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5th Edition

PHARMACOLOGY

for Dental & Allied Health Sciences



Padmaja Udaykumar

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SECTION

3 Drugs Acting on the Kidney

SECTION OUTLINE

Chapter 10: Diuretics and Antidiuretics

- Diuretics
- Physiology of Urine Formation
- Classification
- High Efficacy, High Ceiling or Loop Diuretics
- Thiazides and Thiazide-like Diuretics
- Potassium-sparing Diuretics
- Carbonic Anhydrase Inhibitors
- Osmotic Diuretics
- Diuretics and Dentistry
- Antidiuretics

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CHAPTER

10

Diuretics and Antidiuretics

DIURETICS

Kidney, the excretory organ of our body serves the important functions of excretion of waste products, regulation of fluid volume and electrolyte content of the extracellular fluid.

PHYSIOLOGY OF URINE FORMATION

Normally about 180 L of fluid is filtered everyday, of which 99% gets reabsorbed and about 1.5 L of urine is formed. For simplification, the nephron can be divided into four sites **(Fig. 10.1)**. They are:

1. *Proximal tubule:* Sodium bicarbonate, sodium chloride, amino acids and glucose are reabsorbed in the proximal tubule along with water by specific transport mechanisms. Osmotic diuretics act here.
2. *Henle's loop:* In the thin descending limb of the loop of Henle, water is reabsorbed by osmotic forces. Hence osmotic diuretics are acting here too. The thick ascending limb actively reabsorbs sodium chloride from the lumen (but is impermeable to water) by $Na^+/K^+/2Cl^-$ cotransporter. 'Loop diuretics' selectively block this transporter.
3. *Distal convoluted tubule:* In the early distal tubule, sodium chloride is reabsorbed by an electrically neutral Na^+ and Cl^- transporter. This transporter is blocked by thiazide diuretics.
4. *Collecting tubule:* In the late distal tubule and collecting duct, $NaCl^-$ is actively reabsorbed, in exchange for K^+ and H^+ to maintain the ionic balance regulated by aldosterone. Absorption of water is under the control of antidiuretic hormone (ADH).

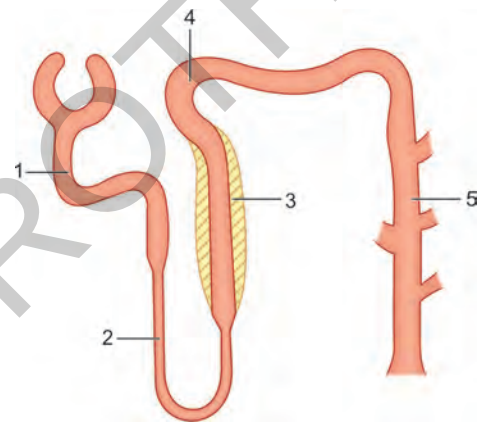

Fig. 10.1: Simplified diagram of a nephron showing sites of action of diuretics: (1) Proximal tubule—acetazolamide, (2) Descending limb of Henle's loop—osmotic diuretics, mannitol, (3) Ascending limb of Henle's loop—loop diuretics, (4) Early distal tubule—thiazides, (5) Distal tubule and collecting duct—K+sparing diuretics.

Diuretic is an agent which increases urine and solute excretion. Diuretics may be classified as follows:

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CLASSIFICATION

1. **High efficacy diuretics**
   Furosemide, bumetanide, piretanide, torsemide, azosemide
2. **Moderate efficacy diuretics**
   a. **Thiazides**
   Benzothiadiazines—chlorothiazide, hydrochlorothiazide, polythiazide, bendroflumethiazide
   b. **Thiazide-like agents**
   Chlorthalidone, clopamide, indapamide, metolazone, xipamide
3. **Low-efficacy diuretics**
   a. **Potassium-sparing diuretics**
   Triamterene, amiloride, spironolactone, eplerenone
   b. **Carbonic anhydrase inhibitors**
   Acetazolamide, methazolamide dorzolamide
   c. **Osmotic diuretics**
   Mannitol, urea, glycerol
   d. **Methylxanthines**
   Theophylline
4. **Newer agents**
   Vasopressin antagonists:
   Conivaptan, tolvaptan, lixivaptan

HIGH EFFICACY, HIGH CEILING OR LOOP DIURETICS

Loop diuretics act on the ascending limb of the loop of Henle. They are **highly efficacious** as diuretics.

