Diuretics (Saluretics)
Lecture 2

- High ceiling, loop, high efficacy diuretics:

Furosemide (Frusemide) O; I.V

Bumetanide O; I.V

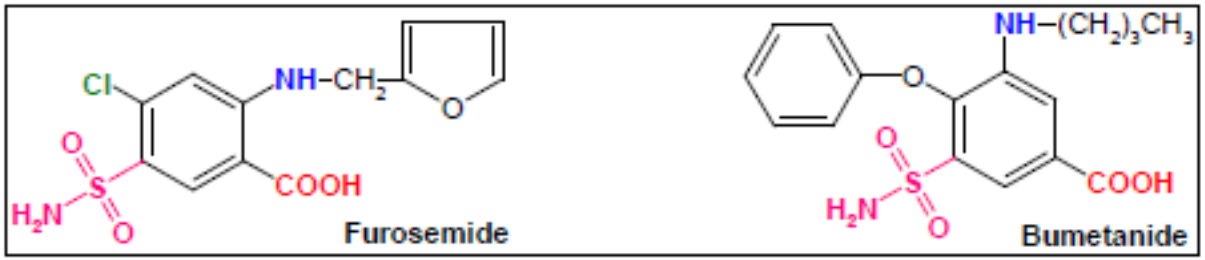
Ethacrynic acid (prodrug) O; I.V

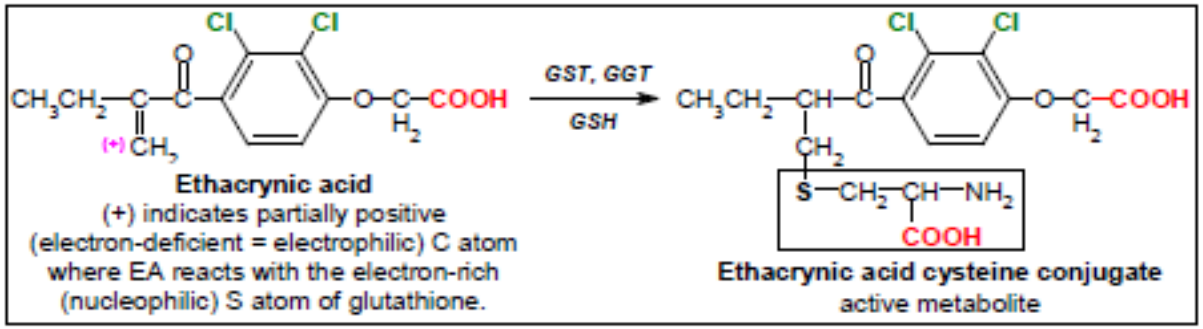
Torsemide (active metabolites) O; I.V

The strongest diuretics, have rapid OOA and short DOA

- Site of action

Thick segment of ascending loop of Henle


Furosemide
Bumetanide


GST, GGT
GSH
Ethacrynic acid
(+) indicates partially positive (electron-deficient = electrophilic) C atom where EA reacts with the electron-rich (nucleophilic) S atom of glutathione.
Ethacrynic acid cysteine conjugate
active metabolite

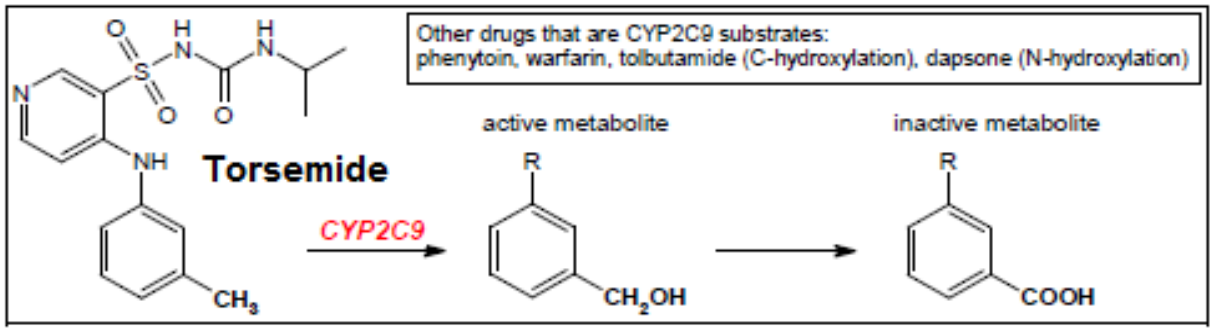

Other drugs that are CYP2C9 substrates:
phenytoin, warfarin, tolbutamide (C-hydroxylation), dapsone (N-hydroxylation)
Torsemide
CYP2C9
active metabolite
inactive metabolite

