A randomized trial of furosemide vs hydrochlorothiazide in patients with chronic renal failure and hypertension

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Abstract

Background. Loop diuretics are the drugs of choice for the treatment of hypertension in chronic renal failure patients. However, the adaptive changes in the distal nephron and the short half-life of these drugs may decrease their long-term efficacy. Thiazides are not believed to be efficient in advanced renal failure, but this is debated.

Methods. We compared the efficacy of long-acting furosemide (60 mg/day) and hydrochlorothiazide (25 mg/day) in a double-blind, randomized crossover trial in seven patients with severe renal failure and hypertension (seven men, 54±10 years old). The primary end-points were sodium and chloride fractional excretions after 1 month of each diuretic and then after their combination. During the trial, other treatments and the diet were controlled.

Results. A trend towards an increase in the fractional excretion of sodium and of chloride was observed with furosemide, but the difference did not reach the level of statistical significance (P = NS). Hydrochlorothiazide significantly increased fractional excretion of sodium and chloride from 3.7±0.9 to 5.5±0.3 and from 3.9±0.19 to 6.5±0.3, respectively (P < 0.05). The combination of the two diuretics had no additional effect on the increase in sodium and chloride fractional excretion. Furosemide, hydrochlorothiazide and the combination of the two diuretics decreased mean arterial blood pressure by the same extent from 112 to 97, 99 and 97 mmHg, respectively (P < 0.05).

Conclusions. Hydrochlorothiazide increased the fractional excretion of sodium and chloride more than furosemide did and hydrochlorothiazide did not increase the efficacy of hydrochlorothiazide.

Keywords: fractional excretion; furosemide; hydrochlorothiazide; hypertension; renal failure; sodium

Introduction

The pathophysiology of hypertension in renal insufficiency involves the expansion of the extracellular fluid because of the decreased capacity of the kidneys to excrete sodium [1]. Hypertension is the only independent factor for the progression of renal failure [2]. Thus, antihypertensive therapy is the cornerstone of the so-called conservative treatment of renal failure [3].

For these reasons, diuretics are widely used in the management of hypertension in patients with chronic renal failure (CRF). In this setting, loop diuretics are the drugs of choice because they can increase the sodium fractional excretion by 20% and because they are efficient whatever the glomerular filtration rate (GFR) [4]. Conversely, thiazides are rarely used in patients with CRF because they lose their effectiveness if the GFR is lower than 40 ml/min.

The efficacy of loop diuretics may decrease with time because of the so-called ‘braking phenomenon’ [5]. This phenomenon results from the adaptive changes in the distal nephron that are due to the chronically increased delivery of sodium in this segment [5]. These pathological and functional changes increase sodium reabsorption below Henle’s loop [6,7]. Increased sodium reabsorption is even more pronounced in CRF patients in whom endogenous factors inhibit sodium reabsorption in proximal nephron segments so that a high sodium load is delivered to the distal tubule [4]. Another cause of resistance to loop diuretics is due to their short half-life. The compensatory increase in sodium reabsorption after the action of the diuretic

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has waned is called the ‘rebound phase’ and may be sufficient to nullify the prior natriuresis [8].

While the general belief is that thiazides are not efficient in CRF, various authors have demonstrated that they are efficient in patients with low GFR [9,10]. Furthermore, the long-lasting action of thiazides precludes them from rebound antinatriuresis.

The purpose of the present study was to compare the fractional excretion of sodium and chloride following chronic administration of furosemide (FUR) and hydrochlorothiazide (HCTZ).

**Methods**

**Study population**

The study protocol was approved by the local Comité Consultatif pour la Protection des Personnes relatif à la Recherche Biologique (CCPPRB). All patients gave written informed consent.

