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Actual Place of Diuretics in Hypertension Treatment

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Abstract

Diuretics represent a large and heterogeneous class of drugs, differing from each other by structure, site and mechanism of action. Diuretics are widely used, and have several indications in different cardiovascular disorders, particularly in hypertension and heart failure.

Despite the large number of available anti-hypertensive drugs, diuretics remained a cornerstone of hypertension treatment. In the current editorial, we assessed the actual place of different diuretics in the hypertension guidelines focusing on the concept of tailored approach in prescribing them for hypertensive patients.

Keywords: Diuretics; Hypertension; Hydrochlorothiazide; Indapamide; Guidelines

Introduction

Diuretics represent a large and heterogeneous class of drugs, differing from each other by structure, site and mechanism of action. Diuretics are widely used, and have several indications in different cardiovascular disorders, particularly in hypertension and heart failure.

Despite the large number of available anti-hypertensive drugs, diuretics remained a cornerstone of hypertension treatment [1]. Indeed, they are the second most commonly prescribed class of antihypertensive medication. For instance, 12% of US adults were prescribed a diuretic, and the relative increase in prescriptions from 1999 through 2012 was 1.4 [2]. However, a question remains looking for an answer: which diuretic for which hypertensive patient?

Mechanisms of Action of Diuretics

The overall action of diuretics (except osmotic diuretics) can be summarized as the blockage of sodium reabsorption at the nephron major sites leading to an increase in water excretion. Figure 1 illustrates the sites of action of different diuretic agents; Table 1 describes their mechanisms of action.

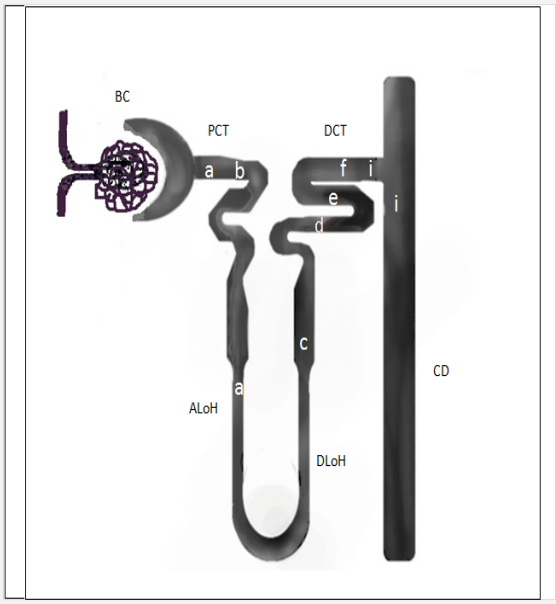

Figure 1: Site of action of different diuretic agents.

a: Osmotic diuretics; b: Carbonic anhydrase inhibitors; c: Loop diuretics: d: Indapamide & Chlorthalidone; e: Hydrochlorothiazide; f: Amiloride & Triamterene; i: Spironolactone.

ALoH: Ascending Loop of Henle; BC: Bowman Capsule; CD: Collecting Duct; DCT: Distal Convoluted Tubule; DLoH: Descending Loop of Henle; PCT: Proximal Convoluted Tubule

Table 1: Mechanisms of action of diuretics agents.

Diuretic*	Site of Action	Mechanisms
Loop diuretics	Ascending loop of Henle	Act directly on the ascending limb of the loop of Henle to inhibit chloride and sodium resorption by inhibiting Na+/K+/2Cl- transporter protein. Produce decrease in interstitial hyper-tonicity and thus to a reduced water reabsorption.
Thiazide/ Thiazide like		
Hydrochlorothiazide	Distal convoluted tubule	Inhibits tubular resorption of sodium, chloride, and potassium ions. Prevents NaCl reabsorption through direct suppression of the sodium chloride co-transporter. Lowers peripheral vascular resistance.
Indapamide/chlorthalidone	Proximal segment of the distal convoluted tubule	Inhibits tubular resorption of sodium, chloride through blocking the sodium chloride co-transporter with less effect on kaliuresis. Reduces vascular reactivity.
Potassium-Sparing Diuretics		
Spironolactone	Cortical collecting duct and late distal convoluted tubule.	Blocks the entry of aldosterone into the principle cells by competitively binding to aldosterone receptors.
Amiloride/Triamterene	Late distal convoluted tubule. Cortical collecting duct.	Prevents sodium entering by blocking the epithelial sodium channel which are found in the apical membrane.

