# Loop Diuretics

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# Introduction

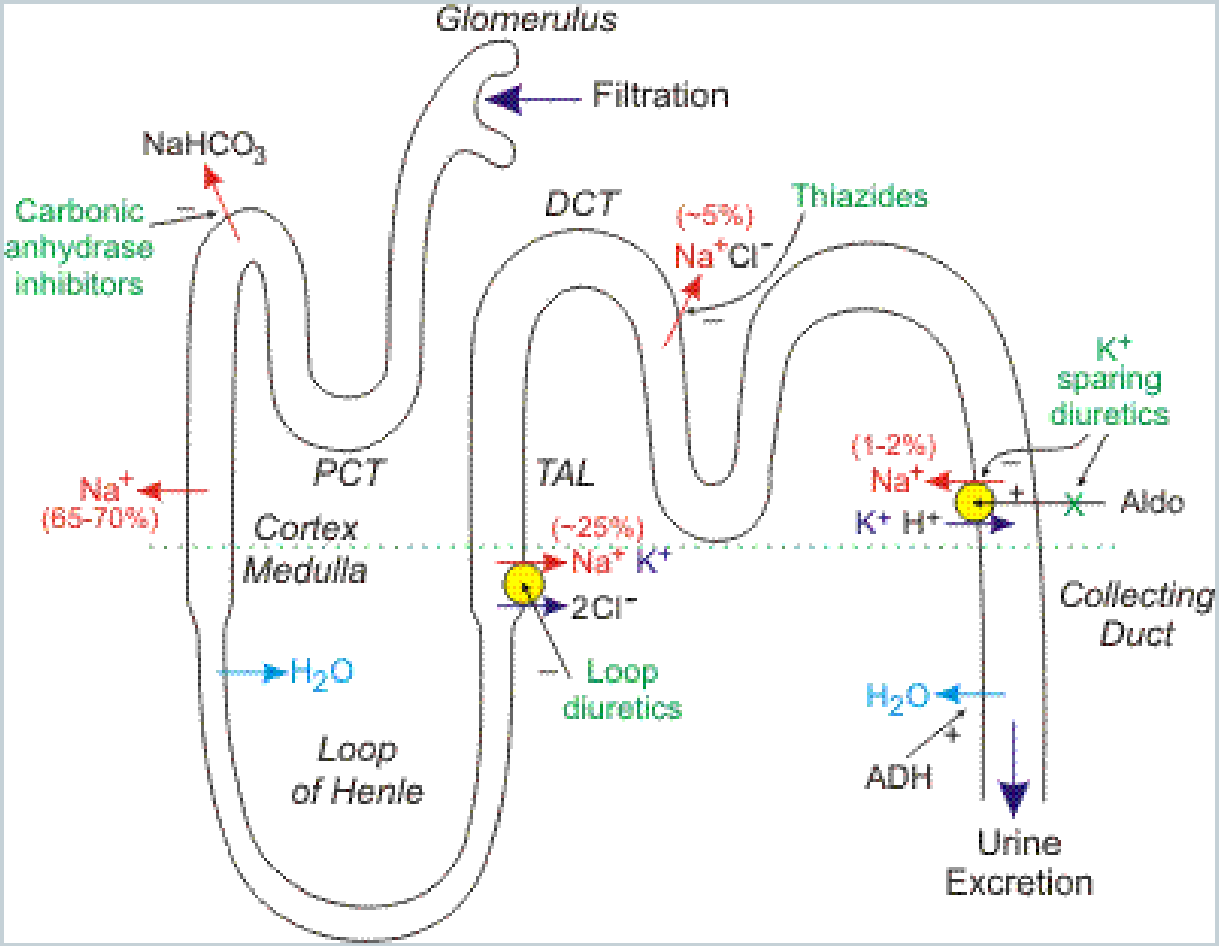
- Loop diuretics are used in pulmonary oedema due to left ventricular failure; intravenous administration produces relief of breathlessness and reduces pre-load sooner than would be expected from the time of onset of diuresis. Loop diuretics are also used in patients with chronic heart failure. Diuretic-resistant oedema (except lymphoedema and oedema due to peripheral venous stasis or calcium-channel blockers) can be treated with a loop diuretic combined with a thiazide or related diuretic (e.g. bendroflumethiazide or metolazone 5-20mg daily)