Frusemide (furosemide) is a sulfonamide derivative. It is a powerful diuretic and is the most commonly used loop diuretic.

Mechanism of action: Frusemide acts by inhibiting $NaCl^-$ reabsorption in the thick ascending limb of the Henle's loop **(Fig. 10.2)**. It blocks the Na^+ K^+ $2Cl^-$ symporter in the thick ascending limb of the Henle's loop because of which it is called a loop diuretic. It greatly increases the excretion of Na^+ and

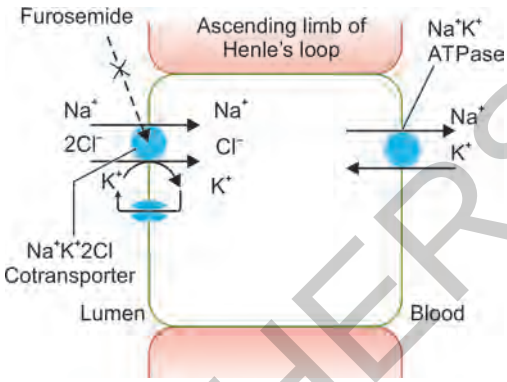
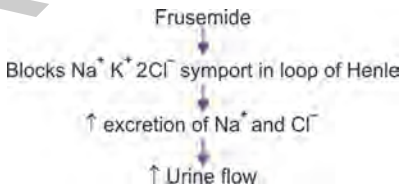


Fig. 10.2: Mechanism of action of loop diuretics.

Cl^- in the urine. As a large amount of $NaCl^-$ is absorbed in this segment, loop diuretics are highly efficacious. Diuretic response increases with dose (high ceiling of effect) and over-enthusiastic treatment can cause dehydration **(Table 10.1)**.



Other Actions

- Loop diuretics also increase the excretion of K^+, Ca^{++} and Mg^{++} (but Ca^{++} is reabsorbed in the distal tubule—hence no hypocalcemia).
- They increase reabsorption of uric acid in the proximal tubule.
- On long-term use, they also alter renal hemodynamics to reduce fluid and electrolyte reabsorption in the proximal tubule. Loop diuretics enhance renin release.
- Frusemide is a weak carbonic anhydrase inhibitor hence it increases the excretion of HCO_3^- and phosphate.
- Intravenous frusemide causes venodilation and reduces left ventricular filling pressure. It thus relieves pulmonary congestion in congestive heart failure (CHF) and in

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Table 10.1: Compare and contrast hydrochlorothiazide and frusemide.

Features	*Hydrochlorothiazide*	*Frusemide*
Efficacy	Low	High
Site of action	Early distal tubule	Ascending limb of loop of Henle
Mechanism of action	Inhibits Na^+ Cl^- symport	Inhibits Na^+ K^+ $2Cl^-$ cotransport
Onset of action	After 1 hour	In minutes (20–40)
Duration of action	Long (8–12 hours)	Short (3–6 hours)
Response to increasing dose	No significant increase	Increases (dose dependent)
Hyperuricemia	Higher incidence	Low
Blood glucose	May increase Contraindicated in diabetics	No significant effect Not contraindicated
Ototoxicity	Not known to cause	Can cause
Primary use	Hypertension	Edema

pulmonary edema even before the onset of diuresis.

Pharmacokinetics: Furosemide is rapidly absorbed orally **(Table 10.3)** highly bound to plasma proteins, metabolized in the liver and excreted by kidneys. Given intravenously frusemide acts in 2–5 minutes, while following oral use, it takes 20–40 minutes. Plasma t½ is 1½ hours and duration of action is 4–6 hours. Loop diuretics reach the ascending limb of Henle's loop because they are secreted by the organic acid transport system.

Bumetanide is a sulfonamide like frusemide but is 40 times more potent than frusemide. Bioavailability is 80% and is better tolerated.

Torsemide is a recently introduced loop diuretic. It is longer acting and therefore can be given once a day.

Ethacrynic acid is more likely to cause adverse effects particularly ototoxicity and hence is not commonly used.

