**Treatment of Benign Prostatic Hyperplasia**

**Alpha-1 Receptor Blockers**

- Doxazosin
- Tamsulosin
- Terazosin

**5-alpha-reductase Inhibitors**

- Dutaseride
- Finasteride

**ALPHA-1 RECEPTOR ANTAGONISTS** (targeting the smooth muscle)

**Doxazosin** (Cardura). This is a long acting alpha-1 receptor antagonist. This was used as an anti-hypertensive in the cardio/ANS block, but can also be used to increase urinary flow. It has a rapid onset with large effectiveness, but unfortunately produces hypotension and dizziness. For this reason, you start at a low dose and slowly increase it to the desired urinary flow rate with monitoring of blood pressure, up to 8 times the initial does (1mg/day to 8mg/day)

**Tamsulosin** (Flomax). This is the most commonly prescribed prostate–urinary flow medication in the general population today. It is selective for the alpha-1-a receptor that is highly expressed on the prostate. This is a Doxazosin without any of the side effects of systemic alpha-1 blockade. That means you do not have to titrate and there is little risk for hypotension and dizziness, and, because of its increased selectivity, there is a greater improvement of urinary flow.

**** **Terazosin** (Hyrtin). Another long acting alpha-1 receptor antagonist that also induces prostate apoptosis not only improving flow rates but also shrinking the prostate. Same side effects as Doxazosin with a longer half life. When combined, smaller doses of each drug can be used, and therefore less side effects.

**5-ALPHA-REDUCTASE INHIBITORS** (targeting the prostatic growth signal, DHT)

**Dutaseride** (Avodart). This drug targets and competitively inhibits both the type 1 (skin) and type 2 (prostate) 5-alpha-reductase isoenzymes. This drastically drops the formation of DHT (di-hydrotestosterone) which induces prostatic growth. The end result is a shrinking of the prostate and stagnation of further growth. Combination therapy with an alpha-1 blocker shows superior results to monotherapy with either drug. Patients should not donate blood for risk of transferring blood to pregnant females. As it is absorbed through the skin, pregnant females should not handle this medication. It has a huge half-life (like 5 weeks). Because it is based on the growth (or lack thereof) of the prostate, it requires up to a year for maximal results. This should also work as a hair loss drug, but is not marketed as such, as Finasteride is.

**Finasteride.** Another competitive inhibitor but only for type 2 5-alpha-reductase. It’s the same as Dutaseride, but is also marketed for male pattern baldness. This is the drug more frequently prescribed for both, Dutaseride is the original, “learning” drug.
Sildenafil (Viagra). Selective Type 5 Phosphodiesterase Inhibitor (PDE-5), resulting in the maintenance of cGMP and therefore Nitric Oxide elaboration, leading to relaxation/dilation of cavernous smooth muscle. This drug was discussed in the cardio block as a possible blood pressure medication, and, because it works on the nitric oxide pathway, can have serious side effects with coadministration of nitrates (nitroglycerin). Therefore, nitrates + sildenafil is contraindicated. Transient green-blue visual anomalies have been reported because of the weak selectivity of PDE-6 found in the retina. Taken one hour prior to sexual activity, this can enhance and prolong the erection.

Tadalafil (Cialis). Its sildenafil with a long half-life (17.5 hours) and a shorter onset of action (16 minutes). It has higher selectivity for PDE-5 and has no risk of vision abnormalities.

Verdenafil (Levitra). The other Viagra.

Alprostadil (PGE1). This prostaglandin is a direct vasodilator that does not target any other pathway (refractory to Viagra). This we talked about in the inflammation block. You have to inject or rub topical cream directly onto the cavernosa to induce an erection. Penile pain is common, and people don’t like using this drug. This will probably be a distracter on an ED or BPH question.
**Pharm Renal and Urinary By Drug**

**Tubule Diuretics**

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<th>Carbonic Anhydrase Inhibitors (Proximal Tubule)</th>
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<th>Thiazides (Distal Convoluted Tubule)</th>
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<td>Acetazolamide</td>
<td>Furosamide, Torsemide, Ethacrynic Acid</td>
<td>Chlorothiazide, Hydrochlorothiazide</td>
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**PROXIMAL CONVOLUTED TUBULE**

