Abstract Diuretics remain a common medication in Paediatric practice and possibly one of the most important drugs in Nephrology practice. Understanding their mechanism, appropriate rationale for use and prompt identification of side-effects allows for high efficacy and safety in their use. On the background of challenges in our center with regards to the use of frusemide, this review is specifically focused on addressing factors that may affect frusemide efficacy, possible cause of resistance and drug interactions that may occur following its use.

Introduction

Disorders affecting fluid volume and electrolyte composition are common problems in clinical practice. Drugs that block the transport functions of the renal tubules are valuable tools in the treatment of these disorders. Various agents that increase urine flow have been described since antiquity but it was in 1957 that a practical and powerful agent; chlorothiazide became available for widespread use as diuretics.

Technically, the term ‘diuresis’ signifies an increase in urine volume, while ‘natriuresis’ denotes an increase in renal sodium excretion. Because natriuretic drugs almost always also increase water excretion, they are usually called diuretics.

Thus, diuretics are agents that enhance urine formation by altering the total solute content of the extracellular compartment and water balance. An ideal diuretic would be one that caused the excretion of “extra” urine with an electrolyte composition similar to that of normal plasma. No such diuretic exists.

It is important for a practitioner to be armed with the knowledge of the mechanism of action of diuretic drugs and appropriate recognition and respect for their potential side effects in order to use them with a high degree of efficacy and safety.

To understand the actions of diuretics, it is necessary to first review how the kidneys filter fluid and form urine.

Nephron physiology

The kidney is the main organ of excretion of water, electrolytes and waste products. Each human kidney has over one million nephrons. The nephron is the functional unit of the kidney. The nephron is made up of glomerulus, proximal tubule, loop of Henle, distal tubule and the collecting ducts.
Processes involved in urine formation are:
- Glomerular filtration
- Tubular reabsorption
- Tubular excretion
- All these processes occur in the nephron

Glomerular filtration

As blood passes through the glomerular capillaries, the plasma is filtered through the glomerular capillary walls. The ultrafiltrate, which is cell free, contains all the substances in the plasma except proteins (such as albumin and the globulins). The substances in the ultrafilterate are electrolytes, glucose, phosphate, urea, creatinine, peptides, low molecular weight proteins.

The filtrate is collected in Bowman’s space and enters the tubules.

Tubular reabsorption and excretion

Proximal Convoluted Tubule (PCT)

NaHCO$_3$, NaCl, glucose, amino acids, and other organic solutes are reabsorbed in the early PCT. H$_2$O is reabsorbed passively to maintain osmolality of the luminal fluid. NaHCO$_3$ reabsorption at the PCT is dependent on the carbonic anhydrase (CA). Na$^+$/$H^+$ exchanger allows Na$^+$ to enter the cell from the tubular lumen in exchange for an $H^+$ from inside the cell. Na$^+$/K$^+$ ATPase located on the basolateral membrane pumps the reabsorbed Na into the interstitium.

In the late PCT the residual luminal fluid contains predominantly NaCl. A poorly defined exchanger, the Cl$^-$/base exchanger is activated by the free H$^+$ in the distal portion of the PCT. The net effect of parallel Na$^+$/H$^+$ exchange and Cl$^-/base exchange is NaCl reabsorption. Because the PCT is highly permeable to H$_2$O, H$_2$O is reabsorbed in direct proportion to salt reabsorption. Thus the luminal fluid osmolality and Na concentration remain nearly constant along the length of the PCT. The concentration of non-permeable solute in the tubular fluid will rise.

Loop of Henle

The thin limb is permeable to H$_2$O, while the thick portion is impermeable to H$_2$O. In the thin limb, H$_2$O is reabsorbed by osmotic forces created by the medullary interstitium. Presence of non-permeable solute will oppose H$_2$O extraction. NaCl is actively reabsorbed in the thick limb through Na$^+$/K$^+$/2Cl$^-$ cotransporter located in the luminal membrane. Because this portion is impermeable to H$_2$O, salt reabsorption dilutes tubular fluid. Excess K$^+$ accumulates within the cells, it diffuses into the tubular lumen to create a lumen-positive electrical potential. This electrical potential provides a driving force for reabsorption of cations such as Mg$^{2+}$ and Ca$^{2+}$ via the paracellular pathway.