Adverse effects of loop diuretics

1. **Hypokalemia and metabolic alkalosis** (due to loss of H^+) are dose-dependent and can be corrected by K^+ replacement and correction of hypovolemia.
2. **Hyponatremia, dehydration, hypovolemia and hypotension** should be treated with saline infusion.
3. **Hyperuricemia** may precipitate acute attacks of gout.
4. **Hypocalcemia and hypomagnesemia:** After prolonged use this may result in osteoporosis.
5. **Ototoxicity:** Loop diuretics cause hearing loss by a toxic effect on the hair cells in the internal ear. Associated tinnitus and vertigo may also occur. Ototoxicity is more common with ethacrynic acid. It is dose-related, more common on IV administration and generally reversible. Concurrent use of other ototoxic drugs should be avoided.
6. **Hyperglycemia and hyperlipidemia** are mild in therapeutic doses.
7. **GIT disturbances** like nausea, vomiting and diarrhea are common with ethacrynic acid.
8. **Allergic reactions** like skin rashes are more common with sulfonamide derivatives.
9. **Weakness**, fatigue, dizziness and muscle cramps (mostly due to hypokalemia).

Uses

1. ***Edema:*** Loop diuretics are highly effective for the relief of edema of all origins like cardiac, hepatic or renal edema.
2. ***Chronic congestive cardiac failure (CCF)*** loop diuretics reduce edema as well as venous and pulmonary congestion.

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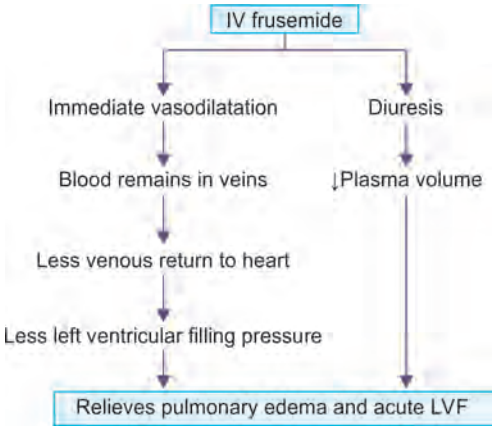
Flowchart 10.1: Frusemide in pulmonary edema.



3. ***Acute renal failure:*** Loop diuretics increase the urine output and K^+ excretion and therefore useful in acute renal failure. They are also useful in impending acute renal failure. In chronic renal failure large doses are needed.
4. ***Acute pulmonary edema:*** It is quickly relieved by IV frusemide due to its immediate vasodilator effect and then by diuretic action **(Flowchart 10.1)**.
5. ***Cerebral edema:*** Frusemide is used as an alternative to osmotic diuretics.
6. ***Forced diuresis:*** In poisoning due to drugs like barbiturates and salicylates, frusemide is used with IV fluids to induce diuresis and promote the excretion of toxic drugs.
7. ***Hypertension:*** With renal impairment may be treated with loop diuretics.
8. ***Acute hypercalcemia and hyperkalemia:*** Loop diuretics increase excretion of Ca^{++} and K^+. However, Na^+ and Cl^- should be replaced to avoid hyponatremia and hypochloremia.

THIAZIDES AND THIAZIDE-LIKE DIURETICS

Chlorothiazide was the first thiazide to be synthesized. All thiazides have a sulfonamide group.

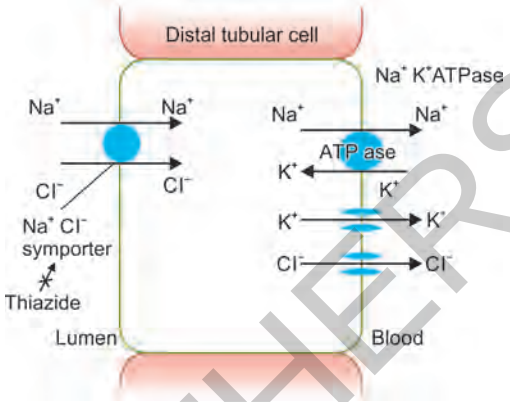
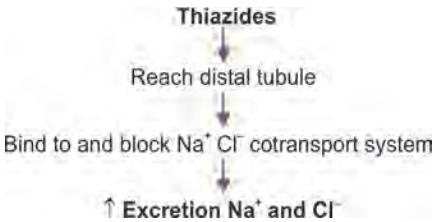


Fig. 10.3: Mechanism of action of thiazide diuretics.

