Thiazide and the Thiazide-Like Diuretics

Dr Reyhane Motamedifard

Nephrologist

INTRODUCTION

- In patients with CKD, lower GFR results in impaired ability to excrete dietary sodium chloride, leading to the onset of positive sodium balance and hypertension
- In patients with CKD stage 4, loop diuretics are generally preferred to thiazides

Thiazide

- Thiazide diuretics emerged in the late 1950s as the first orally effective and well-tolerated antihypertensive agents
- More than a half-century later, they remain among the first-line medications for the treatment of hypertension

Thiazide

- Thiazide diuretics have long been held as being of limited efficacy in CKD
- Thiazides cause a negative sodium balance and reduce body fluids by 1–2 l within the first 2–4 weeks and these effects go along with improvement in hypertension control

Salt-sensitivity of hypertension in CKD

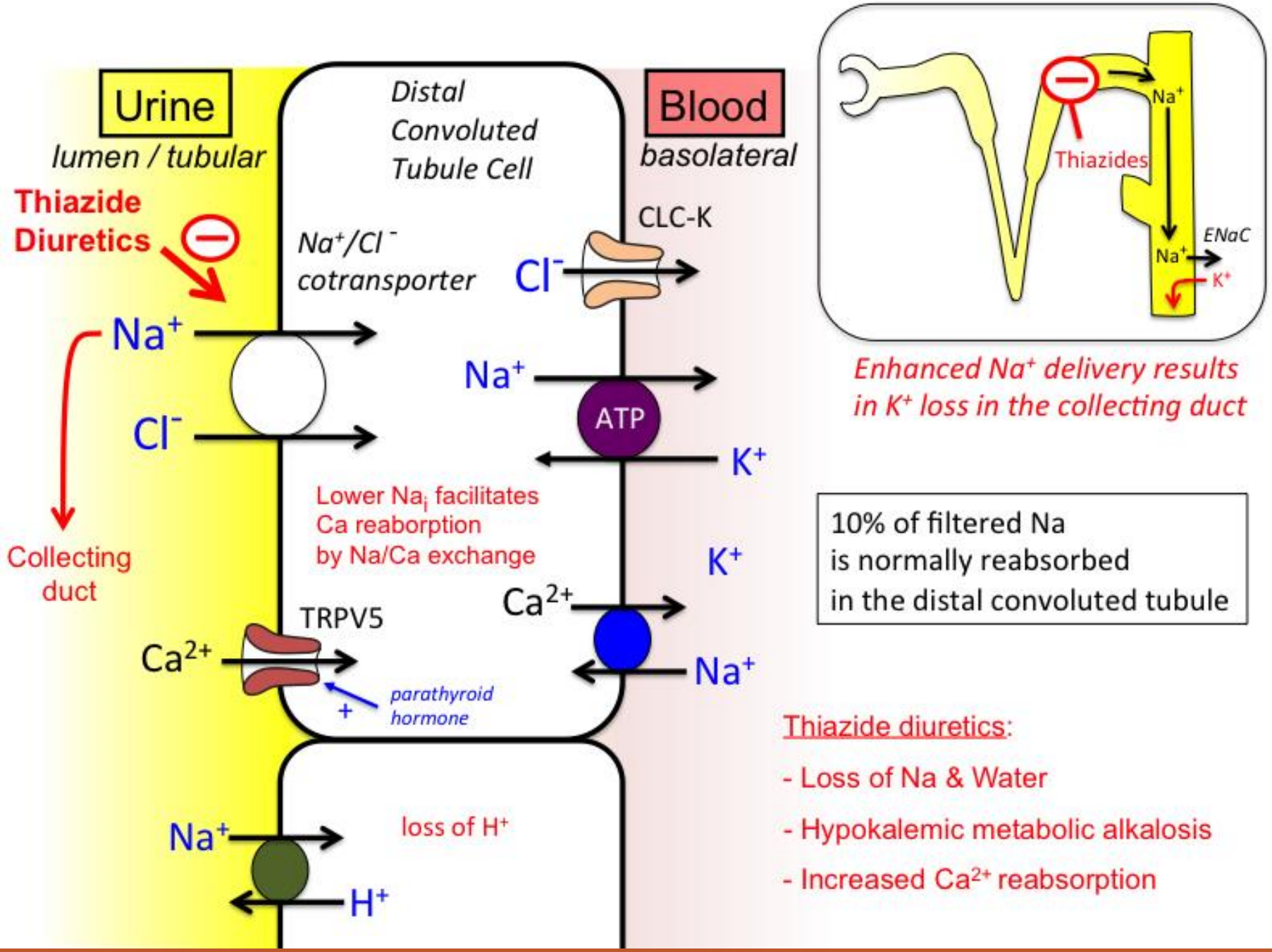
- In CKD
  - Sodium retention, imbalance of vasoconstrictors [RAAS, sympathetic nervous system, endothelin-1] that prevail over vasodilators (nitric oxide, vasodilatory prostaglandins) and vascular stiffness all contribute to raising BP
  - Among these factors, salt retention is unquestionably dominant

