

**Subject:**

Nephrology Rotation

**Homework:**

Loop Diuretics

**Instructor:**

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**Mechanism of action:**

Loop diuretics work by inhibiting sodium-potassium-chloride (Na+/K+/2Cl) co-transporter on the ascending loop on Henle causes diuresis. By inhibiting this co-transporter, the body loses sodium, potassium and chloride, thus the water is drawn down and urine volume increases.

**Indications:**

1. Ascites and edema caused by heart failure, kidney or liver disease.
2. Can be used for hypertension.

**Agents and relative potency:**

1. Furosemide (Lasix®)
2. Bumetanide (Bumex®)
3. Ethacrynic acid (Edecrin®): **50mg PO/IV**
4. Torsemide (Demadex®)



**Side effects:**

1. hyponatremia, hypokalemia and hypomagnesemia.
2. Dehydration.
3. Hyperuricemia and gout.
4. dizziness, postural hypotension and syncope.
5. Hypocalcemia.
6. Ototoxicity (rare and serious), related to high doses and rapid infusion rate, mainly presents as vertigo and tinnitus, but may lead to deafness in some cases.
7. Kidney failure or “Triple whammy” effect may occur if used with ACE inhibiters and NSAIDs.
8. Sulfa allergy may occur in patients with Furosemide, torsemide and bumetanide. However, ethacrynic acid is not a sulfonamide and so doesn’t cause sulfa allergy.

**Notes:**

1. Ethacrynic acid is linked with the highest risk of ototoxicity especially at high doses or rapid infusions so it is reserved for patients with sulfa allergies from other loop diuretics.
2. The most potent agents are bumetanide and furosemide.
3. Loop diuretics are highly bound to plasma protein, mainly albumin.
* **Furosemide:**

**Mechanism of action:** (Na+/K+/2Cl) co-transporter inhibitor on the ascending loop of Henle.

**Contraindications:** hypersensitivity to furosemide or any component in the formulation.

Based on Canadian labeling: complete renal shut down, uncorrected state of electrolytes depletion, hypovolemia or hypotension, hepatic coma or precoma.

**Uses:** edema associated with heart failure, cirrhosis of the liver (i.e. ascites), renal disease (including nephrotic syndrome) and acute pulmonary edema.

**Administration in adults:**

* IV infusion:
* 1mg/mL or 2mg/mL or undiluted as 10mg/mL.
* Undiluted injections can be given at rate of 20-40mg/minute. High doses (eg. ≥160mg) should be given as short-term infusion at maxiumu rate of 4mg/minute to avoid risk of ototoxicity.
* Oral: with or without food.

**Dosing for adults:**

* **Edema:**

For naïve patients: Oral, IV: initial 20-40mg once daily, titrate to effect.

Refractory edema: IV bolus/intermittent: administer 1-2.5 times the total daily oral maintenance dose once then titrate as needed.

Continuous infusion (only for patients who have responded to bolus therapy):

* eGFR ≥ 30 ml/minute/1.73m2: IV: initial: 5 mg/hour, if diuretic response is not adequate, repeat IV bolus dose and increase continuous infusion to 10mg/hour, continue to bolus and titrate infusion as needed up to 40mg/hour.
* eGFR < 30ml/minute/1.73m2: IV: initial: 20 mg/hour, if diuretic response is not adequate, repeat IV bolus dose and increase continuous infusion to 40mg/hour.
* **Ascites due to cirrhosis:**
* Generally used with spironolactone but may be used alone for patients with hyperkalemia, with general dosing ratio of 100mg spironolactone:40mg furosemide. Can be adjusted for electrolyte abnormalities.
* Oral: initial: 40mg once daily, titrate every 3-5days based on response and tolerability, once daily is preferred. Maximum dose: 160mg/day.
* For small volume ascites in patients who weigh <50kg, starting dose of 20mg/day is preferred.

**Dosing in renal impairment:**

* Acute renal failure: doses up to 1-3g/day to initiate response. Avoid in oliguric states.
* Dialysis: not removed by dialysis (HD or PD), supplemental dose is not necessary.

**Avoid concomitant use with:** bromperidol, chloral hydrate, desmopressin, ethacrynic acid, fexinidazole, levosulpiride, mecamylamine and promazine.