Actions and mechanism of action: Thiazides act on the early distal tubule. Thiazides have a moderate efficacy because 90% of the filtered sodium is already reabsorbed before reaching the distal tubule. This group of drugs **blocks Na^+/Cl^- cotransport system (Fig. 10.3) in the early distal tubule** (site 3). They also inhibit carbonic anhydrase activity and increase bicarbonate loss. Thiazides also increase the excretion of Mg^+ and K^+ (in distal segments, Na^+ in the lumen is exchanged for K^+ which is then excreted). However, they inhibit the urinary excretion of Ca^{++} and uric acid resulting in **hypercalcemia** and **hyperuricemia**.



Pharmacokinetics: Thiazides are well absorbed orally and are rapid acting. Duration varies from 6 to 48 hours **(Table 10.2)**. They are excreted by the kidney.

Adverse effects:

1. **Hypokalemia** is the, most important side effect of thiazide use

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Table 10.2: Dose and duration of action of commonly used diuretics.

Diuretic	Daily dose (mg)	Duration (hrs)
Furosemide	20–80	3–6
Bumetanide	0.5–2	3–6
Hydrochlorothiazide	25–100	8–12
Polythiazide	1–3	24–48
Chlorthalidone	50–100	48–72
Xipamide	20–60	24–36
Metolazone	5–10	18–24
Spironolactone	50–100	6–12
Triamterene	50–100	4–6
Amiloride	5–10	20–24

2. **Metabolic alkalosis, hyperuricemia**, hypovolemia, hypotension, dehydration, hyponatremia, hypomagnesemia, hypochloremia, hypercalcemia, and hyperlipidemia are similar to that seen with loop diuretics.
3. **Hyperglycemia** induced by thiazides may precipitate diabetes mellitus probably by inhibition of insulin secretion. It is more common when long-acting thiazides are used for a long time.
4. Thiazides can cause **impotence** in men.
5. **Weakness,** fatigue, anorexia, gastrointestinal disturbances and **allergic reactions** like rashes and photosensitivity can be seen.

Uses:

1. **Hypertension:** Thiazides are the first line drugs.
2. **Congestive heart failure:** Thiazides are useful in the management of edema due to mild to moderate CHF.
3. **Edema:** Thiazides may be tried in hepatic (cirrhosis) or renal edema. Renal edema may be due to nephrotic syndrome, acute glomerulonephritis or chronic renal failure. Metolazone may be combined with loop diuretics in severe refractory edema.
4. ***Renal stones:*** Hypercalciuria with renal stones can be treated with thiazides which reduce calcium excretion.
5. ***Diabetes insipidus:*** Thiazides reduce plasma volume and GFR—a paradoxical effect—and benefit such patients.

Indapamide is particularly suitable in hypertension because it is claimed to lower blood pressure in subdiuretic doses and in such doses adverse effects are milder. It is well absorbed orally and has a long duration of action to permit once a day dosing.

POTASSIUM-SPARING DIURETICS

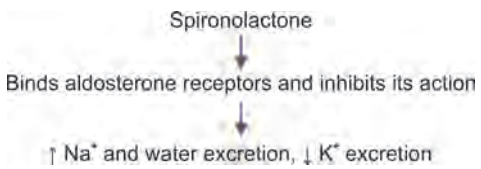
Potassium-sparing diuretics may act by two ways. They may be aldosterone antagonists or directly inhibit ion channels in distal tubule and collecting duct.

Spironolactone

Aldosterone increases the Na^+ reabsorption through Na^+ channels in the collecting tubule and increases K^+ secretion. It binds aldosterone receptors on distal tubule and collecting duct and competitively inhibits the action of aldosterone.

Spironolactone is an aldosterone antagonist **(Fig. 10.4)**. As major amount of Na^+ is already reabsorbed in the proximal parts, spironolactone has low efficacy. Spironolactone also reduces K^+ loss due to other diuretics.

It increases the excretion of calcium by a direct action on the renal tubules. Spironolactone is metabolized in the liver and its active metabolite canrenone is long acting.



Adverse effects include gynecomastia, sexual dysfunction in men, drowsiness, hyperkalemia

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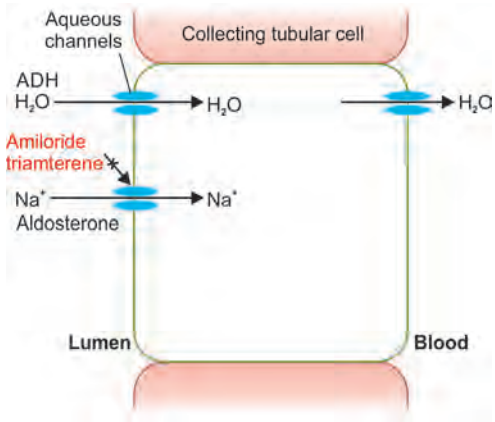

Fig. 10.4: Mechanism of action of potassium sparing diuretics. Spironolactone antagonizes the action of aldosterone while amiloride and triamterene directly inhibit the Na^+ channels (ADH promotes reabsorption of water through aqueous channels—it also increases the number of these channels).

especially in renal insufficiency; metabolic acidosis and skin rashes **(Table 10.3)**.