Table 1. Loop Diuretic Comparison to Furosemide

Loop Diuretic	Bioavailability*	Equivalent Dosing*	Dosing Frequency
Bumetanide (Bumex®) **IV**	100%	1 mg	Daily to Q12H
Bumetanide (Bumex®) **Oral**	80%-90%	1 mg	Daily to Q12H
Torsemide (Demadex®) **IV**	100%	20 mg	Daily to Q12H
Torsemide (Demadex®) **Oral**	80%-100%	20 mg	Daily to Q12H
Furosemide (Lasix®) **IV**	100%	20 mg	Daily to Q8H
Furosemide (Lasix®) **Oral**	~50% (varies)	40 mg	Daily to Q8H
Ethacrynic Acid (Edecrin®) **IV**	100%	50 mg	Daily to Q8H
Ethacrynate Sodium (Edecrin®) **Oral**	100%	50 mg	Daily to Q8H

*Bioavailability and dose response depends on disease state and prior exposure to diuretics.

- Loop diuretics MOA

Inhibition of $Na^+/K^+/2Cl^-$ transporter leading to 10-25% loss of filtered Na^+

↑ dose → ↑ diuretic effect; over-treatment → dehydration

Effective even at GFR below 10 ml/min (loop diuretics are most effective in patients with renal insufficiency = creatinine level > 2.5 mg/dl) or resistant cases to other diuretics

Loop diuretics ↑ excretion of Na^+, Cl^-, K^+, H^+, H_2O and HCO_3^- (weak CA inhibitory effect)

They are effective orally (OOA 30-60 min ; DOA ≈ 6 hrs) and parenterally (OOA 5 min; DOA ≈ 2 hrs)

They are albumin bound, eliminated in urine by filtration and tubular secretion and 1/3 rd of oral dose is excreted in bile

- Clinical uses to loop diuretics:

- Acute pulmonary edema
- Edematous states (ascitis; CHF; renal failure…etc)
- Considered 1st line therapy in patients with CHF
- Hypertension
- Hypercalcemia
- Syndrome of Inappropriate ADH secretion

- Side effects to loop diuretics:

- Hypokalemia; hypomagnesemia
- Hypocalcemia
- Irreversible ototoxicity (usually dose related and more common with I.V administration)
- Dehydration; hyperglycemia; hyperuricemia
- Headache; dizziness (due to ↓ in BP)
- Allergic reactions; alkalosis

- Potassium sparing, low efficacy diuretics;

a. Aldosterone antagonists

Spironolactone; Eplerenone

Aldosterone → ↑ synthesis of Na^+-K^+ ATPase → ↑ Na^+ reabsorption, ↓ reabsorption of K^+ (↑excretion of K^+ & H^+)

Aldosterone antagonists →↑ Na^+ excretion & ↓ K^+ excretion

- Site of action of potassium sparing diuretics

Collecting ducts

Only effective in presence of aldosterone (competitive antagonists)

Given orally; have delayed OOA

Weak diuretics, usually combined with other antihypertensives or thiazides

Have great benefit in improving myocardial function in patients with heart failure

Eplerenone is more potent than Spironolactone

- Clinical uses to potassium sparing diuretics:

- Hypertension
- CHF
- Hyperaldosteronism (1° or 2°)
- Hypokalemia
- Hirsutism (antiandrogenic effect)

- Side effects to potassium sparing diuretics:

- Hyperkalemia → cardiac arrhythmias

More common in patients with diabetes, chronic renal disease or patients on ACE inhibitors

More severe with eplerenone

- Gynecomastia in ♂'s (rare with Eplerenone)

- Breast tenderness in ♀'s (rare with Eplerenone)

b. None steroidal potassium sparing diuretics:

Amiloride; Triamterene

- Site of action: DCT, collecting duct
- MOA

Blockade of epithelial Na^+ channels →↓ Na^+ reabsorption, ↓ K^+ excretion

Orally effective and available alone or combined with thiazides

- Clinical uses:

- Hypertension

- Hypokalemia

- Side effects:

- Hyperkalemia

- Renal tubular damage especially reported following the use of Triamterene + Hydrochlorothiazide

- The problem of diuretic-induced hypokalemia:

- Thiazide or loop diuretic + oral K^+ supplement

- Combine thiazide or loop diuretic with a K^+ sparing diuretic

** Unlike thiazide diuretics, loop and K^+ sparing diuretics have no effects on blood lipids

- Reasons for diuretic resistance or refractoriness (Therapeutic Failure):