Salt-sensitivity of hypertension in CKD

- Due to reduced proximal sodium reabsorption, distal sodium delivery is augmented in CKD, which triggers a 4- to 5-fold increase in distal sodium reabsorption

Thiazides
Mechanism of action

- Thiazides act by inhibiting the sodium–chloride cotransporter mainly located in the distal convoluted tubule of the nephron, which is responsible for ~7% of total sodium reabsorption


Urine
lumen / tubular
Thiazide Diuretics
Distal Convoluted Tubule Cell
Blood
basolateral
Na+/Cl- cotransporter
CLC-K
Cl-
Na+
Cl-
Na+
ATP
K+
Lower Nai facilitates Ca reaborption by Na/Ca exchange
Collecting duct
K+
Ca2+
TRPV5
Ca2+
Na+
parathyroid hormone
+
Na+
loss of H+
H+
Thiazides
Na+
ENaC
Na+
K+
Enhanced Na+ delivery results in K+ loss in the collecting duct
10% of filtered Na is normally reabsorbed in the distal convoluted tubule
Thiazide diuretics:
- Loss of Na & Water
- Hypokalemic metabolic alkalosis
- Increased Ca2+ reabsorption

Thiazides
Mechanism of action

- The main mechanism of the BP-lowering effect of these drugs is enhanced natriuresis, which in turn reduces ECV, cardiac preload and output
- The antihypertensive effect of chronic thiazide use is abolished by a very high salt intake (20 g/day of NaCl for 2 week)

Thiazides
Mechanism of action

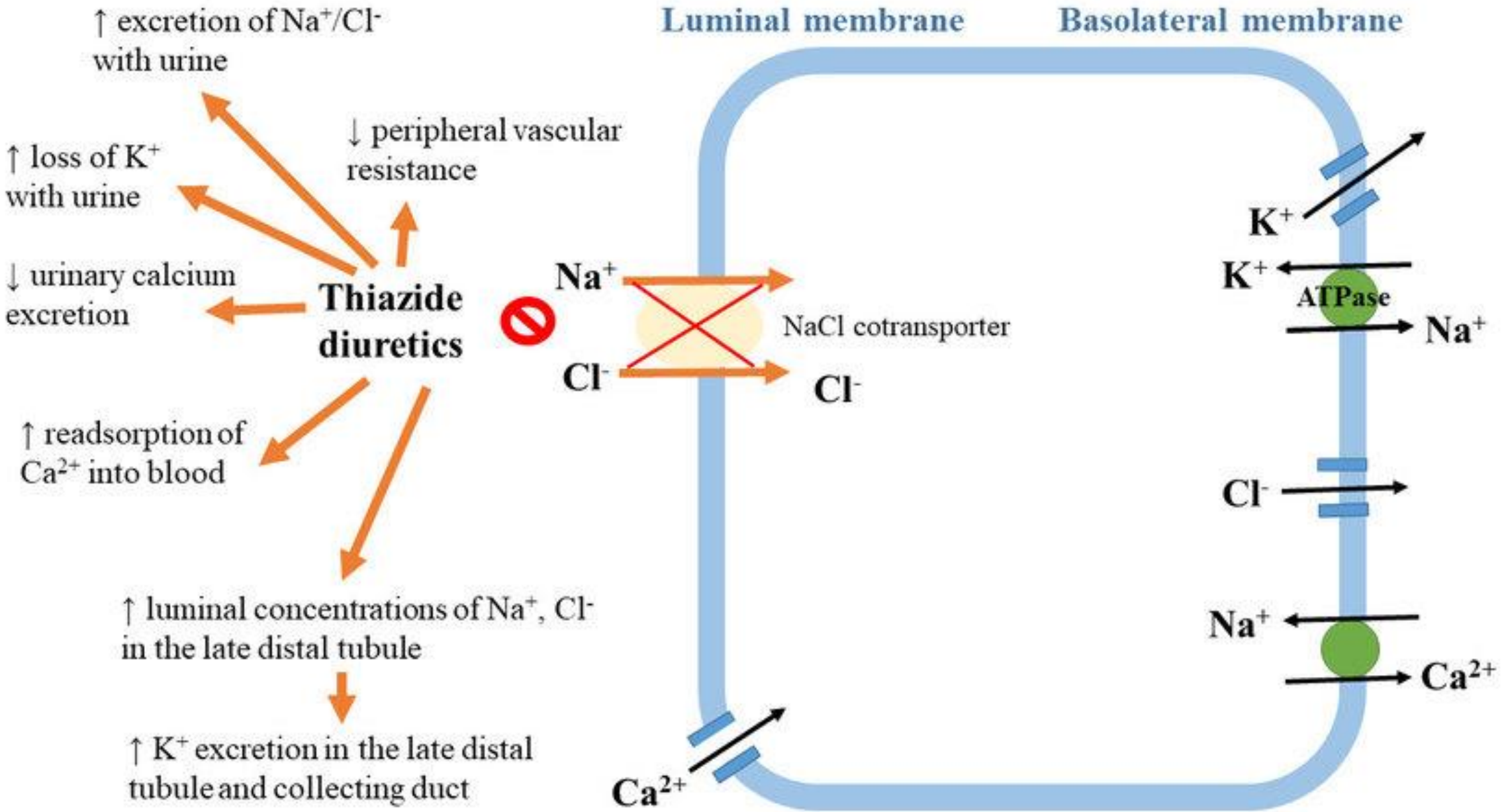
- The long-term antihypertensive response to thiazides seems unrelated to the initial reduction of plasma volume
- Patients with Gitelman's syndrome who lack a functional NCC have been shown to respond with a decrease in BP and arterial dilatation, suggesting a secondary site or mechanism of action of thiazide

