Volume (l.) | G.F.R. (Creatinine Clearance) (ml./min.) | G.F.R. Corrected to 1·73 sq.m. (ml./min.) | Serum Na+ (mEq/l.) | Serum K+ (mEq/l.) | Urine Osmolarity (m.osm./l.) | S.G. Corrected to 20° C. | Day |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | lb. | kg. | | | | | | | | |
| Hydrochlorothiazide .. | 2,570 | 93 | 42·2 | — | 25 | 33 | 138 | 3·9 | 188 | 1007 | 7 (Fig. 1) |
| Nil .. .. .. | 8,510 | 98 | 44·5 | 2·20 | 71 | 95 | 147 | 4·6 | 163 | 1005 | 2 ( ,, 2) |
| Hydrochlorothiazide .. | 3,300 | 93 | 42·2 | 1·76 | 22 | 29 | 134 | 3·0 | 185 | 1007 | 8 ( ,, 2) |

G.F.R. = Glomerular filtration rate.

The serum sodium level fell by 13 mEq/l. (Table I). There was a similar though smaller fall in the serum chlorides, and the alkali reserve increased by a few milliequivalents per litre. Serum potassium levels were reduced during treatment but never fell below 3 mEq/l. Urine osmolarity increased by 6.5% (from 163 to 185 m.osmols/l.), and the specific gravity of the urine rose from 1005 to 1007.

The blood-pressure did not alter significantly. An increase in the pulse frequency of 25 a minute constantly accompanied hydrochlorothiazide therapy, but this was not seen during the period of salt replacement. Though the urinary volume was not reduced to within normal limits, subjective improvement was considerable; thirst was reduced to the limits of comfort and the need to pass urine at night was relieved.

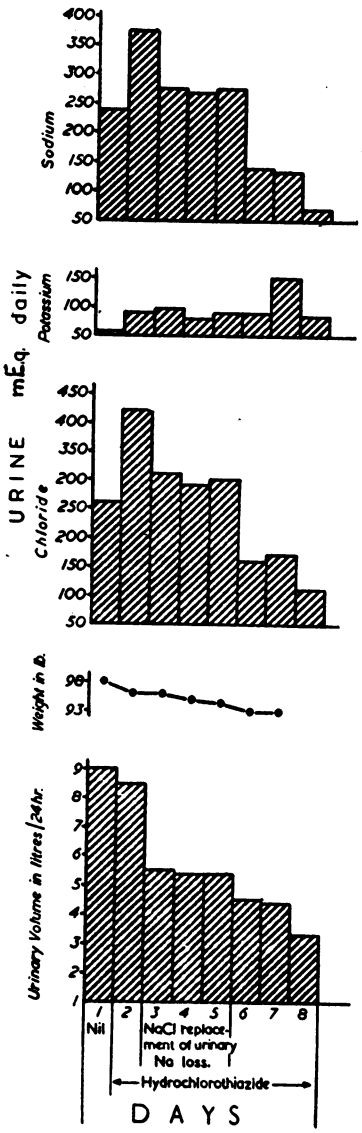


FIG. 2.—Urinary volume, electrolyte excretion, and body weight during the administration of hydrochlorothiazide and replacement of increased sodium loss.

### Response to Salt Treatment

The antidiuretic effect of hydrochlorothiazide therapy was largely thwarted by replacing the increased urinary loss of sodium (Fig. 2). Approximately 5.5 l. of urine was passed each day. The creatinine clearance diminished from 71 to 45 ml. a minute, a reduction of 37% (Table II); and a loss of 2 lb. (0.9 kg.) in body weight was observed. Urine osmolarity increased from 163 to 223 m.osmols/l., a reflection of the added salt load being excreted, and in consequence the specific gravity increased to 1007. When salt replacement was discontinued the urinary volume diminished, being reduced to 3.2 litres per 24 hours three days after the extra salt was omitted.

### Response to Hydrochlorothiazide Maintenance Therapy

Initially, subjective improvement was maintained while the patient received 100 mg. of hydrochlorothiazide on alternate days, but after three weeks symptoms of polyuria returned. When she was readmitted five weeks after leaving hospital the 24-hour urinary volume had risen to 6.9 litres and the creatinine clearance to 75 ml. a minute, and the specific gravity of the urine had fallen to 1004 (Table III). Serum electrolytes had returned to normal levels.

