Section of Endocrinology

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[*Abridged*]

Dr C W H Havard
(*St Bartholomew's Hospital, London*)

Thiazide-induced Antidiuresis in Diabetes Insipidus

In 1905 it was first observed that diuretics reduced the urine volume in diabetes insipidus (Meyer 1905). Little attention was given to this observation and no investigation of the mechanism was reported until 1959, when Crawford & Kennedy showed that in experimental animals with diabetes insipidus the urine volume was reduced by approximately half when they were given hydrochlorothiazide. Kennedy & Crawford (1961) confirmed this effect in man, and suggested that it was due to blockade of the adrenal mineralocorticoid action on the kidney. In 1960 we studied the effects of various diuretics in 8 patients with vasopressin insufficiency diabetes insipidus. We found (Havard & Wood 1960, 1961) that after the thiazide treatment there was an immediate rise in urine osmolality, proportionate to the increased excretion of sodium chloride, with a slight reduction in urine volume, and this was accompanied by decreased thirst. After the first twenty-four hours the urinary sodium output fell and within three days was less than before thiazide treatment and urine volume became reduced to approximately one half; the initial increase in urine osmolality was further enhanced although it did not attain that of plasma (Fig 1). Various thiazide diuretics given in doses of equivalent saluretic action had an equal antidiuretic effect. These changes were associated with a fall in plasma volume, body weight and glomerular filtration rate. Serum sodium concentration during treatment fell, and there was a similar reduction in serum chlorides. Serum potassium levels also fell. Salt replacement of the urinary loss due to the diuretic largely thwarted the antidiuretic effect and we attributed the

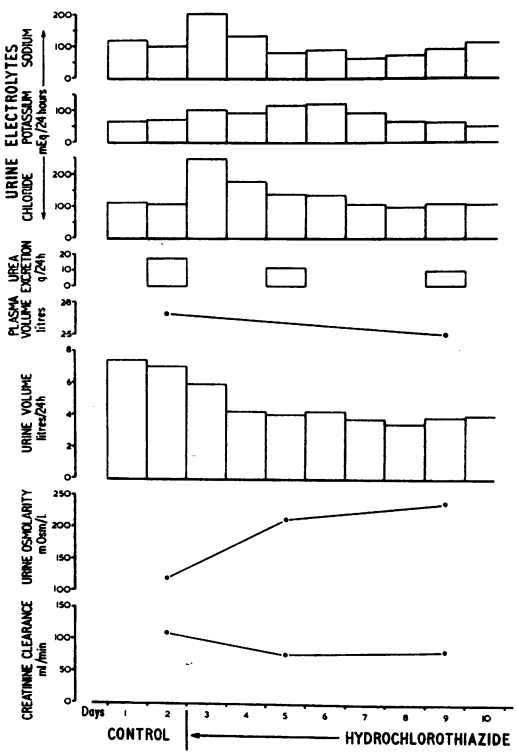

Fig 1 *Response to hydrochlorothiazide 50 mg twice daily in a representative patient with diabetes insipidus*

reduction in urine volume to the urinary loss of sodium chloride and a consequent fall in plasma volume and glomerular filtration. However, the thiazide drugs caused a greater reduction in urine volume than organic mercurial diuretics and appeared to reduce glomerular filtration before significant salt loss had occurred (Table 1). We therefore suggested that the thiazides may owe their additional effect to a direct action on the renal vasculature.