- Continued ingestion of salt

- Impairment of organic acid secretion mechanisms in the proximal tubules due to: diseases or drugs

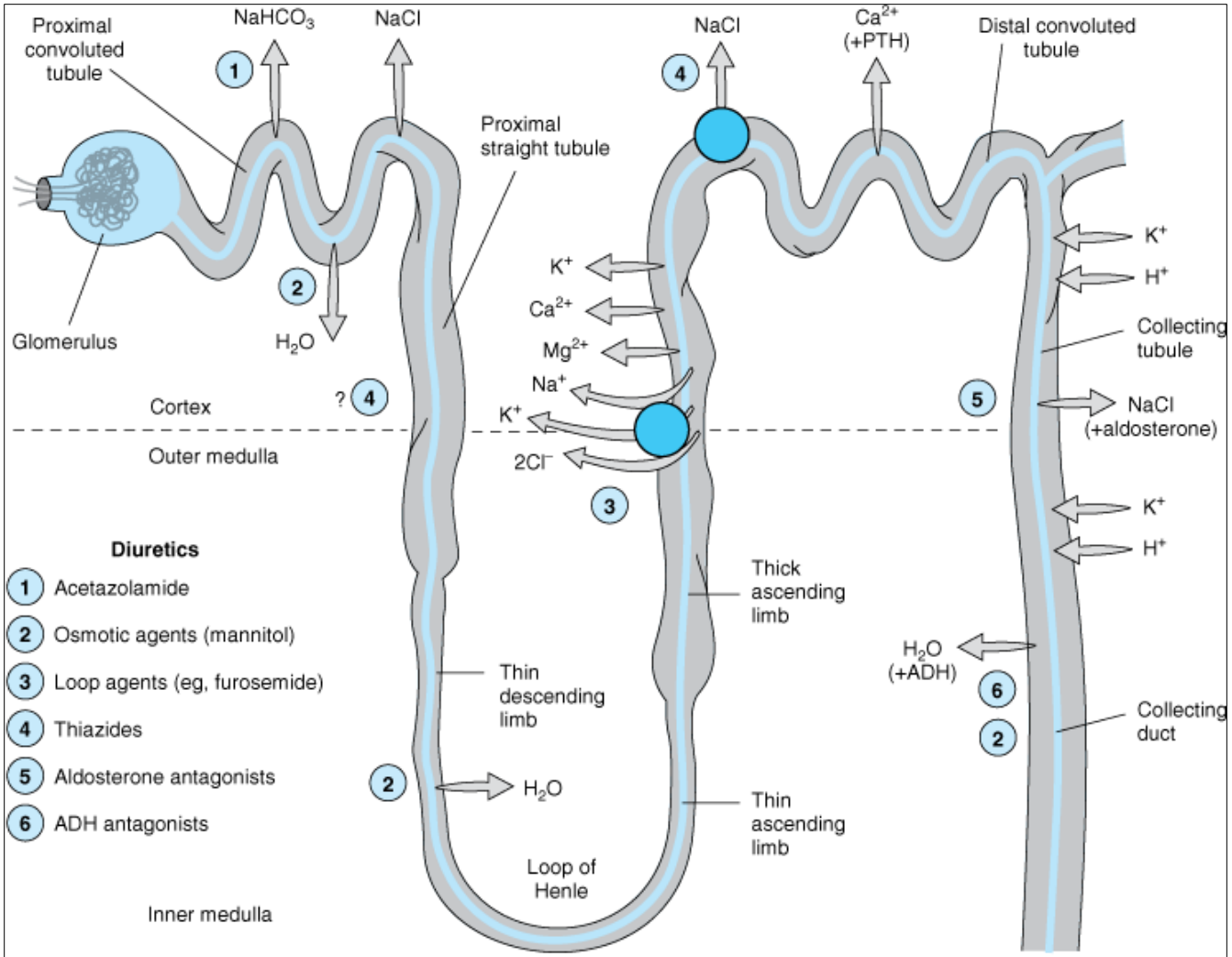
- Secondary hyperaldosteronism

Cont. diuretic therapeutic failure...

- Lowered renal blood flow $\rightarrow\uparrow$ Na^+ reabsorption (postdiuretic salt retention)
- Lowered bioavailability of the drug

- Management of diuretic resistance

Restriction of sodium intake, changes in dose, changes in timing, and combination of diuretic therapy



Source: Katzung BG: *Basic & Clinical Pharmacology*, 10th Edition: http://www.accessmedicine.com

Mechanism and site of action of diuretics