**Monitoring parameters:**

Renal function, serum electrolytes (esp. potassium), volume status (input and output), blood pressure, orthostasis and hearing especially at high doses or rapid IV administration.

**Warnings/precautions:**

* Fluid/electrolyte loss.
* Hyperuricemia, may cause gout.
* Nephrotoxicity: monitor renal function to avoid oliguria.
* Ototoxicity: tinnitus and hearing loss, risk increases in patients with severe renal impairment, high doses, hypoproteinemia and concurrent use of ototoxins.
* Photosensitivity.
* Sulfonamide allergy.
* Thyroid effects: doses.80mg may cause transient elevation in thyroid hormones.
* Adrenal insufficiency: avoid in patients with primary adrenal insufficiency (Addison’s disease).
* Diabetes: use with caution in patients with DM.
* Bariatric surgery: avoid use in the immediate postoperative period as dehydration and electrolyte imbalance can occur.
* Systemic lupus erythematous: may cause SLE exacerbation or activation.
* Prostatic hyperplasia/urinary stricture: may cause urinary retention.

**Storage and stability:**

* Injection, tablet and solution: at room temperature, avoid from light as it may cause discoloration.
* Stable in basic solutions but not in acidic media.
* Infusion solution in D5W, NS and LR is stable for 24 hours.

**Side effects:** as all loop diuretics, mentioned above.

* **Torsemide:**

**Mechanism of action:** (Na+/K+/2Cl) co-transporter inhibitor on the ascending loop of Henle.

**Contraindications:** hypersensitivity to torsemide or any component in the formulation, anuria and hepatic coma.

**Uses:** edema associated with heart failure, hepatic cirrhosis and chronic kidney disease. Also, as alternative agent for hypertension.

**Administration in adults:**

* Oral: with or without food.

**Dosing for adults:**

* **Edema:**

Chronic kidney disease: Oral: initial: 20mg/day, may increase gradually by doubling the dose until the desired diuretic effect is obtained.

Heart failure: Oral: 10-20mg/day, may increase gradually by doubling the dose. Maximum dose= 200mg/day.

Hepatic cirrhosis: Oral: Initial: 5-10mg/day, may increase gradually by doubling the dose until the desired diuretic effect is obtained. (Maximum recommended single dose=40mg)
- Administer with aldosterone antagonist of potassium-sparing diuretics to avoid hypokalemia.

* **Hypertension (alternative therapy):** Oral: initial 5mg/day, may increase to 10mg/day after 4-6weeks if inadequate response.

**Dosing in renal impairment:**

* No dosage adjustments provided in manufacturer’s labelling.

**Avoid concomitant use with:** desmopressin, fexinidazole, levosulpiride, mecamylamine and promazine.

**Storage and stability:**

* Store at 15-30oC.

**Monitoring parameters:**

Renal function, serum electrolytes (esp. potassium), volume status, blood pressure, serum glucose.

**Warnings/precautions:**

* Fluid/electrolyte loss.
* Hyperuricemia, may cause gout.
* Nephrotoxicity: monitor renal function to avoid oliguria.
* Ototoxicity: tinnitus and hearing loss, risk increases in patients with severe renal impairment, high doses, hypoproteinemia and concurrent use of ototoxins.
* Sulfonamide allergy.
* Adrenal insufficiency: avoid in patients with primary adrenal insufficiency (Addison’s disease).
* Diabetes: use with caution in patients with DM.
* Hepatic impairment: use with caution in patients with hepatic impairment.
* Bariatric surgery: avoid use in the immediate postoperative period as dehydration and electrolyte imbalance can occur.

**Side effects:** as all loop diuretics, mentioned above.

* **Bumetanide:**

**Mechanism of action:** (Na+/K+/2Cl) co-transporter inhibitor on the ascending loop of Henle.

**Contraindications:** hypersensitivity to bumetanide or any component in the formulation, anuria, hepatic coma and patients with severe electrolyte depletion until the condition is corrected.

Based on Canadian labelling: hypersensitivity to other sulfonamides, hepatic encephalopathy, galactose intolerance and glucose-galactose malabsorption.