TABLE II.—*Glomerular Filtration Rate and Urine Concentration During the Administration of Hydrochlorothiazide and Replacement of Increased Sodium Loss*

| Urine Volume ml./24 hrs. | Weight | | G.F.R. (Creatinine Clearance) (ml./min.) | G.F.R. Corrected to 1·73 sq.m. (ml./min.) | Urine Osmolarity (m.osm./l.) | S.G. Corrected to 20° C. | Day |
|---|---|---|---|---|---|---|---|
| | lb. | kg. | | | | | |
| 5,250 | 96 | 43·5 | 45 | 60 | 223 | 1007 | 4 (Fig. 2) |

TABLE III.—*Glomerular Filtration Rate and Urine Concentration After Five Weeks' Treatment with Hydrochlorothiazide*

| Urine Volume (ml./24 hrs.) | G.F.R. (Creatinine Clearance) (ml./min.) | G.F.R. Corrected to 1·73 sq.m. (ml./min.) | S.G. Corrected to 20° C. |
|---|---|---|---|
| 6,900 | 75 | 100 | 1004 |

## Discussion

The healthy kidney reabsorbs water by three distinct mechanisms operating in different anatomical sites. In the proximal tubule water diffuses passively through the tubular membrane along an established osmotic gradient. This "obligatory water reabsorption" comprises approximately 85% of the glomerular filtrate (Berliner *et al.*, 1958). In contrast to the proximal tubule, the distal tubule is relatively impermeable to water in the absence of antidiuretic hormone so that, though an osmotic gradient exists, little or no water may be reabsorbed. In the collecting tubules water is reabsorbed without solutes, so that this is the only site where a fluid hypertonic to the glomerular filtrate can be formed (Wesson and Anslow, 1952; Page and Reem, 1952). The most important contribution to the conservation of water is the change from dilute to isotonic urine under the influence of antidiuretic hormone on the distal tubule, for this may involve a change in water excretion of more than 10 ml. a minute. The further saving of water by the formation of a hypertonic urine in the collecting tubules is relatively small, amounting to only 1–2 ml. a minute (Berliner and Davidson, 1957).

A reduction in glomerular filtration rate, with ensuing diminution of the flow of urine to the collecting tubules, may alter the final urine concentration significantly. Indeed, it has long been realized that a concentrated urine may be formed in severely dehydrated dogs with diabetes insipidus (Shannon, 1942); and, more recently, del Greco and de Wardener (1956) and Berliner and Davidson (1957) have shown that in experimental animals with diabetes insipidus a reduction in glomerular filtration rate may be associated

with a fall in urinary volume and the formation of hypertonic urine. Furthermore, Kleeman *et al.* (1957), by lowering the blood-pressure of two patients with diabetes insipidus, reduced the urinary volume and increased its concentration to greater than that of the plasma. In all these experiments the glomerular filtration rate was reduced to 20–40% of normal. Smaller reductions in filtration might be expected to lower urinary volume without appreciably increasing the concentration, as occurs when patients with diabetes insipidus develop hypopituitarism (Leaf *et al.*, 1952); however, if hypopituitarism is complete the urine may even become hypertonic (Martin, 1959).

The beneficial effect of salt restriction on the polyuria of diabetes insipidus has long been recognized (Fitz, 1914; Beaser, 1947), though there is an unpredictable variation from patient to patient (Allen and Sherrill, 1923). This is in part the result of a reduction in solute load (Smith, 1951), but there is little doubt that depletion of blood volume follows salt restriction (McCance and Widdowson, 1937; Lyons *et al.*, 1946), and changes in extracellular volume result in marked changes in glomerular filtration rate (Cort, 1952).

Our studies of a patient with diabetes insipidus show that treatment with hydrochlorothiazide results in a marked reduction in urinary volume. This was preceded by a considerable loss of sodium and chloride in the urine on the first day of treatment. A 20% reduction in plasma volume and a loss of 5 lb. (2.3 kg.) in body weight were associated with these changes. The constant tachycardia which accompanied treatment with hydrochlorothiazide alone and its absence during the period of salt replacement suggest that it may be due to these changes. Provided hydrochlorothiazide does not directly affect creatinine metabolism the clearance of this substance may be used to demonstrate fluctuations in glomerular filtration. On this basis the glomerular filtration rate was reduced by 65% after treatment. The fact that the antidiuretic effect was delayed for 24 hours suggests that the reduction in glomerular filtration was predominantly the result of loss of salt and the ensuing diminution in plasma volume.

However, salt replacement of the increased urinary sodium loss did not entirely thwart the antidiuretic effect, and the glomerular filtration rate was reduced by 37% (Fig. 2 and Table II). This was probably due to the time interval elapsing before replacement began; hydrochlorothiazide exerted its action unimpaired for 24 hours before the urinary sodium content, and hence the amount necessary for replacement, was determined. On the other hand, the drug may have a primary action on the glomerular filtration rate, which is unrelated to electrolyte loss, as has been suggested by Januszewicz *et al.* (1959). We have found that chlorothiazide in a dose of 0.5 g. twice daily has a comparable effect, and this drug may have a similar primary action on glomerular filtration (Heinemann *et al.*, 1959). An injection of mersalyl (2 ml.) produced less marked reduction in urinary volume.