Among the patients with Cockcroft clearances lower than 40 ml/min attending the clinics of the Nephrology Unit, seven were randomly recruited. They were under steady-state conditions and aged between 18 and 75 years (Table 1). Primary renal diseases were diabetes (n = 1), polycystic kidney (n = 2), nephroangiosclerosis (n = 3) and undetermined (n = 1). All patients had antihypertensive medications before the study, including β-blockers (n = 5), angiotensin-converting enzyme (ACE) inhibitors (n = 5), angiotensin 1 (AT1) receptor inhibitors (n = 2), calcium channel blockers (n = 3), loop diuretics (n = 1) and vasodilatators (n = 1). No patients had recombinant human erythropoietin. All participants were Caucasians.

**Protocol**

All participants were studied under out-patient conditions. We used a double-blind, randomized crossover trial. The scheme of the study is depicted in Figure 1. The study was preceded by a 2 month run-in period during which diuretics were withheld at least 1 month prior to the start of the study. Other antihypertensive agents were not washed out, but their dosage was kept unchanged throughout the study. Erythropoietin was not allowed during the study. Pills were prepared at the Central Pharmacy and were indistinguishable. The patients were allocated to the different treatment sequences by using random numbers.

**Table 1. Clinical data of the patients at entry in the study**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>BMI</th>
<th>Renal disease</th>
<th>Cockcroft clearance</th>
<th>GFR</th>
<th>RPF</th>
<th>FF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pa. R.</td>
<td>56</td>
<td>M</td>
<td>34</td>
<td>Diabetes</td>
<td>33</td>
<td>16</td>
<td>95</td>
<td>0.17</td>
</tr>
<tr>
<td>Va. D</td>
<td>51</td>
<td>M</td>
<td>24</td>
<td>PKD</td>
<td>37</td>
<td>41</td>
<td>126</td>
<td>0.33</td>
</tr>
<tr>
<td>We. R.</td>
<td>71</td>
<td>M</td>
<td>28</td>
<td>PKD</td>
<td>27</td>
<td>29</td>
<td>79</td>
<td>0.37</td>
</tr>
<tr>
<td>Le. JC</td>
<td>53</td>
<td>M</td>
<td>26</td>
<td>NAS</td>
<td>35</td>
<td>17</td>
<td>63</td>
<td>0.27</td>
</tr>
<tr>
<td>Me. M</td>
<td>40</td>
<td>M</td>
<td>24</td>
<td>Und</td>
<td>32</td>
<td>12</td>
<td>57</td>
<td>0.21</td>
</tr>
<tr>
<td>Me. JP</td>
<td>55</td>
<td>M</td>
<td>37</td>
<td>NAS</td>
<td>40</td>
<td>36</td>
<td>178</td>
<td>0.20</td>
</tr>
<tr>
<td>Do. G</td>
<td>49</td>
<td>M</td>
<td>32</td>
<td>NAS</td>
<td>40</td>
<td>27</td>
<td>83</td>
<td>0.32</td>
</tr>
</tbody>
</table>

M = male; PKD = polycystic kidney disease; Und = undetermined; NAS = nephroangiosclerosis; GFR = glomerular filtration rate (ml/min); RPF = renal plasma flow (ml/min); FF = filtration fraction (%).

**Fig. 1.** Scheme of the study. The study was double-blinded until D120 and then open from D120 until D150. After a run-in period of 2 months (from D–60 to D0), patients were randomized to receive either long-acting furosemide (60 mg) or hydrochlorothiazide (25 mg) for 1 month (until D30). After a 1 month washout (D60), patients received the other diuretic for 1 month (until D90). After a second washout of 1 month (D120), patients received the combined regimen (both diuretics) for 1 month. The fractional excretions of sodium and chloride, and renal parameters were determined at D0, D30, D90 and D150. FUR = furosemide; HCT = hydrochlorothiazide; FENa = fractional excretion of sodium; FECI = fractional excretion of chloride.
At day 0 (D0), the patients were randomized to start either long-acting FUR 60 mg once a day or HCTZ 25 mg once a day for 1 month (until D30). The absorption of FUR is ~60%, with small inter-individual variability in stable patients. A 30 day washout period until D60 preceded the second sequence when patients had FUR or HCTZ for 1 month (until D90). The double-blind phase of the study ended at D90. After a second washout period until D120, patients had, during an open phase, both diuretics (combined regimen) for 1 month (until D150). Compliance with treatments was monitored during the protocol by telephone calls. The patients took study drugs in the early morning, including on the days of renal parameter assessments.