Table 1

Two-hourly water and osmolar excretion on control day (C) and after the administration of hydrochlorothiazide (50 mg) (H) at 8 a.m. and 8 p.m. to a patient with diabetes insipidus

Period		*Urine flow* (*ml/min*)	*Urinary sodium* (*μEq/min*)	*Urinary osmolarity* (*mOsm/l.*)	*Creatinine clearance* (*ml/min*)
8 a.m.	C	11·7	200	72	106
	H	9·8	133	115	114
10 a.m.	C	14·6	258	70	108
	H	13·3	325	86	114
12 noon	C	9·7	183	86	118
	H	8·1	241	122	80
2 p.m.	C	9·8	183	94	115
	H	12·4	408	139	74
4 p.m.	C	10·5	141	84	120
	H	7·5	241	135	77
6 p.m.	C	11·8	141	66	113
	H	7·9	208	128	86
8 p.m.	C	11·2	125	92	109
	H	7·2	166	149	69

Subsequent work has thrown further light on the mechanism of this therapeutic paradox. In particular, Earley & Orloff (1962) have shown that a reduction in glomerular filtration is not essential for the antidiuretic effect, nor is it a constant occurrence. They believe that the reduced urine volume is the result of sodium loss and not due to any unique property of the thiazide drugs. Their studies demonstrate that the antidiuretic effect is associated with a maintained deficit of sodium and reduction in body weight and that the continued administration of thiazide is not necessary for continued antidiuresis provided repair of the sodium deficit is prevented by a rigidly restricted dietary intake. These conclusions are supported by the fact that a similar antidiuresis may be achieved by severe restriction of dietary sodium intake (Winter *et al.* 1943) or may follow adrenalectomy in animals with diabetes insipidus (Kennedy & Crawford 1961).

The serum osmolality is raised in diabetes insipidus (Barlow & de Wardener 1959) and this is probably an expression of the sodium retention characteristic of this condition (Friedman *et al.* 1962). Robson & Lambie (1962) have stressed the fall in tonicity which occurs in patients with diabetes insipidus given thiazide drugs. It occurs early and precedes any marked diminution of the urine volume. As the tonicity of the extracellular fluid has a profound effect on thirst they feel that changes in the serum osmolality could relieve thirst and reduce urine volume without involving renal mechanisms.

It appears, therefore, that the immediate response of patients with diabetes insipidus given thiazide drugs is: (1) Rise in urine osmolality. (2) Slight reduction in urine volume despite rise in solute output. (3) Fall in serum osmolality. (4) Reduced thirst. (5) Inconstant changes in creatinine clearance. This immediate response is followed over the next three days by a further increase in urine osmolality and the urine volume becomes reduced to approximately half.

Thiazide drugs prevent sodium reabsorption in the distal tubule at the site where urinary dilution occurs. This accounts for the increased urine osmolality in the first twenty-four hours after thiazide administration, but it cannot account for the antidiuretic effect. The antidiuretic effect is associated with the sodium deficit induced by the drug. By virtue of the predominantly distal tubular site of action of thiazides sodium is lost in excess of water. Serum osmolality is thus reduced and thirst decreased. This probably contributes to the antidiuresis but is unlikely to be the entire explanation as it has been shown in animals that a reduction of water intake to the amount taken during thiazide treatment will lead to dehydration and death of the untreated animal (Kennedy & Crawford 1961). There is no evidence that thiazide drugs alter the permeability of the distal tubule, and indeed antidiuresis is not dependent on the continued administration of the drug (Earley & Orloff 1962). Nor does hydrochlorothiazide influence the sodium concentration gradient from renal cortex to medulla (Baer *et al.* 1962). As the maintenance of this concentration gradient depends on the active transport of sodium from the lumen of the ascending limb of the loop of Henle it is unlikely that thiazides interfere with sodium reabsorption at this site. As in the absence of antidiuretic hormone the distal tubule is impermeable to water the reduced urine volume must be the result of a reduced volume of filtrate reaching the distal segments. This may be due to enhanced proximal tubular reabsorption or lowered glomerular filtration. Reduction in glomerular filtration rate is inconstant. Not only have some workers found a reduction and others not, but many have found reduced glomerular filtration in some of their patients with diabetes insipidus and no reduction in others. It would appear that the patients with the larger urine volume tend to be those who show a reduction in glomerular filtration after thiazides. It is perhaps pertinent that in maintained water diuresis in human subjects the administration of thiazides is associated with an early fall in glomerular filtration rate, which is unrelated to electrolyte loss (Januszewicz *et al.* 1959). Nevertheless, as glomerular filtration is not constantly reduced, enhanced proximal tubular reabsorption of sodium resulting from the negative sodium balance and decreased blood volume induced by the thiazides is probably responsible for the antidiuresis. This is not

mediated by aldosterone as Doca does not mimic the antidiuretic effect of thiazides nor does spironolactone antagonize it (Earley & Orloff 1962).