*Carbonic anhydrase inhibitors and osmotic diuretics are not included.

In addition to their nephrogenic effects, some diuretics according to their structural proprieties can lower blood pressure via other pathways. For instance, indapamide has calcium antagonist-like vasorelaxant effects that strengthen its lowering blood pressure action [3]. Spironolactone likewise has another site of action on arterioles receptors, where it antagonizes aldosterone-induced vasoconstriction, resulting in diastolic and mean pressure reduction [4].

Nonetheless, the most worrying adverse effects of this class of agents is electrolytes derangement. Serum potassium level may be lowered by thiazides and loop diuretics and elevated by aldosterone antagonists. Hyponatremia is more common with chlorthaliadone than hydrochlorthiazide but not at equipotent doses and the incidence of hyponatremia for both medications is very strongly age related [5].

Place of Diuretics in Hypertension Guidelines

Formerly, diuretics were considered to be one of the most effective antihypertensive treatments. Nowadays, after the onset of new potent anti-hypertensive drugs, diuretics may be no longer considered the most privileged first-line strategy [6,7].

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 [8-12].

The recent Australian guidelines emphasize that the choice of a drug to initiate or to maintain an anti-hypertensive therapy should consider several parameters: patient's age, race, co-morbidities, potential interaction with other drugs, cost, patient's choice and implication for adherence [12]. Hence, these guidelines suggest to the practitioner 4 or 5 different class drugs, giving him the freedom to choose the most suitable drug for each patient as a personalized treatment approach.

Among the diuretics, thiazide and thiazide like diuretics are those recommended as first-line strategy for primary hypertensive treatment in different guidelines [8-12]. Table 2 summarized the evolution of the place given to diuretics in hypertension treatment in different guidelines.

Table 2: The place of diuretics in hypertension treatment guidelines.

Guidelines	Year	Preferred Agent(s)
WHO [6]	2003	Thiazide-type diuretic
Management of Hypertension in Blacks [13]	2010	Thiazide-type diuretic Calcium channel blockers
NICE [8]	2011	>55 years or African American/ Caribbean Consider thiazide diuretic if calcium channel blocker not suitable for evidence of oedema, intolerance or high risk of heart failure.

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ESC [9]	2013	Recommendation allows selection among 5 medication classes i. Thiazide diuretics ii. ACE inhibitors iii. Angiotensin receptor antagonist iv. Calcium channel blockers (long-acting) v. Beta-blocker
CHEP guidelines [10]	2014	Four agents can be considered as first choice: a. Thiazide-type diuretics b. Beta-blocker c. ACE inhibitors d. Calcium channel blockers
JNC 8 [11]	2014	Recommendation allows selection among 4 medication classes a) Thiazide diuretics b) ACE inhibitors c) Angiotensin receptor antagonist d) Calcium channel blockers (long-acting)
NHFA guidelines [12]	2016	Recommendation allows selection among 4 medication classes A. Thiazide diuretics B. ACE inhibitors C. Angiotensin receptor antagonist D. Calcium channel blockers (long-acting)

CHEP: Canadian Hypertension Education Program; ESC: European Society of Cardiology; JNC8: The Eighth Joint National Committee; NHFA: National Heart Foundation of Australia, NICE: National Institute for Health and Clinical Excellence; WHO: World Health Organization.

The Concept of Tailored Approach

Thiazide diuretics are privileged as the appropriate option in a variety of circumstances like for salt sensitive patients (such as black patients) and for those elderly with systolic hypertension [13]. In other clinical scenarios, they can be prescribed as one of 5 first-line antihypertensive alternatives [8-12].

However, other types of diuretics are barely mentioned in different guidelines and thereby are underutilized in daily practice [1]. Table 3 summarized the ideal clinical indications of each diuretic.

Table 3: Indications of different diuretic agents.

Diuretics	Indications
Loop diuretics	Chronic kidney disease with serum creatinine is >1.5mg/dL or eGFR is <30mL/min/1.73m^2 Volume overload Heart failure as a second line therapy for volume control
Thiazide/Thiazide like	
If diuretic is to be initiated or changed prefer indapamide or chlorthalidone over conventional hydrochlorothiazide	1st or 2nd alternative particularly in black patients and those aged >55 years
Potassium-Sparing Diuretics	
Mineralocorticoid receptor antagonists	Heart Failure Resistant hypertension Primary aldosteronism
Amiloride	Resistant hypertension in addition to thiazide or thiazide-like diuretics Hyperaldosteronism if spironolactone is not tolerated
Triamterene	Hyperaldosteronism if spironolactone is not tolerated

eGFR: estimated Glomerular Fraction Rate.