- If necessary, a loop diuretic can be added to antihypertensive treatment to achieve better control of blood pressure in those with resistant hypertension, or in patients with impaired renal function or heart failure.
- Loop diuretics inhibit reabsorption from the ascending limb of the loop of Henle in the renal tubule and are powerful diuretics.
- Furosemide and bumetanide are similar in activity, both act within 1 hour or oral administration and diuresis is complete within 6 hours so that, if necessary, they can be given twice in one day without interfering with sleep. Following IV administration they have a peak effect within 30 minutes. The diuresis associated with these drugs is dose related.
- Torasemide has properties similar to those of furosemide and bemetanide, and is indicated for oedema and for hypertension.

- **Furosemide (Furosemide, Lasix)**
- Bumetanide (Bumetanide, Burinex)
- Torasemide (Torasemide, Torem)

# Mechanism of Action

- Inhibits water reabsorption in the nephron by blocking the sodium-potassium-chloride co-transporter in the thick ascending limb of the loop of Henle.
- This is achieved through competitive inhibition at the chloride binding site on the co-transporter, thus preventing the transport of sodium from the lumen of the loop of Henle into the basolateral interstitium.
- Consequently, the lumen becomes more hypertonic while the interstitium becomes less hypertonic, which in turn diminishes the osmotic gradient for water reabsorption throughout the nephron.
- Because the thick ascending limb is responsible for 25% of sodium reabsorption in the nephron, furosemide is a very potent diuretic.


Glomerulus
Filtration
NaHCO3
Carbonic anhydrase inhibitors
DCT
(~5%)
Na+Cl−
Thiazides
K+ sparing diuretics
(1-2%)
Na+
X
Aldo
K+ H+
Na+ (65-70%)
PCT
TAL
Cortex
Medulla
(~25%)
Na+ K+
2Cl−
Collecting Duct
H2O
Loop diuretics
H2O
Loop of Henle
ADH
Urine Excretion

# Indications

- In pulmonary oedema due to left ventricular failure
- In patients with chronic heart failure

# Adverse Effects

- Mild GI disturbances
- Pancreatitis
- Hepatic encephalopathy
- Postural hypotension
- Temporary increase in serum cholesterol and triglyceride concentration, hyperglycaemia
- Less common than with thiazides
- Acute urinary retention
- Electrolyte disturbances
- Incl. hyponatraemia, hypokalaemia, hypochloraemia and hypomagnesaemia
- Metabolic alkalosis

Blood disorders incl. bone marrow depression, thrombocytopenia and leucopenia
Hyperuricaemia
Visual disturbances
Tinnitus and deafness
Usually with high parenteral doses and rapid administration, and in renal impairment
Hypersensitivity reactions
Incl. rash, photosensitivity and pruritus
Intraheptic cholestasis
Gout

# Interactions

- May increase the ototoxic potential of aminoglycoside antibiotics (e.g. gentamicin), esp. in the presence of impaired renal function. Except in life-threatening situations, avoid this combination
- Should not be used concomitantly with ethacrynic acid (loop diuretic) because of the possibility to ototoxicity
- If used with high doses of salicylates (aspirin), as in rheumatic disease, salicylate toxicity may occur de to competitive renal excretory sites
- Nephrotoxic effects of certain drugs, such as cisplatin (anti-neoplastic) may be enhanced, if furosemide is not given in lower doses and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment
- Can antagonize the skeletal muscle relaxing effect of tubocurarine (nicotinic antagonist) and may potentiate the action of succinylcholine (anaesthetic).

- Lithium (mood stabilizer) generally should not be give with diuretics because they reduce lithium's renal clearance and add a high risk of lithium toxicity
- If combined with ACE inhibitors (e.g. ramipril) or ARBs (e.g. losartan), may lead to severe hypotension and deterioration in renal function, incl. renal failure. An interruption of reduction in the dosage of furosemide, the ACE inhibitor or ARB may be necessary
- Potentiation occurs with ganglionic (trimethaphan) or peripheral adrenergic (propranolol) blocking drugs
- May decrease arterial responsiveness to norepinephrine. However, norepinephrine may still be used effectively
- Simultaneous administration with sucralfate (anti-ulcer) may reduce the natriuretic and anti-hypertensive affects of furosemide. Patients receiving both drugs should be observed closely to determine if the desired diuretic and/or antihypertensive effect is achieved. The intake of furosemide and sucralfate should be separated by at least two hours