Thiazides
Mechanism of action

- Reduction in vascular reactivity
- Hyperpolarization of the vascular smooth muscle cell
- Inhibition of voltage-dependent L-type calcium channels
- Enhanced nitric oxide release

Thiazides
Mechanism of action

- It is likely therefore that the antihypertensive efficacy of thiazides may be initially induced by their natriuretic properties and complemented in the long-term by direct vasodilating effects


↑ excretion of Na+/Cl- with urine
↓ peripheral vascular resistance
↑ loss of K+ with urine
↓ urinary calcium excretion
Thiazide diuretics
↑ readsorption of Ca2+ into blood
↑ luminal concentrations of Na+, Cl- in the late distal tubule
↑ K+ excretion in the late distal tubule and collecting duct
Luminal membrane
Basolateral membrane
Na+
Cl-
NaCl cotransporter
Cl-
K+
K+
ATPase
Na+
Cl-
Na+
Ca2+
Ca2+

Onset of diuresis

- The onset of diuresis appears within 1–3 hours and lasts for 6–18 hours with thiazide-type agents and longer with thiazide-like diuretics
- Most thiazides have a half-life of ~8–12 hours, thus allowing effective once-daily administration

Difference in pharmacological properties and efficacy

Table 2: Pharmacological properties of thiazide-type and thiazide-like diuretics.

Diuretics	Bioavailability (%)	Onset (hours)	Peak (hours)	Protein binding (%)	Half-life (hours)	Duration of action (hours)	Route of excretion (%)	Daily dose (mg)
Thiazide-type								
Hydrochlorothiazide	70	2	4–6	58	6–14	6–12	Renal (95)	12.5–25
Hydroflumethiazide	50				17	12–18	Renal (40–80)	12.5–25
Polythiazide	100				25		Renal (25)	2–4
Bendroflumethiazide	95	2	3–6	96	3–4	8–16	Renal (30)	1.25–5
Thiazide-like								
Xipamide	95	1	1–2	98	5–8	12–20	Renal (30)	5–40
Chlorthalidone	65	2.5	2–6	98	47	40–60	Renal (65)	12.5–50
Metolazone	65	1	2–4	96	8–14	24–48	Renal (80)	2.5–10
Indapamide	95	1–4		79	18	24	Renal (60)	1.25–2.5

