REVIEW

Are all diuretics equal for the treatment of hypertensive patients?

F. Feihl, B. Waeber∗

Division of Clinical Pathophysiology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland

Received 10 October 2012; accepted 10 October 2012
Available online 13 November 2012

Keywords
Thiazide diuretics; Hydrochlorothiazide; Chlortalidone; Indapamide; Cardiovascular complications; Antihypertensive treatment; Renin-angiotensin system

Abstract
Thiazide (hydrochlorothiazide, etc.) and thiazide-like (chlortalidone, indapamide, etc.) diuretics are widely used to treat hypertensive patients. There is growing evidence that these diuretics are not interchangeable and that it might be preferable to choose a thiazide-like diuretic whenever the use of a diuretic is considered. This is in order to prevent optimally the development of cardiovascular complications and the occurrence of metabolic side effects, in particular diabetes.

© 2012 SEHLELHA. Published by Elsevier España, S.L. All rights reserved.

Introduction

Ever since their introduction in 1958, diuretics have played an essential role in the treatment of arterial hypertension. These agents were scrutinized in all major mortality–morbidity studies and today represent one option for first-line treatment. Moreover, they are indispensable...
for increasing the therapeutic efficiency of other drug classes, notably the blockers of the renin-angiotensin system, hence the present existence of numerous fixed dose combinations which include a diuretic.

The usual classification of diuretics comprises the following groups: thiazide diuretics (with hydrochlorothiazide being the most common one in many countries), “thiazide-like” diuretics (chlortalidone, indapamide, metolazone), loop diuretics (furosemide, torasemide), and potassium-sparing diuretics (aldosterone antagonists such as spironolactone or eplerenone, and amiloride). Loop diuretics are indicated when kidney function is altered or in occasional cases of severe refractory hypertension. Aldosterone antagonists potentiate the action of other diuretics while preserving potassium stores. Amiloride is only weakly antihypertensive, but it is useful for preventing hypokalemia when co-administered with a thiazide or a loop diuretic.

According to the latest recommendations on the management and treatment of hypertension (the NICE Guidelines, issued by a group of British experts), preference should be given to a thiazide-like agent whenever it becomes necessary to prescribe a diuretic. This is not surprising considering the doubts recently expressed on the interchangeability of thiazide and thiazide-like diuretics. The aim of the present review is to examine the possible advantages of using one or another type of diuretic in everyday practice. The discussion will be limited to hydrochlorothiazide, chlortalidone, and indapamide. Unfortunately, very few data are available on metolazone, although this compound is of interest because, compared to hydrochlorothiazide, chlortalidone, and indapamide, its natriuretic effect persists for longer duration when renal function deteriorates.

**Mechanism of action**

The diuretic action of thiazide and thiazide-like diuretics is explained by the inhibition of the sodium/chloride co-transporter located in the initial portion of distal tubules. Diminished sodium stores lead to activation of the renin-angiotensin system. The ensuing hyperreninemia is a limiting factor for the efficacy of these drugs. When used in monotherapy, thiazide and thiazide-like diuretics tend to be the most efficient in salt-sensitive patients – i.e. whose blood pressure increases in response to a sodium overload – as well as in elderly and in black patients. Thiazide and thiazide-like diuretics also have a vasodilator effect, best documented and most important in the case of indapamide, as shown by the ability of this agent to reduce blood pressure in anuric patients on haemodialysis. This vasodilator effect has been linked to a reduced calcium flux into vascular smooth muscle cells, perhaps due to the high liposolubility of indapamide which thus accumulates into cell membranes.

**Antihypertensive efficacy**

Only a few controlled clinical trials have directly compared the antihypertensive efficacy of different diuretics. Chlortalidone (25 mg/day) reduced systolic blood pressure significantly more than did hydrochlorothiazide (50 mg/day), with an average difference amounting to 5 mmHg when evaluated with ambulatory blood pressure monitoring after 8 weeks of treatment. In fact, compared to the latter agent, the former has a longer half-life. The superiority of chlortalidone has been confirmed in two recent meta-analyses. The last one comprised 26 clinical trials involving hydrochlorothiazide, but only 3 studies with chlortalidone. The daily dose of chlortalidone required to reduce systolic pressure by 10 mmHg was estimated at 8.6 mg, versus 26.4 mg for hydrochlorothiazide.

Two formulations are available for indapamide: immediate release (IR) and slow-release (SR). Compared to the IR formulation, SR indapamide can be administered at lower doses, with the advantage of reducing the undesirable metabolic side-effect, which is dose-dependent. In fact, evaluations with both office blood pressure measurement and ambulatory blood pressure monitoring have confirmed that 1.5 mg/day of SR and 2.5 mg/day of IR indapamide have the same antihypertensive efficacy. The respective efficacies of various antihypertensive drugs have been compared in one meta-analysis which included only controlled randomized double-blind trials. Results regarding SR indapamide 1.5 mg/day versus various doses of hydrochlorothiazide are shown in Table 1.