Distal convoluted tubule

This segment is relatively impermeable to H$_2$O; thus luminal fluid is further diluted with NaCl reabsorption. NaCl is reabsorbed via a neutral Na$^+$ and Cl$^-$ cotransport. Ca$^{2+}$ is actively reabsorbed by the DCT epithelial cell via an apical Ca$^{2+}$ channel and basolateral Na$^+/Ca^{2+}$ exchanger. This process is regulated by parathyroid hormone (PTH).
Collecting tubule

As the final site of NaCl reabsorption, this segment is responsible for volume regulation and for determining the final Na⁺ concentration of urine. The principal cells are the site of Na⁺, K⁺, and H₂O transport. The intercalated cells are the primary sites of H⁺ secretion. There are no co-transport systems in the principal cells, rather they have separate ion channels for Na⁺ and K⁺. The driving force for Na⁺ entry exceeds that of K⁺ exit, Na⁺ reabsorption predominates K⁺ secretion – this leads to lumen-negative electrical potential. The lumen-negative electrical potential drives the transport of Cl⁻ back to the blood, it also pulls K⁺ out of the cell through the apical membrane K⁺ channel. The reabsorption of Na⁺ via the epithelial Na channel and its coupled secretion of K⁺ is regulated by aldosterone. Antidiuretic hormone (ADH) is a key determinant of final urine concentration. Permeability of principal cells to H₂O is increased by ADH-induced fusion of vesicles preformed water channels with the apical membranes.

Classification of diuretics

Diuretics are classified according to their mechanism and site of action within the nephron.

- Carbonic anhydrase inhibitors
- Osmotic diuretics
- Loop diuretics
- Thiazide diuretics
- Potassium-sparing diuretics
  - Na channel blockers
  - Aldosterone antagonists
- Others - mercurial, xanthines, etc

Tubular transport and site of action of diuretics

**Carbonic anhydrase (CA) inhibitors - Acetazolamide, dichlorphenamide**

- They are weak diuretics, used clinically to correct acid-base disturbances (alkalosis) and reduction of aqueous humour formation in glaucoma, rather than for diuretic action.
- Act by inhibiting CA at the PCT, Inhibition of CA inhibits HCO₃⁻ absorption from tubule.
- Presence in lumen of HCO₃⁻ reduces Na⁺ and H₂O reabsorption.

**Osmotic diuretics – Mannitol, Urea, Sorbitol**

The PCT and the descending limb of Henle’s loop are freely permeable to H₂O. Osmotic agent that is not reabsorbed causes H₂O to be retained in these segments and promote diuresis. Such agents can be used to reduce increased intracranial pressure and to promote prompt removal of renal toxins. They must be given parenterally because they are poorly absorbed in the GIT and also cause osmotic diarrhea.

**Loop diuretics – furosemide, bumetanide, torsemide, ethacrynic acid**

- They are often described as "high ceiling" diuretics due to their high diuretic potential.
- They can cause up to 20% of the filtered load of NaCl and H₂O to be excreted in the urine. They act by inhibiting the Na⁺/K⁺/2Cl⁻ co-transporter in the thick ascending limb of the loop of Henle, they also interfere with the reabsorption of K⁺, Ca²⁺, and Mg²⁺ in the loop.
**Thiazides – chlorothiazide, hydrochlorothiazide, benzthiazide, chlorothalidone,**

- Exert their diuretic effect by inhibiting the Na+/Cl⁻ co-transport in the early distal convoluted tubules.
- They elicit a weaker diuretic response compared to the loop diuretics.
- Increase the loss of K⁺ and Mg²⁺, but reduce Ca²⁺ excretion

**Na channel blockers – Amiloride, triamterene**

- They act by blocking the Na⁺ channels in the luminal membrane of the principal cells of the cortical collecting ducts. This reduces the Na⁺ entry through the luminal membrane and hence the net reabsorption of NaCl. Action is independent of aldosterone.
- They have weak diuretic effect.

**Aldosterone antagonists - spironolactone**

- Act at the late distal tubule and the cortical collecting tubule and competes with aldosterone for receptor sites in DCT and the collecting tubule.
- Results in decreased Na⁺ reabsorption in DCT and the collecting tubule and promotes Na⁺ and water loss. Decreased Na⁺ reabsorption balanced by K⁺ retention at this site (and H⁺) – K sparing.

**Furosemide (Frusemide)**

- The most efficacious agent available for inducing marked water and electrolyte excretion.
- It can increase diuresis even in patients who are already responding maximally to other diuretics. It has no significant pharmacological effects other than on renal function.

**Chemical properties**

- It is an anthranilic acid derivative
- It is practically insoluble in water
- Sparingly soluble in alcohol
- Freely soluble in dilute alkali solutions and insoluble in dilute acids.
- Chemically, it is 4chloro-N-furfuryl-5-sulfamoylanthranilic acid

![The structural formula of furosemide](image)

**Pharmacodynamics**

Furosemide’s mechanism of action is by inhibiting Na⁺/K⁺/2Cl⁻ transporter in the thick ascending loop of Henle. This inhibits the reabsorption of NaCl leading to increased NaCl and H₂O excretion.

**Pharmacokinetics**

Furosemide is available for both oral and parenteral administration. Its onset of action is rapid, usually within 30 minutes after oral and five minutes after intravenous administration. It produces peak diuresis in about two hours, with a total duration of diuretic action of approximately six to eight hours.