Dietary counselling by a nutritionist was given to all participants, who were advised to ingest a diet containing 70 mmol of NaCl (4 g) per day, 50 mmol of KCl per day and 0.8 g/kg protein per day. They were advised not to make any dietary changes during the study. At D0, D30, D60, D90, D120 and D150, patients were examined in a quiet environment. Weight, heart rate, blood pressure and adverse effects of treatments were recorded. Patients collected urine during the 24 h before measurement of urinary electrolytes. Blood tests were done for serum electrolytes and creatinine, and, on the same days, the GFR and renal plasma flow (RPF) were determined.

Measurements and calculations

Plasma and urine chemistry was analysed by enzymatic methods. GFR was assessed by DTPA clearance, and RPF by hippuran clearance. Replicate measurements of DTPA and hippuran clearances in the same individual showed a mean coefficient of variation of <5%. GFR was measured by using a clearance of 99m Technetium-DTPA, and RPF by using a clearance of [131I]hippuran (Elumatic III and Hippi-131, Shering Cis-Bio International, Gif sur Yvette, France).

Mean blood pressure was measured oscillometrically by an automatic blood pressure device (Dinamap, Critikon Co.). We considered the mean of five measures taken at 10 min intervals in the supine position.

Study end points

The primary end-points were the Na\(^+\) and Cl\(^-\) fractional excretions. The fractional excretions of sodium (FENa) and chloride (FECl) were calculated as the ratio between urinary Na\(^+\) or Cl\(^-\) excretion rates and filtered Na\(^+\) or Cl\(^-\) load.

Filtration fraction (FF) was the ratio between the GFR and RPF (%).

Statistical analysis

The SAS package was used for statistical analysis. The primary efficacy parameters were the differences in FENa and in FECl after diuretics. Data were analysed by the non-parametric Wilcoxon test for paired samples. Differences were considered statistically significant at a P level of 0.05.

Results

The main results are shown in Table 2. A trend toward an increase in the fractional excretion of sodium and of chloride was observed with FUR. Conversely, HCTZ significantly increased the fractional excretion of sodium from 3.7±0.9 to 5.5±0.3 and of chloride from 3.9±0.2 to 6.5±0.3 (P<0.05). The combined regimen increased the fractional excretion of sodium from 3.7±0.9 to 5.5±0.4 and of chloride from 3.9±0.2 to 6.3±0.5 (P<0.05). Mean arterial blood pressure decreased by the same extent after FUR, HCTZ and combined regimen from 112 to 97, 99 and 97 mmHg, respectively (P<0.05).

FUR and HCTZ decreased the GFR by the same extent from 29±11 to 23±8 and to 21±8, respectively (P<0.05). The combined regimen had no additional effect on the GFR decrease. A higher and significant decrease in RPF was observed with HCTZ from 114±54 to 94±37 ml/min and with the combined regimen, but FUR did not decrease it significantly. This result was at first glance paradoxical since the absolute value of RPF with HCTZ was higher than that with FUR. This apparent discrepancy was easily explained by the design of the study, in which each patient was his own control. Another explanation is the low number of patients investigated.

Body weights and 24 h diuresis were stable throughout the study (Table 3). No patients had adverse effects with FUR or HCTZ. With the combined regimen,