The antidiuretic effect of thiazides is thus the result of the induced sodium deficit. The fall in serum osmolality may be contributory by reducing thirst. As depletion of body sodium will be self-limiting the major hazard to the use of thiazides is potassium depletion. Treatment of patients with vasopressin insufficiency type of diabetes insipidus with thiazides is only indicated for those who are intolerant of hormone replacement. In nephrogenic diabetes insipidus thiazides have a more important therapeutic application.

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Dr Oliver Wrong
and Miss Ann Metcalfe-Gibson
(Department of Medicine,
Postgraduate Medical School of London)

The Electrolyte Content of Fæces[1]

Stool is the Cinderella of electrolyte studies. It is a fascinating material. Despite its solid appearance it contains 70% or more of water. It is also known to contain many electrolytes, which are usually identified after ashing in a muffle furnace – a procedure which destroys all organic material and tells us nothing about the physical state of the inorganic constituents.

[1]Much of the material used in this paper has previously appeared in *Clinical Science* (Wrong *et al.* 1965) and is reproduced here with kind permission

Table 1
Composition of fæcal dialysate from 8 normal subjects

	Mean	*Range*
Osmolality (mOsm/kg)	376	336–423
pH	7·02	5·62–7·98
Sodium (mEq/l.)	31·6	4·4–112
Potassium (mEq/l.)	75	29–147
Na/K ratio	0·31	0·043–3·78
Ammonium (mEq/l.)	14·2	2·4–34
Calcium (mEq/l.)	38	5·6–72
Magnesium (mEq/l.)	49	13–98
Chloride (mEq/l.)	16·0	5–38
Total carbon dioxide (mM/l.)	40	4–66
Phosphate (mM/l.)	2·72	0·48–11·8
Sulphate (mEq/l.)	2·8	1·78–4·50
Organic anion (mEq/l.)	179	133–238
Total nitrogen (mM/l.)	95	38–206
Total phosphorus (mM/l.)	3·6	0·81–8·9

The electrolytes in stool might exist in an insoluble form or be dissolved in stool water. Stool water itself can be thought of as existing in two compartments – an 'extracellular' or continuous phase in which the stool solids are suspended, and an 'intracellular' phase imprisoned in bacteria, protozoa, cells derived from the intestine, vegetable fibres and seeds. The first of these is the component of greatest physiological interest, for it is influenced by the secretory and absorptive activity of the colon. Theoretically this fluid, and its contained solute, should be dialysable through a semipermeable membrane.

We have dialysed stools in the colon of the living subject, a procedure which takes advantage of the mixing effect of peristalsis. For this purpose we have constructed dialysing bags of Visking cellulose tubing, filled with an inert colloidal solution (either 8% polyvinyl pyrrolidone or 10% dextran) which are swallowed and passed in the stool 24–120 hours after swallowing. Radiological studies have demonstrated bags in the large bowel within three hours of swallowing, and our *in vitro* experiments have shown that their contents reach chemical equilibrium with their environment in about one hour; these two facts indicate that the bags have ample time to reach diffusion equilibrium with the contents of the large intestine.

The fluid contained in these bags is easier and pleasanter to handle than fæces and it can be analysed easily by conventional techniques. Table 1 shows results obtained from 8 normal subjects. Osmolalities were slightly higher than plasma, even after correction for the presence of colloid; this slight hyperosmolality was the result of bacterial action, for the fluid collected after giving intestinal antibiotics was isotonic. The pH of dialysate varied from 5·4 to 8·0, almost as