Pharmacokinetics

- There is a direct relationship between the elimination half-life of thiazides and their expected duration of action
- Synergy resulting from coadministration with other antihypertensive classes can serve to effectively prolong the duration of thiazide antihypertensive action

Chlorthalidone

- Chlorthalidone use could be considered in patients with treatment-resistant hypertension when spironolactone cannot be administered or must be withdrawn due to side effects

Pharmacokinetics
Chlorthalidone

- Chlorthalidone is unique among thiazides due to its substantially longer elimination half-life, averaging 50–60 hours with chronic dosing
- The prolonged half-life is a distinct practical advantage of chlorthalidone, as it remains a viably effective antihypertensive even when dosed less frequently than daily

Pharmacokinetics
Indapamide

- Indapamide has a pharmacokinetic profile residing between that of hydrochlorothiazide and chlorthalidone
- It is widely distributed throughout the body with a large (25 L) volume of distribution, and highly protein bound
- It is extensively hepatically metabolized (<7% excreted as unchanged drug in urine), and also has a much longer half-life than hydrochlorothiazide, with a biphasic terminal half-life of about 16 hours

Pharmacokinetics

Indapamide and chlorthalidone

- Indapamide and chlorthalidone have shown greater effects in decreasing platelet aggregation
- Chlorthalidone also decreases vascular endothelial growth factor C, which is implicated in angiogenesis and has favorable effects on vascular permeability which could provide benefit in lowering risk of heart failure

Pharmacokinetics

- Indapamide reduces oxidative stress that may contribute to benefit in lowering cardiovascular events
- Both chlorthalidone and indapamide increase renal prostaglandins
- Hydrochlorothiazide, indapamide, and chlorthalidone all appear to have similar antiproteinuric effects

Pharmacokinetics

- Chlorthalidone ranges from 1.5 to 3 times more potent than hydrochlorothiazide, when considering doses required to achieve similar levels of blood pressure reduction

Thiazide	Elimination half-life	Vd	Metabolism	Oral bioavailability	Protein binding	Red blood cell distribution
Hydrochlorothiazide	Biphasic, ranges from 2 to 15 hours, averaging about 6 hours	2–4 L/kg	50–70% excreted renally	70%	40%	3.5:1 RBC to plasma
Chlorthalidone	40–60 hours	3–13 L/kg	50–74% excreted renally as unchanged drug	65%	75%	98% (bound to carbonic anhydrase)
Indapamide	14 hours	25 L	Hepatic (extensive)	100%	71-79%	6:1 RBC to plasma

Pharmacokinetics

- The 2017 AHA Guidelines which recommends preferential use of thiazide-like diuretics over conventional thiazides
- The 2018 Resistant Hypertension Guidelines which recommend that thiazides be replaced by thiazide-like diuretics as a first step in management

Pharmacological properties

- The absorption of thiazides occurs rapidly in the gastrointestinal tract and is influenced by food intake, which increases absorption, and renal disease or heart failure, which have an opposite effect
- Thiazides are extensively bound to plasma proteins, which limit their glomerular filtration, and are excreted in the urine by proximal tubular secretion

Chlorthalidone

- Chlorthalidone has the longest half-life because >90% of the drug is bound to erythrocyte carbonic anhydrase, thus reaching a 10-fold greater concentration in red blood cells than in plasma
- Therefore erythrocytes act as a reservoir that allows a constant flow back of the chlorthalidone to the plasma with persistence of diuretic efficacy when the drug is administered less frequently than once a day or a dose of the drug is missed

Clinical Use Of Thiazide Diuretics

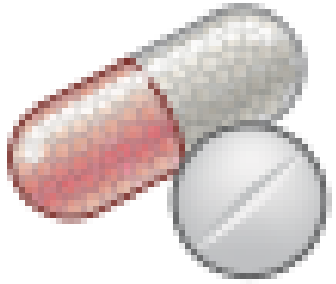
- The use of thiazide diuretics has also been proposed in combination with loop diuretics in patients with HF in order to overcome diuretic resistance induced by increased sodium avidity in distal tubules accompanied with chronic loop diuretic use
- The most commonly used agent is metolazone, which has been suggested to be superior to other thiazide molecules in CKD patients

chronic kidney disease

- Thiazides were believed to lose efficacy with diminished renal function in part due to decreased drug delivery to the site of action and the small amount of sodium reabsorbed there under normal conditions
- Chlorthalidone, perhaps because of its long-acting nature, has more recently been shown to remain effective at usual low doses in patients with poorly controlled hypertension and advanced chronic kidney disease

Side effects

- Hypovolemia, hypokalaemia, hypomagnesemia, hyponatremia, hypercalcemia and hyperchloremic alkalosis are all well-known side effects of thiazides
- Other metabolic adverse effects of chronic thiazide use are hyperglycaemia and hyperuricemia
- Hyperglycaemia may depend on hypokalaemia because low-plasma potassium impairs insulin secretion



Thiazides: natriuretic properties and direct vasodilating effects.