Furosemide is extensively bound to plasma proteins and is eliminated in the urine by both glomerular filtration and tubular secretion. Approximately a third of an administered dose is excreted by the liver into the bile, from where it may be eliminated in the feces.

**Dosage**

Conventional: 1- 2mg/kg/dose, maximum of 6mg/kg/day. Higher dose may be given in certain situations – up to 600mg/day

**Formulations**

Furosemide is available in tablets for oral administration and injectable for I.V. administration. The tablets are a white to off-white odorless crystalline powder. They are available in dosage strengths of 20, 40 and 80 mg. The injection comes as 20mg/2ml; clear colourless solution. 500mg tablet and 250mg injection also available for use in selected patients who do not respond to conventional doses.

**Clinical use of diuretics**

Diuretics interfere with sodium reabsorption and lower extracellular fluid volume. Therefore useful in the following conditions:

- Heart failure and pulmonary oedema.
- Chronic kidney disease
- Acute renal failure
- Hypertension
- Liver cirrhosis
- Poisoning.
- Diabetes insipidus.
- Glaucoma
- Prevent cardiovascular complications of chronic kidney disease.
- Potentiate the effect of antihypertensive and for resistant hypertension.

**Adverse effects of diuretics**

- Hypovolaemia (Loop and thiazides)
- Hypokalaemia (Loop, thiazides, carbonic anhydrase)
Hyperkalaemia (K sparing diuretics)  
Hyponatraemia (Loop and thiazides)  
Hypocalcaemia (hypercalciuria)  
Hyperuricaemia  
Otoxicity  
Nipple tenderness, erectile dysfunction, menstrual irregularities (spironolactone)  
Hypomagnesaemia (thiazide and loop)  
Metabolic alkalosis (Thiazides and loop)  
Metabolic acidosis (K sparing diuretics & carbonic anhydrase inhibitors)  
Allergic reaction similar to those seen in sulphonamide containing drugs.  
Interstitial nephritis (loop).  
Osmotic diarrhea.

<table>
<thead>
<tr>
<th>Systolic blood pressure</th>
<th>≥120mmHg</th>
<th>110 – 119mmHg</th>
<th>&lt;110mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline GFR(ml/min/1.73m²)</td>
<td>≥60</td>
<td>30-59</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Serum K (For thiazide and loop) mmol/l</td>
<td>≥4.5</td>
<td>4.1-4.5</td>
<td>≤4.0</td>
</tr>
<tr>
<td>Serum K (For K sparing diuretics) mmol/l</td>
<td>≤4</td>
<td>4.1-4.5</td>
<td>&gt;4.5</td>
</tr>
<tr>
<td>Interval (weeks)</td>
<td>4-12 weeks</td>
<td>2-4 weeks</td>
<td>≤2 weeks</td>
</tr>
</tbody>
</table>

**Principles for monitoring for adverse effects when initiating diuretics**

- Measuring baseline blood pressure, glomerular filtration rate and serum potassium.
- Counselling to reduce risk of volume depletion or rapid volume loss, hypokalaemia and allergic reactions.
- Determine interval for follow-up measurement.
- Counselling mothers of child bearing age of potential side-effects especially spironolactone.

**Sigmoidal-shaped-dose-response relationship**

A- Represents pharmacokinetic determinants of diuretic response for an orally administered diuretic.

**Threshold:** Diuretic delivery rate sufficient to produce first diuresis.

**Efficiency:** Rate of delivery that produces optimal response for any amount of diuretic.

**Maximal response:** Delivery at which no additional diuretic response can occur.

B- Represents altered pharmacodynamic determinants in diuretic resistance. This is termed the breaking phenomenon, it occurs in both long and short-term therapy. Due to the haemodynamic and neurohumoral changes produced by rapid diuresis it causes a rebound antinatriuretic effect. This can be overcome by administering multiple doses.

**Resistance to frusemide**

- Due to alteration in pharmacokinetic determinants of tubular delivery
- Pharmacodynamic determinants of diuretic action in the tubular space.
  - High dietary sodium intake: Can be ascertained by estimating sodium excretion rate. If > 100mmol/day may suggest excessive dietary sodium intake.
  - Independent cause of increased tubular reabsorption of sodium e.g. NSAIDS.
  - Diuretic tolerance causing a breaking phenomenon.
  - Excessive exposure of distal tubule to high sodium load resulting in distal tubular hypertrophy and an excessive recapturing of sodium delivered from proximal locations.
  - This can be altered by combining thiazide type diuretic with a loop diuretic.

**Drug interactions with frusemide**

- Drugs that make frusemide less effective: NSAIDS and Phenytoin.
- Increase risk of ototoxicity: Aminoglycosides and Ethacrynic acid.
- Increases risk of hypokalaemia: Corticosteroids, Laxatives and Liquorice
- Increase risk of hyperuricaemia (gout): Cycsporine.

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References

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