**Effects on cardiovascular morbidity and mortality**

It is difficult to evaluate whether any one of the diuretics considered in the present paper has an advantage in terms of protection against cardiovascular and renal diseases. Indeed, no direct comparison of these various agents has been carried out in any of the available randomized morbidity-mortality clinical trials. Furthermore, in studies where one treatment comprised hydrochlorothiazide, chlortalidone or indapamide, these were co-administered in more than 50% of cases with other antihypertensive agents, most often a β-blocker or an inhibitor of the renin-angiotensin system. In the field of hypertension indeed, the design of most clinical trials is based on therapeutic schemes to be followed in order to reach predefined blood pressure targets.

The best evidence for an advantage of chlortalidone over hydrochlorothiazide comes from the retrospective analysis of a cohort of hypertensive male patients whose age at inclusion ranged from 35 to 57 years. These were observed for 7 years while on treatment which initially consisted in either hydrochlorothiazide (n = 4,049) or chlortalidone (n = 2,392) at large doses (50–100 mg/day), with the possibility to add a sympatholytic agent or an arteriolar vasodilator as necessary to lower blood pressure under 89 mmHg or at least by 10 mmHg. Cardiovascular events were significantly less frequent in patients who received chlortalidone, compared to those treated with hydrochlorothiazide (hazard ratio 0.79, 95% confidence interval 0.68–0.92, p < 0.0016). Chlortalidone also presented with a significant advantage in terms of several parameters: compared to the other diuretic, systolic blood pressure, LDL-cholesterol and triglyceride levels were lower, and kaliemia was higher.

The clinical trials that have included hydrochlorothiazide, chlortalidone or indapamide in one treatment arm
have been recently reviewed. The authors concluded that chlortalidone and indapamide might indeed be superior to hydrochlorothiazide in terms of impact on cardiovascular risk.

Undesirable metabolic effects

The undesirable metabolic effects of thiazide and thiazide-like diuretics are dose-dependent and typically comprise hypokalemia, hyperuricemia, hyperglycemia and a potentially deleterious impact on lipid profile (increased LDL-cholesterol and triglyceride levels). The alterations in lipid profile occur mainly at the beginning of treatment and do not seem to persist over the long term. In that respect, indapamide has an advantage: 1.5 mg/day of its SR formulation have practically no metabolic impact.

One remark is in order concerning the glucose intolerance caused by hydrochlorothiazide and chlortalidone. This effect seems potentiated by potassium depletion. In hypertensive patients, the diabetogenic impact of hydrochlorothiazide might be avoided by the co-administration of a potassium-sparing diuretic such as amilorida.

Conclusions

When treating hypertensive patients, the prescription of thiazide and thiazide-like diuretics is often unavoidable. According to expert recommendations, including those by the European Society of Hypertension, these compounds presently may still be used as first-line antihypertensive agents. Furthermore, they are very useful when combined treatment becomes necessary. In such an occurrence, their association with blockers of the renin-angiotensin system is the most rational one and has the best documented beneficial effects. Of note, thiazide and thiazide-like diuretics do not seem interchangeable, recently leading British experts to express a preference for chlortalidone or indapamide whenever a diuretic must be prescribed. Formulations based on fixed-dose combinations are presently gaining in popularity, but in spite of the latter recommendation, most of those based on a blocker of the renin-angiotensin system contain hydrochlorothiazide, with one exception associating an angiotensin converting enzyme inhibitor (perindopril) and indapamide.

<table>
<thead>
<tr>
<th>HCTZ (mg/day)</th>
<th>n</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>317</td>
<td>-18.9 (−20.8, −16.9)</td>
<td>-11.0 (−11.9, −10.1)</td>
</tr>
<tr>
<td>12.5−25</td>
<td>94</td>
<td>-10.8 (−14.3, −7.3)</td>
<td>-7.9 (−9.5, −6.3)</td>
</tr>
<tr>
<td>50</td>
<td>56</td>
<td>-19.3 (−22.6, −16.0)</td>
<td>-14.0 (−16.0, −12.0)</td>
</tr>
<tr>
<td>SR indapamide</td>
<td>265</td>
<td>-22.23 (−23.9, −20.6)</td>
<td>-11.7 (−12.8, −10.7)</td>
</tr>
</tbody>
</table>

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of Data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Conflict of interest

The authors declare no conflict of interest.

References