The patient's subsequent relapse during treatment with hydrochlorothiazide was accompanied by a rise in glomerular filtration rate and return to normal of serum electrolytes. This was probably not due to the reduced dosage, as the patient remained symptom-free for three weeks. It is possible that a compensatory mechanism of salt retention may have developed; in these circumstances an ensuing potassium loss might be anticipated.

It would appear, therefore, that the antidiuretic effect of hydrochlorothiazide in diabetes insipidus is predominantly the result of a loss of sodium and water with consequent reduction in plasma volume and glomerular filtration rate. A further reduction in glomerular filtration may be effected by a direct action of the drug not dependent upon electrolyte loss. We cannot suggest that hydrochlorothiazide has a major place in the management of patients with diabetes insipidus. This drug achieves a reduction in urinary volume with amelioration of symptoms, but vasopressin is obviously the treatment of choice, being the natural replacement of a hormonal insufficiency. Nevertheless, some patients tolerate vasopressin by injection badly, and in the form of snuff it may cause unpleasant rhinorrhoea or even asthma. Under these circumstances hydrochlorothiazide may be of value. The hazards of prolonged therapy with diuretics are well recognized, and in patients with diabetes insipidus receiving hydrochlorothiazide compensatory mechanisms of salt retention with ensuing potassium loss may be anticipated


## Summary

The antidiuretic properties of hydrochlorothiazide in a patient with diabetes insipidus have been demonstrated. The effect has been shown to be chiefly the result of a urinary loss of sodium chloride and a consequent reduction in plasma volume and glomerular filtration rate. Hypokalaemia is a potential hazard of this form of therapy, and we believe that hydrochlorothiazide has little place in the management of patients with diabetes insipidus.


We thank Dr. K. O. Black for permission to study this patient; Dr. A. G. Spencer and Dr. J. C. B. Fenton for much helpful criticism and advice; Mrs. Eileen Akers for many of the chemical estimations; and Mr. N. K. Harrison for preparing the Charts. In addition, we thank the nursing staff for their willing co-operation.

## REFERENCES


Allen, F. M., and Sherrill, J. W. (1923). *J. metab. Res.*, **3**, 479.
Beaser, S. B. (1947). *Amer. J. med. Sci.*, **213**, 441.
Berliner, R. W., and Davidson, D. G. (1957). *J. clin. Invest.*, **36**, 1416
—— Levinsky, N. G., Davidson, D. G., and Eden, M. (1958). *Amer. J. Med.*, **24**, 730.
Cort, J. H. (1952). *J. Physiol. (Lond.)*, **116**, 307.
Fitz, R. (1914). *Arch. intern. Med.*, **14**, 706.
del Greco, F., and de Wardener, H. E. (1956). *J. Physiol. (Lond.)*, **131**, 307.
Heinemann, H. O., Demartini, F. E., and Laragh, J. H. (1959). *Amer. J. Med.*, **26**, 853.
Januszewicz, W., Heinemann, H. O., Demartini, F. E., and Laragh, J. H (1959). *New Engl. J. Med.*, **261**, 264.
Kennedy, G. C., and Crawford, J. D. (1959). *Lancet*, **1**, 866.
Kleeman, C. R., Maxwell, M. H., and Rockney, R. (1957). *Proc. Soc. exp. Biol. (N.Y.)*, **96**, 189.
Leaf, A., Mamby, A. R., Rasmussen, H., and Marasco, J. P. (1952). *J. clin. Invest.*, **31**, 914.
Løken, F. (1954). *Scand. J. clin. Lab. Invest.*, **6**, 325.
Lyons, R. H., Jacobson, S. D., and Avery, N. L. (1946). *Amer. J. med. Sci.*, **211**, 460.
McCance, R. A., and Widdowson, E. M. (1937). *J. Physiol. (Lond.)*, **91**, 222.
Martin, M. M. (1959). *J. clin. Invest.*, **38**, 882.
Page, L. B., and Reem, G. H. (1952). *Amer. J. Physiol.*, **171**, 572.
Shannon, J. A. (1942). *J. exp. Med.*, **76**, 371.
Smith, H. W. (1951). *The Kidney, Structure and Function in Health and Disease* p. 252. Oxford Univ. Press, New York.
Wesson, L. G., and Anslow, W. P. (1952). *Amer. J. Physiol.*, **170**, 255.