### Table 2. Fractional excretion of sodium and chloride and renal parameters during the study

<table>
<thead>
<tr>
<th></th>
<th>Basal state</th>
<th>FUR</th>
<th>HCTZ</th>
<th>Combined regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FENa</td>
<td>3.7±0.9</td>
<td>4.5±0.2</td>
<td>5.5±0.3</td>
</tr>
<tr>
<td></td>
<td>FECl</td>
<td>3.9±0.2</td>
<td>5.0±0.2</td>
<td>6.5±0.3</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>112±11</td>
<td>97±9</td>
<td>99±7</td>
<td>97±9</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>29±11</td>
<td>23±8</td>
<td>94±37</td>
<td>95±37</td>
</tr>
<tr>
<td>RPF (ml/min)</td>
<td>114±54</td>
<td>87±22</td>
<td>94±37</td>
<td>95±37</td>
</tr>
<tr>
<td>FF (%)</td>
<td>0.25±0.1</td>
<td>0.24±0.06</td>
<td>0.20±0.06</td>
<td>0.21±0.04</td>
</tr>
</tbody>
</table>

\(^aP<0.05\) vs basal and FUR.

\(^bP<0.05\) vs basal.

FUR = furosemide; HCTZ = hydrochlorothiazide; FENa = fractional excretion of sodium; FECl = fractional excretion of chloride; GFR = glomerular filtration rate; RPF = renal plasma flow; FF = filtration fraction.
two patients complained of asthenia and polyuria, and one of muscular cramps.

No major alterations of the serum electrolytes were observed during the study except for one patient who experienced hypokalaemia with the combined regimen. A significant decrease in serum potassium and serum chloride level was observed with the combined regimen relative to the basal state, FUR and HCTZ ($P < 0.05$).

Serum urea, serum creatinine and serum uric acid significantly increased with FUR and HCTZ ($P < 0.05$), and the increase was even more pronounced with the combined regimen ($P < 0.05$ vs FUR and HCTZ, Table 3). Glycaemia and lipids (not shown) were stable, as was serum albumin.

No differences were observed for 24 h urinary urea. Twenty four hour proteinuria significantly decreased with FUR, HCTZ and the combined regimen.

### Discussion

This study agrees with data from experimental studies in humans that also demonstrated the efficacy of HCTZ in CRF patients [9,10]. The amplitude of the increase in FENa and FECl under HCTZ was surprisingly high. Thiazide diuretics are ‘low ceiling’, because they act under normal circumstances in the distal tubule, where only small amounts of sodium and chloride are delivered [4]. However, if sodium delivery is increased in this part of the nephron, thiazides may be very effective indeed. This is the case in severe renal failure, in which fractional natriuresis is increased to as much as 8% due to the so-called ‘magnification phenomenon’ [4]. The mechanisms responsible for this phenomenon are not completely elucidated. It is thought that poorly defined endogenous forces are responsible for the decreased sodium reabsorption.

In contrast, FUR did not significantly increase FENa and FECl. This unexpected result may be explained by the negative impact of both the rebound and the braking phenomena on the efficacy of the drug [8]. Because of the design of the study, it was not possible to determine the exact cause of the effectiveness of FUR. To determine if effectiveness was due to rebound and/or to brake effects, we should have performed repeated time-controlled urine collections. The alternative explanation is a type 2 statistical error (power defect) due to the low number of patients. To discard a type 2 statistical error, we should have included many more patients, but this was beyond our goal. We considered this study as a pilot preliminary study useful to determine the number of patients needed in further studies seeking to show a statistical difference between the two treatments.

The pharmacodynamics of diuretics and the physiology of sodium reabsorption in CRF make the results of our study not so unexpected. On the one hand, the real efficacy of thiazides in CRF, their long half-life of action and the increased delivery of sodium to the distal tubule in CRF easily explain the increase in FENa and FECl with HCTZ. On the other hand, the braking and the rebound phenomena may account for the loss of efficacy of FUR. We used a long-acting form of FUR but, even with this form, the half-life is not long enough to prevent the rebound phenomenon.

The combined regimen (FUR + HCTZ) was not more potent than HCTZ alone for increasing FENa and FECl. The effectiveness of the combination is speculative, but one can imagine that if furosemide alone is ineffective in increasing sodium chloride excretion, to combine it with any other diuretics would not increase its efficacy.

