GENITOURINARY SYSTEM

SUBJECT : Pharma table

LEC NO. : Lec2

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Loop Diuretics

Drug	Furosemide(Lasix): most commonly used ? Bumetanide ? Torsemide ? Ethacrynic acid: used infrequently due to its adverse effect profile.	All, but ethacrynic acid contain sulfonamide group, but generally don't cause allergic rxn in patients who are allergic to sulfonamide antibiotics.			
MOA	Diuresis	inhibition of Na/K/2Cl cotransporter results in reduced reabsorption of these ions into the renal medulla, creating a lower osmotic pressure in the medulla, which then reduces water reabsorption in water permeable segments.	25% to 30% of filtered NaCl is filtered in the ascending loop therefore loop diuretics have the greatest diuretic effect .	They show 'high celling effect' with great diuretic response to a small change in the dose.	
	Increased urinary calcium excretion: Unlike thiazides, loop diuretics increase the Ca2+ content of urine. They are used in hypercalcemia treatment				
	Venodilatation : loop diuretics cause acute venodilatation and reduce left ventricular filling pressures via enhanced prostaglandin synthesis.				
Pharmacokinetics	Loop diuretics are administered orally or parenterally.	Furosemide has unpredictable bioavailability of 10% to 90% after oral administration.	Bumetanide and torsemide have reliable bioavailability of 80% to 100%, which makes these agents preferred for oral therapy.	Furosemide and bumetanide DoA is˜ 6h, and moderately longer for torsemide.	
Therapeutic uses	Edema: loop diuretics are used more for the therapy of edema than long term therapy of hypertension. They are the drugs of choice for treatment of pulmonary edema and acute/ chronic peripheral edema caused from heart failure or renal impairment. Because of their rapid onset of action, the drugs are useful in emergency situations such as acute pulmonary edema.	Hypercalcemia	Hyperkalemia		
Adverse effects	Acute hypovolemia: Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmias. 2. Hypokalemia: t	Hypokalemia: the most common adverse effect of the loop diuretics. The loss of K+ from cells in exchange for H+ leads to hypokalemic alkalosis. Use of potassium-sparing diuretics or supplementation with K+ can prevent the development of hypokalemia.	Hypomagnesemia	Ototoxicity: Reversible or permanent hearing loss may occur with loop diuretics, particularly when at fast rates, at high doses, or when used in conjunction with other ototoxic drugs (for example, aminoglycoside antibiotics). Ethacrynic acid has been known to have a more ototoxic potential than the other members	Hyperuricemia: may cause or exacerbate gouty attacks.
Drug-drug interactions	Aminoglycosides and cephalosporins: Risk of ototoxicity	Digoxin: combination with loop diuretics (also with thiazide and potassium-sparing diuretics) increases the risk of digoxin toxicity (anorexia, nausea, neurological symptoms, fatal arrhythmias).	NSAIDs reduces efficacy of diuretics.	Lithium: can cause lithium retention.	
Causes & management of loop diuretics Resistance	unsatisfactory rate of diuresis/ natriuresis despite an adequate diuretic regimen				
	I. Defective intestinal absorption in decompensated HF (of oral furosemide) Give the diuretic IV.	II. Defective plasma protein binding in hypoalbuminemic states (liver cirrhosis & nephrotic syndrome) → extravascular diffusion of diuretic →↓ renal excretion Mix the diuretic with albumin prior to infusion.	III. Defective excretion of diuretics by the acid secretory system in renal impairment due to accumulation of acids. ↑ Dose of diuretics	Hypertrophy of distal tubular cells (on chronic use →↑ Na+ reabsorption →blunts the action of the diuretic) II. Add thiazides	activation Na retaining mechanism such as aldosterone. Na+ lost by loop diuretics reabsorbed in exchange with K+ in distal tubules (under the effect of aldosterone): Add the aldosterone antagonist spironolactone.

Potassium-Sparing Diuretics

Aldosterone antagonists:	spironolactone and eplerenone				
MAO	Both synthetic antagonists of aldosterone.	Aldosterone promotes expression and translocation of ENac (epithelium sodium channel) and expression of Na/K ATPase.	Aldosterone antagonists prevent Na+ reabsorption and K+ and H+ secretion.	Eplerenone is more selective and causes less endocrine effects (gynecomastia) than spironolactone, which also binds to progesterone and androgen receptors.	
Therapeutic uses	Edema: Given in high doses for trx of edema associated with secondary hyperaldosteronism, such as hepatic cirrhosis and nephrotic syndrome. Spironolactone is the diuretic of choice in patients with hepatic cirrhosis with fluid in the peritoneal cavity (ascites).	Hypokalemia: given in conjunction with thiazide or loop diuretics to prevent K+ excretion that occurs with those diuretics.	Heart failure: given at lower doses to prevent myocardial remodeling mediated by aldosterone. Decrease mortality in patients with reduced ejection fraction.	Resistant hypertension: this effect can be seen in those with or without elevated aldosterone levels.	Polycystic ovary syndrome Spironolactone is often used off-label for the treatment of polycystic ovary syndrome, it blocks androgen receptors and inhibiting steroid synthesis
Adverse eects	Hyperkalemia: The most common side effect. Dose-dependent and increases with renal dysfunction or use of other potassium-sparing agents such as angiotensin-converting enzyme inhibitors and potassium supplements.	Gynecomastia in male patients and menstrual irregulation in female: only associated with Spironolactone use.			
Triamterene and amiloride	Block epithelial sodium channels, resulting in a decrease in Na+ /K+ exchange.	Commonly used in combination with other diuretics, for their potassium-sparing properties.			
Notes	Aldosterone promotes expression and translocation of ENac (epithelium sodium channel) and expression of Na/K ATPase.	Aldosterone antagonists prevent Na+ reabsorption and K+ and H+ secretion.	Eplerenone is more selective and causes less endocrine effects (gynecomastia) than spironolactone, which also binds to progesterone and androgen receptors.		

Other diuretics

Carbonic Anhydrase Inhibitor	Acetazolamide	inhibits carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium.	There is decreased ability to exchange Na+ for H+ • HCO3– (bicarbonate) is retained in the lumen, with marked elevation in urinary pH. The loss of HCO3– causes a hyperchloremic metabolic acidosis.	Less efficacious than the thiazide or loop diuretics. Most of the fluid loss is reclaimed in loop of Henle.
Therapeutic uses	Glaucoma: Oral acetazolamide decreases the production of aqueous humor and reduces intraocular pressure in patients with chronic open-angle glaucoma. Dorzolamide & Brinzolamide are given by topical application to minimize systemic and renal side effects	Altitude sickness used in the prophylaxis of symptoms of altitude sickness.		
Adverse eects	1. Metabolic acidosis (mild) 2. Potassium depletion	3. Renal stone formation 4. Drowsiness 5. Paresthesia (tingling sensation)	The drug should be avoided in patients with hepatic cirrhosis, because it could lead to a decreased excretion of NH_4^+ .	
	Uses			
Osmotic Diuretics	Mannitol	Maintenance of urine flow following acute toxic ingestion of substances capable of producing acute renal failure.	Mainstay of treatment for patients with increased intracranial pressure.	Mannitol is not absorbed when given orally and should be given intravenously
	Adverse effects:	Dehydration and extracellular water expansion from the osmotic effects in the systemic circulation. This causes hyponatremia until diuresis occurs.	Mannitol is not commonly used in patients with edema, because the initially it induces further volume expansion, which can precipitate the development of pulmonary edema in patients with heart failure.	