- IV furosemide within 24 hours of taking chloral hydrate (hypnotic and sedative) may lead to flushing, sweating attacks, restlessness, nausea, increase in BP and tachycardia. Concomitant use is not recommended
- Phenytoin interferes directly with renal action of furosemide. It can lead to decreased interstinal absorption of furosemide, and consequently to lower peak serum furosemide concentrations
- Methotrexate and other drugs that, like furosemide, undergo significant renal tubular secretion may reduce the effect of furosemide. Conversely, furosemide may decerase renal elimination of other drugs that undergo tubular secretion. High dose treatment of both furosemide and these other drugs may result in elevated serum levels of these drugs and may potentiate their toxicity as well as the toxicity of furosemide.
- Can increase the risk of cephalosporin (beta-lactam antibiotic) -induced nephrotoxicity even in the setting of minor or transient renal impairment
- Use with cyclosporine (immunosuppressant) is associated with increased risk of gouty arthritis secondary to furosemide-induced hyperuricaemia and cyclosporine impairment of renal urate excretion

# Cautions

- Hypovolaemia and hypotension should be corrected before initiation of treatment with loop diuretics
- Electrolytes should be monitored during treatment
  - Hypokalaemia can occur with both thiazide and loop diuretics. The risk of hypokalaemia depends on the duration of action as well as the potency and is thus greater with thiazides than with an equipotent dose of a loop diuretic
  - Hypokalaemia is dangerous in severe cardiovascular disease and in patients also being treated with cardiac glycosides (e.g. digoxin). Often, the use of potassium-sparing diuretics avoids the need to take potassium supplements
  - In hepatic failure, hypokalaemia caused by diuretics can precipitate encephalopathy, particularly in alcoholic cirrhosis; diuretics can also increase the risk of hypomagnesaemia in alcoholic cirrhosis, leading to arrhythmias. Spironolactone is chosen for oedema arising from cirrhosis of the liver.
  - Potassium supplements or potassium-sparing diuretics are seldom necessary when thiazides are used in the routine treatment of hypertension

- Can exacerbate diabetes (but hyperglycaemia is less likely than with thiazides) and gout
- If there is an enlarged prostate, urinary retention can occur, although this is less likely if small doses and less potent diuretics are used initially; an adequate urinary output should be established before initiating treatment
- Hypoproteinaemia may replace diuretic effect and increase risk of side-effects
- Hepatorenal syndrome
- IV administration rate should not usually exceed 4mg/minute, however single doses of up to 80mg may be administered more rapidly

# Contraindictions

- Severe hypokalaemia
- Severe hyponatraemia
- Anuria
- Comatose and precomatose states associated with liver cirrhosis
- Renal failure due to nephrotoxic or hepatotoxic drugs

# Adjustments in Special Circumstances

- Elderly
  - Lower initial doses of diuretics should be used in the elderly because they are particularly susceptible to the side-effects. The dose should then be adjusted according to renal function. Diuretics should not be used continuously on a long-term basis to treat simple gravitational oedema (which will usually respond to increased movement, raising the legs and support stockings)
- Hepatic impairment
  - Hypokalaemia induced by loop diuretics may precipitate hepatic encephalopathy and coma
    - Potassium-sparing diuretics can be used to prevent this

- Renal impairment
  - High doses of loop diuretics may occasionally be needed
    - High doses or rapid IV administration can cause tinnitus and deafness
    - High doses of bumetanide can also cause musculoskeletal pain
- Pregnancy
  - Should not be used to treat gestational hypertension because of the maternal hypovolaemia associated with this condition
- Breast-feeding
  - Amount too small to be harmful
  - May inhibit lactation

# Prescribing

- Oedema
  - PO
    - Initially 40mg in the morning
    - Maintenance 20-40mg daily
    - Resistant oedema
      - 80-120mg daily
    - Resistant hypertension
      - 40-80mg daily
  - IM or slow IV
    - Initially 20-50mg
    - Increased if necessary in steps of 20mg not less than every 2 hours
    - Doses greater than 50mg by IV infusion only
    - Max. 1.5g daily