Thiazide and thiazide like diuretics

Thiazide and thiazide like diuretics do not have the same structure neither the same site of action, and that would explain the huge disparities concerning their efficiency and side effects. Despite their differences, the recommendations generally do not favor any agent on the other [8-11]. Indeed, 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. Only Australian guidelines encourage when initiating or changing treatment, to prescribe a thiazide-like diuretic, such as chlorthalidone or indapamide in preference to a conventional thiazide diuretics [12].

Hydrochlorothiazide: Much evidence support the inferiority of hydrochlorothiazide compared to other thiazide like agents [1]. In fact, hydrochlorothiazide duration of antihypertensive action is less than 24hour, while indapamide has even in the immediate release form, at least 24-hour duration of action for blood pressure reduction [14]. Duration of action is important in view of the fact that targeting nighttime blood pressure may reduce cardiovascular events [1]. Hydrochlorothiazide is also less potent than converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium channel blockers.

In a network analysis, hydrochlorothiazide alone was shown to be less effective in preventing cardiovascular events in comparison with chlorthalidone and the association hydrochlorothiazide-amiloride [15]. Furthermore, it is inferior to indapamide in improving endothelial function and longitudinal strain in patients with hypertension and diabetes

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[16]. Hydrochlorothiazide is also inferior to spironolactone in improving coronary flow reserve [17].

The only advantage of hydrochlorothiazide over both chlorthalidone and indapamide seems to be it extensive availability in formulations with other classes of antihypertensive drugs and his low price.

Indapamide: Many authors suggest that indapamide is by far the most efficient and tolerable diuretic for hypertensive patients [8]. 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. Indapamide also proved its capacity to reduce left ventricular hypertrophy more than enalapril [18].

Another important feature, is that indapamide do not share with thiazide diuretics their adverse effects on lipid and glucide metabolism, thereby it can safely prescribed in diabetics patient [1].

Indapamide or chlorthalidone: The choice between indapamide and chlorthalidone is quite a relevant question. But the main obstacle that is faced to answer to this question is that there is no trial through literature that compares chlorthalidone and indapamide in the literature.

Kaplan [19] suggests that the choice between these 2 efficient drugs should be based on the 3 following criteria: (i) the ease of use; (ii) the cost; and (iii) hypokalemia which is a considerable drawback of chlorthalidone [8]. Indeed, the fall in serum potassium with 12.5mg doses of chlorthalidone is nearby 0.1mmol/L greater than that seen with equivalent doses of hydrochlorothiazide [1].

The huge disparities of thiazides prescription may be due to that chlorthalidone is only commercialized with atenolol and azilsartan. Likewise, Indapamide is only combined with perindopril.

Potassium sparing diuretics

Both observational and randomized trials have shown that thiazide and thiazide-like diuretics (generally at higher doses) can cause ventricular ectopy and sudden death [1]; the addition of potassium-sparing diuretics might prevent it [20].

Furthermore, in elderly hypertensive patients, both amiloride and triamterene were showed to be efficient when combined to hydrochlorothiazide to reduce cardiovascular events compared to placebo [21]. While spironolactone did not show appropriate evidence for reducing cardiovascular events in hypertensive patients, its place in reducing total mortality in advanced heart failure is well known [22]. Moreover, its efficiency in resistant hypertension is well established [23].

Spironalctone has several others non blood pressure benefits like reducing proteinuria by 61% in proteinuric kidney disease, albuminuria by 60% in type 1 diabetes, and normalizing left ventricular hypertrophy in primary aldosteronism and low renin hypertension [1].

Both spironalactone and eplerenone are indicated in patients affected by heart failure. Although resulting in similar rates of hyperkalemia, eplerenone was shown to have greater impact on systolic blood pressure and to improve endothelial function in hypertensive patients [24,25].

Loop diuretics

Loop diuretics are mostly indicated as an alternative to thiazide diuretics in case of chronic kidney disease with serum creatinine is >1.5mg/dL or eGFR is <30mL/min/1.73m^2 [1]. The antihypertensive effect of low-dose loop diuretics could be improved with nighttime administration.

Conclusion

Diuretics are a popular, heterogenous class of antihypertensive drugs with several decades of clinical application. The concept to replace "one size fits all" paradigm to a more tailored approach in prescribing diuretics to hypertensive patients seems to be rational and appropriate for a better clinical benefit.

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