**Acetazolamide.** This is an ancient drug that really isn’t used anymore. It turns out that affecting the proximal tubule doesn’t really do that much for diuretics, since the rest of the tubule will ramp up and recover most of what is lost. It is a **carbonic anhydrase inhibitor** which inhibits the formation of CO₂ and water from H⁺ and HCO₃⁻. This causes an **alkalization of the urine** (secretion of HCO₃⁻) and a resultant **metabolic acidosis.** Its primary effect is to limit reabsorption of Na, and therefore water, acting as a diuretic. It is indicated in **CHF-edema, glaucoma,** and **acute mountain sickness.** A common side effect is **parasthesia** (tingling in the extremities) hearing dysfunction, tinnitus, loss of appetite, etc. Basically, this drug is a carbonic anhydrase inhibitor that is not used anymore.

**LOOP OF HENLE**

**Furosamide** (Lasix). Blocks the **sodium-potassium-dichloride cotransporter in the thick ascending limb of Henle.** This causes an increased loss of sodium in the urine. Where salt goes, water follows, causing a diuresis in addition to naturesis. Because this increases distal sodium delivery to the collecting tubules, sodium is reabsorbed and potassium is lost, resulting in **hypokalemia.** Not enough sodium can be reabsorbed here to cancel the effects of furosamide, but sufficient upregulation causes a loss of potassium. Rapid administration IV for pulmonary edema can result in **hearing loss.** There is an additional affect on **left ventricular function** that occurs prior to diuresis and in anuric patients. Lasix **Lasts Six** Hours and so must be taken frequently during the day in order to control blood pressure and edema. NSAIDs and Probenacid compete for excretion in the **renal tubules.** Sulfonamide allergies.

**Torsemide.** The same thing as lasix, with an increased risk of allergies and is hepatically metabolized. See Torsemide, think Furosamide.

**Ethacrynic Acid.** This is lasix that is **not a sulfonamide,** so can be used safely in people with sulfa allergies where Furosamide cannot. Its drug profile was a long winded version of lasix that specifically identified **edema** from CHF or Cirrhosis, **Ascites** from malignancy, or emergent IV use (even though ERs use Lasix). It does have an **increased ototoxicity** over furosamide, so it is not used unless allergies forces its use.
DISTAL CONVOLUTED TUBULE (Thiazides)

**Chlorothiazide.** If you see “Chlorothiazide” whether it is “Hydro” or not, just assume it’s the same drug. This drug increases secretion of Na and Cl while enhancing Calcium reabsorption. It is indicated in hypertension, heart failure, and in calciuric kidney stones. It increases distal sodium delivery to the collecting tubules, where sodium is rescued at the cost of potassium. Therefore, a hypokalemia may result. With hypokalemia comes metabolic alkalosis as the cells kick out potassium (to normalize potassium blood levels) and absorb hydrogen ion in return. Patients have to make urine for this to be effective, so a contraindication is anuria. For the calcium stones, just know that it increases calcium reabsorption, leading to hypercalcemia (↑ in the blood) and hypocalciuria (↓ in the urine).

**Hydrochlorothiazide** (HCTZ). A highly prescribed (and highly board relevant) diuretic, this inhibits luminal Na-Cl symport in the distal convoluted tubule. The effect is the same as Chlorothiazide – increased distal sodium delivery results in a naturesis, diuresis, and hypokalemia. This also carries sulfonamide hypersensitivity contraindication just as in Lasix.

**Indapamide.** This one got stuck in the drug profile sort of randomly. It is an antihypertensive and diuretic with an unknown mechanism of action that should not be given in pregnancy. Kaplan told me it was a thiazide.

**K-SPARING DURETICS**

**Triamterene** and **Amiloride** directly inhibit the sodium leak channels in the collecting tubules. This prevents sodium resorption in the collecting tubules. However, since potassium loss is linked with sodium resorption, there is no loss of potassium as there is with other diuretics. These two are combined since they are both luminal channel inhibitors, added to antihypertensive regimens in order to protect from hypokalemia. When given alone, they can cause hyperkalemia, an equally life-threatening condition. Hyperkalemia is indicated on the ECG by peaked T waves, prolonged QRS (severe), or heart block and can lead to fatal arrhythmias (Vtach/Vifb).

