New insights into the paradoxical effect of thiazides in diabetes insipidus therapy

Antonio J. Magaldi

Hospital das Clínicas da Fac. de Medicina da Univ. de São Paulo, São Paulo, Brazil

Introduction

One of the great advances in the therapy of renal disease occurred in the 1930s and was the synthesis of orally administered diuretic compounds. In 1937 suphanilamides had been introduced as antimicrobial agents. In patients treated with suphanilamides, metabolic acidosis with alkaline urine was observed. Pursuance of this phenomenon led to the accidental discovery of the diuretic effect of suphanilamides. In 1940 it was found that some suphanilamides inhibited carbonic anhydrase. An intensive search for suphanilamides without carbonic anhydrase inhibition led to the synthesis of benzothiazide by Novello and Sprague [1]. Subsequently, numerous congeners were synthesized which are widely used today.

Action of thiazide diuretics

The principal site of thiazide action is the distal convoluted tubule, where they inhibit the NaCl cotransporter in the luminal membrane, thus decreasing the Cl– and Na+ reabsorption. In 1990 Tran et al. [2] studied metolazone, a thiazide type diuretic and suggested that thiazides occupy the Cl– binding site of the Na+Cl–cotransporter. In this position, metolazone impedes the chloride entrance into the transporter molecule, thus blocking the reabsorption of the ion. The principal adverse effect produced by thiazides is potassium loss with consequent hypokalaemia. Such potassium loss is basically due to (i) enhanced delivery of sodium to late nephron segments, (ii) inhibition of carbonic anhydrase with a consecutive decrease of the distal delivery of chloride, and (iii) stimulation of the apical K-Cl symporter in principal cells of the distal tubule.

The principal indications for the use of thiazides are (i) oedematous states and (ii) hypertension of patients with preserved renal function. Ancillary indications are hypercalciuria, nephrolithiasis, and nephrogenic diabetes insipidus (NDI).

The clinical use of thiazides in nephrogenic diabetes insipidus

Drugs are the most important causes of NDI [3]. This condition is characterized by unresponsiveness of the kidney to the action of vasopressin. Thus, the administration of desmopressin (dDAVP, a vasopressin analogue acting on the V2 type vasopressin receptor only) or of other drugs that potentiate arginine–vasopressin, such as carbamazepine, are not effective in NDI. In drug-induced NDI, the treatment of choice is obviously elimination of the responsible drug [3]. Nevertheless, in many cases, such as lithium therapy for affective disorders, discontinuance of the drug is often not feasible because alternative drugs with comparable therapeutic effect are not available. In this psychiatric illness, apart from the bothersome symptoms of diabetes insipidus, persistence of polyuria carries the risk of dehydration with decreased lithium clearance and conversely increased serum lithium concentrations and the potential risk of lithium intoxication. The only therapeutic approach is sodium restriction or administration of thiazide diuretics or both. In 1905, Meyer (in [4]) was the first to observe that diuretics decrease urinary volume in diabetes insipidus, but it was only in 1959 that Crawford and Kennedy [5] used thiazides to treat this form of diabetes insipidus in rats. In 1961 the same authors administered thiazides to patients with NDI [6]. Since that time, thiazides have been an important element in the treatment of NDI [7]. Although it seems paradoxical to treat polyuria with a diuretic, a net decrease of urine flow occurs with lowering of urine volumes to normal or only slightly elevated values (e.g. typically from 8–10 litres to 4 litres or less per day).

 Proposed mechanisms of action

The following mechanism has been proposed to account for the effect of thiazides in this condition [6,8]. An initial reduction of sodium reabsorption in the distal tubule increases sodium excretion and causes extracellular fluid volume contraction. As a result, the glomerular filtration rate decreases and the proximal tubular sodium and water reabsorption increases. Consequently, less water and sodium are delivered to
the collecting tubules and, as a result, less water is excreted. This is schematically shown in Figure 1.

Takemura [9] recently performed a long-term study in dogs with congenital NDI on a low-sodium diet, treated with a low dose of hydrochlorothiazide (2 mg/kg twice daily). The authors observed a significant decrease of urinary volume. Nevertheless, matters are more complex. Shirley et al. [10] and others [8] noted that the decrease of solute reabsorption in the distal nephron segments alone merely enhances urinary osmolality without changing urinary volume. To explain the final effect of the drug, a direct or indirect action of thiazides on water flux in distal segments has been proposed.