**Uses:** edema (peripheral, pulmonary or generalized).

**Dosing for adults:**

* **Edema:**

For naïve patients: Oral, IV: initial 0.5-1mg once daily, titrate to effect.

Refractory edema: IV bolus/intermittent: administer 1-2.5 times the total daily oral maintenance dose once then titrate as needed.

Continuous infusion (only for patients who have responded to bolus therapy):

* eGFR ≥ 30 ml/minute/1.73m2: IV: initial: 0.5 mg/hour, if diuretic response is not adequate, repeat IV bolus dose and increase continuous infusion to 1mg/hour, continue to bolus and titrate infusion as needed up to 2mg/hour.
* eGFR < 30ml/minute/1.73m2: IV: initial: 1mg/hour, if diuretic response is not adequate, repeat IV bolus dose and increase continuous infusion to 2mg/hour.

**Transitioning from IV to oral:** give the same IV dose orally, then monitor urine output and adjust oral dose as needed.

**Avoid concomitant use with:** desmopressin, promazine, levosulpiride, mecamylamine and fexinidazole.

**Dosing in renal impairment:**

* No dosage adjustments provided in manufacturer’s labelling.

**Storage and stability:**

* IV: store vials at 15-30oC. Infusion solutions in D5W, NS, or LR should be used within 24hours after preparation. Light sensitive.
* Tablet: store at 15-30oC. avoid light exposure.

**Monitoring parameters:**

Renal function, serum electrolytes (esp. potassium), volume status (input and output) and blood pressure.

**Warnings/precautions:**

* Fluid/electrolyte loss.
* Hyperuricemia, may cause gout.
* Nephrotoxicity: monitor renal function to avoid oliguria.
* Ototoxicity: tinnitus and hearing loss, risk increases in patients with severe renal impairment, high doses, hypoproteinemia and concurrent use of ototoxins.
* Sulfonamide allergy.
* Renal impairment: large doses may be required in patient with renal impairment to obtain same diuretic effect.
* Hepatic impairment: use with caution in patients with hepatic impairment.
* Bariatric surgery: avoid use in the immediate postoperative period as dehydration and electrolyte imbalance can occur.

**Side effects:** as all loop diuretics, mentioned above.

* **Ethacrynic acid:**

**Mechanism of action:** (Na+/K+/2Cl) co-transporter inhibitor on the ascending loop of Henle.

**Contraindications:** hypersensitivity to ethacrynic acid or any component in the formulation, anuria, history of severe watery diarrhea cause by this agent and infants.

**Uses:** edema (peripheral, pulmonary, generalized); alternative therapy, reserved for patients who develop a hypersensitivity reaction (sulfa allergy) to other loop diuretics.

**Dosing for adults:**

* **Edema:**

For naïve patients: Oral: initial 50mg once daily, increase dose by 25-50mg/day in ≥ 24 hour intervals based on response. Usual effective dose: 50-200 mg/day in 1-2 divided doses. Doses up to 400mg/day in 2 divided doses may be necessary for patients with refractory edema.

IV: 50mg or 0.5-1mg/kg/dose (maximum: 100mg/dose). Repeating dose is not recommended, however, if needed, a repeated dose may be given 8-12 hours later.

**Dosing in renal impairment:**

* No dosage adjustments provided in manufacturer’s labelling, contraindicated in patients with anuria.

**Avoid concomitant use with:** desmopressin, fexinidazole, levosulpiride, promazine, bromperidol and furosemide.

**Storage and stability:**

* Store at 25oC. Discard unused reconstituted injection solution after 24hours.

**Monitoring parameters:**

Renal function, serum electrolytes (esp. potassium), volume status, blood pressure and hearing.

**Warnings/precautions:**

* Fluid/electrolyte loss.
* Nephrotoxicity: monitor renal function to avoid oliguria.
* Ototoxicity: tinnitus and hearing loss, risk increases in patients with severe renal impairment, high doses, hypoproteinemia and concurrent use of ototoxins.
* Hepatic impairment: use with caution in patients with hepatic impairment.
* Bariatric surgery: avoid use in the immediate postoperative period as dehydration and electrolyte imbalance can occur.

**Side effects:** as all loop diuretics, mentioned above.

**References:**

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