Mean arterial blood pressure was similarly decreased by the two diuretics. The mechanism of the hypotensive

### Table 3. Serum and urine parameters during the study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basal state</th>
<th>FUR</th>
<th>HCTZ</th>
<th>Combined regimen (FUR + HCTZ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>85±10</td>
<td>85±11</td>
<td>84±9</td>
<td>83±9</td>
</tr>
<tr>
<td>24 h diuresis (ml)</td>
<td>1850±560</td>
<td>2085±760</td>
<td>1960±510</td>
<td>2135±410</td>
</tr>
<tr>
<td>Serum Na$^+$ (mmol/l)</td>
<td>140±2</td>
<td>140±3</td>
<td>138±3</td>
<td>140±2</td>
</tr>
<tr>
<td>Serum K$^+$ (mmol/l)</td>
<td>4.7±0.5</td>
<td>4.7±0.6</td>
<td>4.5±0.7</td>
<td>4.2±0.6$^a$</td>
</tr>
<tr>
<td>Serum Cl$^-$ (mmol/l)</td>
<td>107±3</td>
<td>107±3</td>
<td>105±3</td>
<td>102±4$^a$</td>
</tr>
<tr>
<td>Serum HCO$_3^-$ (mmol/l)</td>
<td>25±4</td>
<td>26±5</td>
<td>25±3</td>
<td>28±6</td>
</tr>
<tr>
<td>Serum urea (mg/dl)</td>
<td>84±12</td>
<td>114±30$^b$</td>
<td>132±36$^b$</td>
<td>174±72$^{b,c}$</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>2.79±1.09</td>
<td>3.13±1.2$^b$</td>
<td>3.29±1.7$^b$</td>
<td>3.83±1.62$^{b,c}$</td>
</tr>
<tr>
<td>Serum uric acid (mg/dl)</td>
<td>7.3±2.2</td>
<td>8.7±2.6$^b$</td>
<td>9.5±3.1$^b$</td>
<td>10.9±2.6$^{b,c}$</td>
</tr>
<tr>
<td>Serum glucose (mg/dl)</td>
<td>89±20</td>
<td>94±21</td>
<td>94±18</td>
<td>96±19</td>
</tr>
<tr>
<td>24 h urinary urea (g)</td>
<td>20±6</td>
<td>21±4</td>
<td>20±5</td>
<td>22±7</td>
</tr>
<tr>
<td>24 h urinary Na$^+$ (mmol)</td>
<td>70±32</td>
<td>60±26</td>
<td>68±28</td>
<td>60±18</td>
</tr>
<tr>
<td>24 h urinary K$^+$ (mmol)</td>
<td>50±18</td>
<td>60±20</td>
<td>63±15</td>
<td>65±18</td>
</tr>
<tr>
<td>24 h urinary protein (mg)</td>
<td>839±998</td>
<td>698±1057$^b$</td>
<td>538±622$^b$</td>
<td>705±533$^b$</td>
</tr>
</tbody>
</table>

$^aP < 0.05$ combined regimen vs basal, FUR and HCTZ.

$^bP < 0.05$ FUR, HCT and combined regimen vs basal.

$^cP < 0.05$ combined regimen vs FUR and HCTZ.

To convert serum creatinine in mg/dl to mmol/l, multiply by 88.4; to convert serum urea to mmol/l, divide by 6.
effect of the drugs seems to be different. FUR acts mainly on blood pressure by decreasing peripheral vascular resistance while blood volume depletion seems marginal [11]. HCTZ, in contrast, by increasing FENa and FECI, decreases mainly blood volume, as evidenced by the significant decrease in RPF. It has already been shown that the hypotensive effect of thiazides relies on their ability to induce negative sodium balance [12].

We did not have clear-cut explanations for the stable potassium levels in spite of the increase in fractional excretion of sodium. It is possible that the transtubular potassium gradient in the cortical collecting duct was low because of low availability of aldosterone in severe renal failure.

The decrease in proteinuria may be explained both by the decrease in GFR under diuretic treatments and by some changes in the renal microcirculation induced by prostaglandins or other vasoactive peptides.

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Conflict of interest statement. None declared.

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