Indian Heart Journal 69 (2017) 282–285

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

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Which diuretic for which hypertensive patient?

Keywords
Diuretics
Hypertension
Hydrochlorothiazide
Indapamide
Guidelines
Tailored approach

We have read with great interest the editorial by Mishra.[1] Diuretics represent a heterogeneous class of drugs, differing from each other by structure, site and mechanism of action. They are largely prescribed in different cardiovascular diseases, particularly in hypertension and heart failure. However, despite the available data on their efficacy, diuretics are still underused in the management of hypertension.[1]

Formerly, diuretics were considered to be one of the most potent antihypertensive treatments. Nowadays, after the onset of new efficient anti-hypertensive drugs, diuretics may be no longer considered the most privileged first-line strategy.[2,1] Indeed, most of the current guidelines downgraded the place of thiazide diuretics in the management of hypertension from the preferential initial therapy to one of the possible first-line alternatives among a large armamentarium of anti-hypertensive drugs.[3–7]

Interestingly, thiazide and thiazide like diuretics are those recommended as first-line strategy for primary hypertensive treatment in different guidelines.[3–7] Thiazide and thiazide like diuretics neither have the same structure nor the same site of action, and that would explain the huge disparities concerning their efficiency and side effects. However, despite their differences, the recommendations generally do not favor any agent on the other.[3–6] Whereas, other types of diuretics are barely mentioned in different guidelines and thereby are ever more underutilized in daily practice.

Hence, although recommendations encouraged a treatment approach based on considering patient's characteristics, the majority of guidelines are based on evidence for drug classes rather than individual drugs.[3–6] Only NICE recommendations encourage when initiating or changing treatment, to prescribe a thiazide-like diuretic, such as chlorthalidone or indapamide in preference to a conventional thiazide diuretics.[3]

For the above reasons, we should not think any more if patient with hypertension needs or not a diuretic. Indeed, a new question should arise in light: which diuretic for which patient?

Much evidence support the inferiority of hydrochlorothiazide compared to other thiazide like agents.[8] In fact, hydrochlorothiazide duration of antihypertensive action is less than 24 h, while indapamide has even in the immediate release form, at least 24-h duration of action for blood pressure reduction.[8,9] In addition, a network analysis demonstrated that hydrochlorothiazide was less effective in preventing cardiovascular events as compared with chlorthalidone and the association hydrochlorothiazide-amiloride.[10] Moreover, it is inferior to indapamide in improving endothelial function and longitudinal strain in patients with hypertension and diabetes.[11] Hydrochlorothiazide is also inferior to spironolactone in improving coronary flow reserve.[12]

Many authors suggest that indapamide is by far the most efficient and tolerable diuretic for hypertensive patients.[13] Compared to hydrochlorothiazide, it was demonstrated to be more efficient in improving micro-albuminuria (in diabetics), reducing left ventricular mass index, inhibiting platelet aggregation, and reducing oxidative stress.[14] Indapamide was also shown to reduce left ventricular hypertrophy more than enalapril.[13,14] Importantly, indapamide do not share with thiazide diuretics their adverse effects on lipid and glucide metabolism, thereby it can be safely prescribed in diabetic patients.[13]

However, despite this strong evidence, one of the reasons explaining the huge disparities of thiazide/thiazide like diuretics prescription may be due to that chlorthalidone is only commercialized with atenolol and azilsartan. Likewise, indapamide is only combined with perindopril. The only advantages of hydrochlorothiazide seem to be its extensive availability in formulations with other classes of antihypertensive drugs and its low price.

Otherwise, while spironolactone did not show an appropriate evidence for reducing cardiovascular events in hypertensive patients, its place in reducing total mortality in advanced heart failure is well known.[15] Moreover, its efficiency in resistant hypertension is well established.[16] Similarly, eplerenone was shown to have greater impact on systolic blood pressure and to improve endothelial function in hypertensive patients with similar rates of hyperkalemia.[17,18]

Finally, loop diuretics could be of benefit in case of chronic kidney disease with serum creatinine >1.5 mg/dL or eGFR <30 mL/min/1.73 m^2.[4] Their antihypertensive effect might be improved with nighttime administration.[18]

To conclude, diuretics are efficient and quite safe antihypertensive drugs with several decades of clinical application. The concept to replace “one size fits all” (class effect) paradigm to a more tailored approach in prescribing diuretics seems to be rational and appropriate not only to increase their prescription by clinicians, but also to achieve better clinical outcome for patients.

Conflicts of interest

The authors have none to declare.

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Received 1 February 2017
Available online 3 March 2017

http://dx.doi.org/10.1016/j.ihj.2017.02.012

Letter – Diuretics in primary hypertension – Reloaded

Dear Dr. Mishra,

I agree with you that, diuretics are a gold standard[1] in the treatment of hypertension. Increasingly the guidelines are also recognizing the importance of diuretics, especially in uncomplicated hypertension. This is because of the robust data which diuretics have in their favour, for e.g. HYVET[2] trial with Indapamide which showed a 39% reduction in the rate of death from stroke ($P = 0.05$), and a 64% reduction in the rate of heart failure ($P < 0.001$), ALLHAT trial also showed chlorthalidone was superior to lisinopril in lowering BP & preventing aggregate CV events[3]. Hence, we do need to differentiate between Thiazide & Thiazide-like diuretics. A recent meta-analysis states that "Hydrochlorothiazide has often been compared with chlorthalidone, but relatively little is known about Hydrochlorothiazide versus indapamide[4]. This systematic review retrieved 9765 publications, and from these, it identified 14 randomized trials comparing Hydrochlorothiazide with indapamide and chlorthalidone on antihypertensive potency or metabolic effects. Compared with an estimated 9.5 mm Hg reduction in SBP from Hydrochlorothiazide relative to placebo from Peterzan et al.[5], indapamide and chlorthalidone lowered SBP by 54% and 38% more than Hydrochlorothiazide, respectively.

However, there is a general perception, that these diuretics can cause metabolic imbalances. This is especially true for thiazide diuretics at higher dose. But thiazide-like diuretics can also cause some metabolic imbalance, in ALLHAT trial chlorthalidone increased the risk of new-onset diabetes by 43% as compared to lisinopril.[2] In the Trial of Antihypertensive Interventions and Management (TAIM) study,[6] erection-related problems worsened in 28% of men receiving chlorthalidone, this can be a cause of concern as Indian patients are not very comfortable sexual dysfunction with anyone. Though these side-effects are documented with high dose of chlorthalidone and low-dose therapy may minimize the risk of these side effects. However it doesn't appear to be a class effect as Indapamide, a thiazide type diuretic has been found to be metabolically neutral at a dose of 1.5 mg sustained release or 2.5 mg immediate release.[7]

To conclude, diuretics will remain the mainstay of treatment of uncomplicated HT, especially thiazide-like diuretics as they have wealth of evidences. To maximize benefits, both in terms of BP reduction efficacy & life-saving benefits they should be used at dose used in major clinical trials (12.5–25 mg/day of chlorthalidone used in ALLHAT, or 1.5 mg of indapamide SR used in HYVET).

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