**Spironolactone.** This is another potassium sparing diuretic but it does not affect luminal transporters. Instead it is a pharmacologic antagonist to aldosterone, preventing its binding to its receptor. Aldosterone’s affects are to increase the luminal concentration of sodium transporters (leading to sodium resorption and potassium loss). If aldosterone is inhibited, those channels are neither made nor inserted, leading to a potassium sparing naturesis/diuresis. It is particularly useful in conditions of hyperaldosteronism, though any condition in which CHF, edema, or HTN plays a role. Since it is an aldosterone antagonist, it has drug interactions with other drugs that interfere with the renin-angiotensin-aldosterone axis (ACE-I or ARB). Spironolactone has a very short half-life (1-2 hrs) but its metabolites have a longer half-life (15 hrs). Both are effective at producing potassium sparing diuresis.

There is a lot of blibbity blah associated with each drug. What is critically important is knowing (a) which transporter they work on (b) what part of the renal tubule (c) their electrolyte side effect. This is included in the Renal Physiology Review from the T1 Guide, reproduced in the Renal Pathology section. Looking at the Pharm Renal By Class section will also be useful.
Endogenous Renal Vasodilators

Dopamine
PGE₂
PGI₂
Bradykinin

Endogenous Renal Vasoconstrictors

Thromboxane A₂
Catecholamines
Angiotensin II

Angiotensin Converting Enzyme Inhibitors

“prils”
Captopril, Enalapril, Ramipril, Lisinopril

Angiotensin Receptor Blockers

“artans”
Losartan, Irbesartan, Valsartan, Candesartan

ENOGENOUS STUFF IS FOUND ON PAGE 9 OF RENAL HANDBOOK

Vasodilators

Dopamine. Acts on D2 receptors causing renal vessel dilation, increase renal blood flow, increase GFR, and increase Na excretion.

PGE₂ formed in medulla, causes vasodilation and offsets the effects of constrictors on renal blood flow (renoprotective vasodilation). Inhibits Vasopressin/ADH and water reabsorption in the collecting ducts.

PGI₂ formed by the endothelium in the arteries of the kidney. Stimulates Renin and increases cAMP

Bradykinin. Potent vasodilator, may promote prostaglandin synthesis and NO release, is broken down by ACE, and causes a dry cough in the lungs

Vasoconstrictors

Thromboxane A₂: formed by endothelial cells in response to clots, damage, or obstruction

Catecholamines. Resemble stimulation of adrenergic nerves. Alpha stimulation decreases RBF

Angiotensin II: potent vasoconstrictor stimulating aldosterone release and synthesis (Na and water retention) as well as direct affects on the afferent and efferent arteriole

ACE INHIBITORS

ACE is everywhere there is vasculature. Since there is so much vasculature in the lungs, ACE is primarily located in lungs. ACE turns angiotensin 1 into angiotensin 2. By administering an ACE-inhibitor, ANG II never forms, and cannot have either its vasoconstrictive effects nor its water retention effects. Everyone with HTN gets an ACE-I, since they have been shown to reduce morbidity and mortality in every condition of HTN. It is also useful as a diuretic in CHF, and is renoprotective in diabetes. The one time you do not give it is in bilateral renal artery stenosis where the ANGII constriction of the efferent arteriole maintains GFR. Administration of ACE-I or ARB to bilateral renal artery stenosis results in acute renal failure. Serious side effects that must be monitored are hyperkalemia and ventricular disturbances. A dry cough may develop, mandating a switch from ACE-I to ARB (a more expensive drug class that does the same thing). Since hyperkalemia is a side effect, coadministration with other diuretics should be avoided, unless coadministered with a potassium sparing diuretic. Contraindicated in pregnancy.

Angiotensin Receptor Blockers
Angiotensin Receptors are everywhere. Giving an antagonist to the angiotensin receptors results in a peripheral vasodilation and renal protective vasodilation. It is essentially giving some one an ACE-I, but levels of ANGII will not be changed; only their function. These are also contraindicated in pregnancy, and carry the same indications as ACE-I, but they are more expensive, so are not used as often. They block AT1 receptors. Lets say that again. ANG-2 binds to AT-1. AT-1 is blocked by ARBs. Cough is a side effect, but is not as common. The cough is likely from elaboration of prostaglandins or bradykinin in the lungs.