**Microperfusion studies on the inner medullary collecting duct (IMCD)**

Cesar and Magaldi [11] performed a study on normal rat inner medullary collecting duct. It was the principal aim to search for the above postulated effect of thiazides in the distal nephron in addition to the ones already known. A further aim was to elucidate why co-administration of indomethacin is effective in the treatment of NDI.

The IMCD was chosen because of the consideration that water reabsorption mainly takes place in this segment. The technique used was ‘in vitro’ microperfusion, which permits the examination of this segment in isolation. The results showed that in the absence of vasopressin, hydrochlorothiazide, when added to the luminal (but not the basolateral) side, increased osmotic and diffusional water permeabilities. Increased permeability facilitates water reabsorption in the terminal nephron segment, thus decreasing urinary volume. This effect was also shown in rats with congenital central diabetes insipidus (Brattleboro rats). These data confirm the hypothesis proposed [8,10] that thiazides act in segments beyond the distal tubule. The effect is seen only when a diuretic is applied to the luminal side whilst the vasopressin receptor is located in the basolateral side. Thiazide obviously must enter the cell through the luminal membrane in order to gain access to the cytosol.

It had been noted that in patients with congenital NDI, urinary prostaglandin E2 excretion was increased [12]. This led to attempts to use indomethacin, a prostaglandin E2 synthesis blocker, together with thiazides [13]. It is well known that prostaglandin E2 decreases water absorption by decreasing the vasopressin-induced water permeability in the IMCD [14,15]. Conversely, a prostaglandin inhibitor increases water absorption and decreases urinary volume. Instead of using indomethacin, we used prostaglandin E2 itself in our experiments; this was added to the bath of the perfusion system. Addition of prostaglandin decreased the thiazide effect. This observation explains why indomethacin potentiates the thiazide effect. Prostaglandin E2 inhibits the adenylate cyclase that is stimulated by vasopressin. Such inhibition of the adenylate cyclase constitutes a ‘negative feedback loop’ in the vasopressin cascade, since vasopressin stimulates the synthesis of prostaglandin E2 in IMCD.

To exclude the possibility that the above results are explained as an artefact resulting from inhibition of the Na+Cl− cotransporter, we adopted the following strategy. We added ouabain, an inhibitor of NaK−ATPase to our system. This did not abrogate the effect of thiazides on water transport, leading us to conclude that thiazide-stimulated water transport is not linked to inhibition of the NaCl cotransporter. The results show that thiazides act only when they are applied to the luminal side. This finding led us to conclude that thiazides do not directly interact with the vasopressin receptor, which is located at the basolateral side. The data on the effect of prostaglandin E2, and the results from our laboratory that an inhibitor of protein kinase A blocks the effect of thiazide (unpublished data) led us to the hypothesis that the action of thiazides takes place at some point in the vasopressin cascade inside the cell. The exact mechanism of this thiazide-mediated effect obviously requires further investigation.

**Some practical points**

First, the clinician has to be aware that there is more than one reason to explain polyuria. When thiazides are used in primary NDI or patients on lithium treatment, potassium depletion may occur. Potassium depletion per se causes polydipsia and vasopressin-resistant polyuria. To prevent hypokalaemia, addition of the potassium-sparing diuretic amiloride has been recommended [16]. This inhibits the apical Na+ channel in the cortical collecting duct, thus diminishing the activity of the NaK−ATPase in the basolateral membrane and also K+ entry into the cell. These effects provide a diminished driving force for K+ secretion. This explains the beneficial effect of amiloride in children with congenital NDI [17].
The clinician who co-administers thiazides together with amiloride or indomethacin in patients with NDI should be aware that this does not completely eliminate polyuria. Urinary volume is reduced, but not normalized. Nevertheless, a polyuria of 3–4 l/day allows the patient to live an almost normal life and to be socially integrated. The clinician has to be aware of the potential of this treatment strategy to cause side-effects: thiazides may cause electrolyte disorders and indomethacin may cause gastrointestinal symptoms or reduction of the glomerular filtration rate. Only combined treatment strategies at the earliest possible moment will result in prevention of complications such as mental retardation, seizures, and cerebral calcifications in infants with congenital NDI [17,18]. Such complications have a strong relationship to repeated episodes of hypernatraemic dehydration that may develop when these infants undergo additional water loss (fever, diarrhoea, and vomiting).

We feel that our rat studies are indeed relevant for understanding and managing NDI in humans. The effect of thiazide on water transport in the IMCD provides a clear rationale for the use of this compound in the treatment of nephrogenic diabetes insipidus. Although gene therapy for congenital disorders is an exciting possibility [19], the above studies show that the effort to understand and improve pharmacological intervention is certainly worthwhile.

References