BUT:

Low K^+

Low Mg^{++}

High Ca^{++}

Alkalosis

AKI

Side effects
hyperuricemia

- Thiazides decrease urate clearance and increase serum urate levels by up to 35% in a dose-dependent manner

Side effects
hyperuricemia

- Reabsorption in the proximal tubule dependent on the diureticinduced volume contraction and impaired tubular secretion of uric acid, because thiazides and uric acid compete for the same tubular transporter

Side effects
Hyponatremia

- Hyponatremia is another common finding with thiazides, appearing similarly across agents when adjusted for potency

- Risk factors predispose patients to thiazide-induced hyponatremia:
  - Older age
  - Female gender
  - Psychogenic polydipsia
  - Concurrent antidepressant use

Side effects
Hypomagnesemia

- Less commonly, hypomagnesemia can occur with thiazides
- It is thought that blockage of the sodium chloride transporter in the distal tubule by thiazides inhibits magnesium reabsorption, either through direct or indirect mechanisms

Safety and tolerability

- Coadministration of a thiazide with a potassium-sparing agent has been shown to blunt hypomagnesaemia, so it is theorized that the urinary excretion of potassium induced by thiazides may be related to the mechanism producing hypomagnesaemia

Safety and tolerability

- Given that magnesium is not as routinely monitored as other electrolytes, evaluation for hypomagnesemia should be considered in patients taking chronic thiazide therapy, especially at high potency doses, or when they are used in combination with other medications that induce hypomagnesemia (e.g., proton-pump inhibitors)

Contemporary use patterns

- Chlorthalidone is only available in a 25 mg, unscored tablet, lacks availability in combination with ACE inhibitors, or potassium-sparing agents, while hydrochlorothiazide is widely available in popular combinations
- Indapamide is rarely used in the United States, likely for similar pragmatic reasons as chlorthalidone


NDC 57664-640-88
Chlorthalidone
Tablets USP
25 mg
Rx Only
100 Tablets
SUN
PHARMA


NDC 0591-5783-01
Atenolol and
Chlorthalidone
Tablets USP
100 mg/
25 mg
Watson
100 Tablets
Rx only
Each tablet contains:
Usual dosage:
Dispense
Store
Manufactured By:
Watson Pharma Private Limited
Distributed by: Watson Pharma, Inc.


chlorthalidone
dreamstime.com


Indapamide
2.5mg Tablets
2.5mg
28 tablets
Niche Generics Limited


Indapamide
Generis® 1,5 mg
Prolonged-release
tablets MG
30


1.5
NORMALIX®
Indapamide SR


NATRILIX® SR
30 comprimés - 30 tablets - 30 comprim

Thiazide and the Thiazide-Like Diuretics: Review of Hydrochlorothiazide, Chlorthalidone, and Indapamide

Michael E. Ernst[1,2,•] and Michelle A. Fravel[1]

The term *thiazide* is universally understood to refer to diuretics that exert their principal action in the distal tubule. The thiazide class is heterogenous and can be further subdivided into compounds containing the benzothiadiazine ring structure—the *thiazide-type* (e.g., hydrochlorothiazide)—and those lacking the benzothiadiazine ring—the *thiazide-like* (e.g., chlorthalidone and indapamide) drugs. *Thiazide-like* agents are longer acting and constitute the diuretics used in most of the cardiovascular outcome trials that est
benefits of treatment with diuretics, but pragmatic aspe
as lack of availability in convenient formulations, limit t
Regardless of class heterogeneity, thiazides have retai
portance in the management of hypertension for over

GRAPHICAL ABSTRACT

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CKJ Review

CKJ REVIEW

Thiazide diuretics are back in CKD: the case of chlorthalidone

Roberto Minutolo [1], Luca De Nicola [1], Francesca Mallamaci[2,3] and Carmine Zoccali [4]


Thank You!