Are all diuretics equal for the treatment of hypertensive patients?

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

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.

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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.1,2 Moreover, they are indispensable

PALABRAS CLAVE
Tiazidas; Hidroclorotiazida; Chlortalidona; Indapamida; Complicaciones cardiovasculares; Tratamiento antihipertensivo; Sistema renina-angiotensina

¿Son todos los diuréticos iguales para el tratamiento de la hipertensión?

Resumen  Las tiazidas (hidroclorotiazida, etc.) y los diuréticos de tipo tiazídico (chlortalidona, indapamida, etc.) son fármacos ampliamente utilizados para tratar la hipertensión. Existe pruebas crecientes de que estos diuréticos no son intercambiables y sería preferible elegir un diurético de tipo tiazídico siempre que se considere el uso de los mismos. La razón para ello es evitar de manera óptima el desarrollo de complicaciones cardiovasculares y la aparición de efectos secundarios metabólicos, en particular la diabetes.

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for increasing the therapeutic efficiency of other drug
classes, notably the blockers of the renin-angiotensin sys-
tem, hence the present existence of numerous fixed dose
combinations which include a diuretic.

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

According to the latest recommendations on the man-
gement 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 inter-
changeability 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, chlo-
rtalidone, and indapamide. Unfortunately, very few data
are available on metolazone, although this compound is of
interest because, compared to hydrochlorothiazide, chlo-
rtalidone, 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. Dimi-
nished 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. Chloro-
talidone (25 mg/day) reduced systolic blood pressure sig-
ificantly 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 superior-
ity of chlortalidone has been confirmed in two recent
meta-analyses. The last one comprised 26 clinical tri-
als 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: imme-
diate release (IR) and slow-release (SR). Compared to
the IR formulation, SR indapamide can be admin-
istered 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 antihyper-
tensive efficacy. The respective efficacies of various
antihypertensive drugs have been compared in one
meta-analysis which included only controlled random-
ized 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 diure-
tics considered in the present paper has an advantage in
terms of protection against cardiovascular and renal dis-
eases. 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, chlo-
rtalidone 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 tar-
gets.

The best evidence for an advantage of chlortalidone over
hydrochlorothiazide comes from the retrospective analy-
sis 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 chlo-
rtalidone (n = 2,392) at large doses (50–100 mg/day), with
the possibility to add a sympatholytic agent or an arte-
riolar 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 potassium was higher.

The clinical trials that have included hydrochloroth-
iazide, chlortalidone or indapamide in one treatment arm
have been recently reviewed.\textsuperscript{4} 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.\textsuperscript{17,18} In that respect, indapamide has an advantage: 1.5 mg/day of its SR formulation have practically no metabolic impact.\textsuperscript{19}

One remark is in order concerning the glucose intolerance caused by hydrochlorothiazide and chlortalidone. This effect seems potentiated by potassium depletion.\textsuperscript{20,21} In hypertensive patients, the diabetogenic impact of hydrochlorothiazide might be avoided by the co-administration of a potassium-sparing diuretic such as amiloride.\textsuperscript{22}

**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,\textsuperscript{2} 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.\textsuperscript{3} 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.

**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.

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