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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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Letter – Diuretics in primary hypertension – Reloaded

Dear Sir,

This is in reference to your editorial[1] which appeared in Indian heart journal titled "Diuretics reloaded in primary hypertension". Its an interesting article, and I would like to highlight a few points:

1 Diuretics as a first line drug in elderly hypertensives is slowly getting forgotten by many due to fear of its metabolic side-effects- In high dose, yes it might cause problem especially Thiazide diuretics and its equivalent but with the advent of low dose chlorthalidone (12.5 and 25 mg)and Indapamide has decreased this fear.
2 Low dose chlorthalidone and indapamide has shown superiority over the thiazide diuretics in reducing the CV outcomes, systolic BP and improving the MACE events and thereby improving the mortality and morbidity benefits.[2, 3]
3 Coming to the metabolic side effects profile, even low dose chlorthalidone seem to cause metabolic imbalance to some extent, whereas indapamide either alone or in combination with perindropril has or showed improvement in all-cause mortality and morbidity – MACE events and CV outcomes. Several trials namely PROGRESS, ADVANCE to name a few have proved it.[4]

Hence we can say that, diuretics are here to stay like other classes of anti-hypertensives in essential hypertension especially in elderly subsets.

My experiances-

I have used indapamide as well as low dose chlorthalidone in hypertensive subsets and I have noticed better control with indapamide as add on drug in improving outcomes even better than chlorthalidone(one of my family member is on indapamide).

I conclude by saying that this article is an eye opener for many as it reiterates the fact that many new group of drugs may come but diuretics have their own stand, which was beautifully brought out in your article.

Conflict of interests

All the authors declare that they have no conflict of interest.

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Renoprotection with indapamide, additional feature to look for

To the Editor,

At the outset I would like to congratulate you for choosing a topic which has even a larger relevance in a country like India. You have rightly pointed out that despite several trials have demonstrated mortality benefit with diuretic therapy in uncomplicated hypertension their use in real world practice is going down.[1] The declining trend in prescription may be related to several misconceptions prevailing about the use of diuretics in primary hypertension. You also recommended that among the available options of diuretics, low dose chlorthalidone and indapamide are preferred because they are less likely to be associated with significant adverse metabolic effects (increased lipid levels, adverse effects on glucose metabolism, effects on arrhythmias, etc.). In this letter, I would like to add a few more points in favor of indapamide in terms of renoprotection and other effects which may boost our confidence on this molecule.

In 1991 Gambardella et al. first published the renoprotective effect of long-term indapamide treatment, defined as a reduction in urinary protein loss in patients with type 2 diabetes and persistent microalbuminuria.[2] Several other reports also claimed the similar effects, some of them stating the drug being as effective as ACEIs.[3,4] These apparent renoprotective effects of thiazide diuretics may be specific to diabetic patients.

Apart from the above mentioned advantages, indapamide is likely to cause less hypokalemia when compared to equivalent doses of chlorthalidone and hydrochlorthiazide.[5] Not only that, indapamide is most effective in terms of nocturnal BP control among all the available diuretic options. These benefits of indapamide are proven at the therapeutic dosage of either 2.5 mg immediate release or the superior 1.5 mg sustained release. The SR formulation avoids unnecessary peak in the plasma level of the drug and ensures that only a subclinical diuresis is there, while indapamide controls BP by its predominantly vascular effect (normalization of hyperreactivity of vasculature to noradrenalin). This minimizes the risk of diuretic related side effects like electrolytic or metabolic disturbances. Indapamide also causes venorelaxation, which explains why the risk of pedal edema is minimized when indapamide is added to amlodipine.

So, I fully agree with you that we should increase our prescriptions of diuretics in uncomplicated primary hypertension. Among the available diuretic options, indapamide is probably having an edge, particularly in diabetic subpopulation.