Eplerenone an analog of spironolactone has greater selectivity for mineralocorticoid receptors and milder activity on androgen and progesterone receptors. Thus the hormonal adverse effects are very much milder.

Amiloride and triamterene are directly acting agents which enhance Na^+ excretion and reduce K^+ loss by acting on ion channels in the distal tubule and collecting duct. They block the Na^+ transport through ion-channels in the luminal membrane. Since K^+ secretion is dependent on Na^+ entry, these drugs reduce K^+ excretion.

Adverse effects are gastrointestinal disturbances, hyperkalemia and metabolic acidosis.

Uses of K^+-Sparing Diuretics

1. **With thiazides** and loop diuretics to prevent potassium loss.
2. **Edema:** In cirrhosis and renal edema where aldosterone levels may be high.
3. **Hypertension:** Along with thiazides to avoid hypokalemia and for additive effect.
4. **CCF:** Used along with frusemide in moderate to severe heart failure.
5. **Primary or secondary aldosteronism:** Spironolactone is used.

CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrase is an enzyme that catalyzes the formation of carbonic acid which spontaneously ionizes to H^+ and HCO_3^-. This HCO_3^- combines with Na^+ and is reabsorbed.

$$H_2O + CO_2 \rightleftarrows H_2CO_3$$

$$H_2CO_3 \rightleftarrows H^+ + HCO_3^-$$

Table 10.3: Compare and contrast frusemide and spironolactone.

Features	*Frusemide*	*Spironolactone*
Chemistry	Sulfonamide	Synthetic steroid
Sites of action	Ascending limb of loop of Henle	Distal tubule and collecting duct
Mechanism of action	Blocks Na^+ K^+ $2Cl^-$ cotransport	Aldosterone antagonist
Efficacy	High	Low
Onset of action	Quick—2–5 minutes	Slow—may take several days
Effect on K^+	↑Excretion—Hypokalemia	↓Excretion—hyperkalemia
Unique adverse effects	Ototoxicity	Gynecomastia, hirsutism
Primary use	• CCF, edema, ascitis • Pulmonary edema	• Hyperaldosteronism • As adjuvant to other diuretics to reduce K^+ loss
Contraindications	Allergy to sulfonamides	Peptic ulcer

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Carbonic anhydrase inhibitors block sodium bicarbonate reabsorption and cause HCO_3^- diuresis. Carbonic anhydrase is present in the nephron, eyes, gastric mucosa, pancreas and other sites.

Acetazolamide, a sulfonamide derivative is a carbonic anhydrase inhibitor and increases the excretion of sodium, potassium, bicarbonate and water. The loss of bicarbonate leads to metabolic acidosis.

Other actions:

- **Eye:** Bicarbonate and sodium ions are required for the production of aqueous humor. Carbonic anhydrase inhibition results in decreased formation of aqueous humor and thereby reduces intraocular pressure.
- **Brain:** Bicarbonate is secreted into cerebrospinal fluid (CSF) and carbonic anhydrase inhibition reduces the formation of CSF.

Adverse effects:

- Metabolic acidosis due to HCO_3^- loss.
- *Renal stones:* Calcium is lost with HCO_3^- resulting in hypercalciuria. This excess Ca^{++} may precipitate resulting in the formation of renal stones.
- Hypokalemia, drowsiness and allergic reactions can occur.

Uses:

1. **Glaucoma:** Intraocular pressure is decreased by acetazolamide; it is given orally. Newer ones—methazolamide and dorzolamide are better tolerated and are available as eye drops.
2. **Alkalinization of urine:** May be required in overdosage of acidic drugs. Also, uric acid and cysteine excretion can be increased as these are soluble in alkaline urine.
3. **Metabolic alkalosis:** Acetazolamide increases HCO_3^- excretion.
4. **Mountain sickness:** In mountain climbers who rapidly ascend great heights, severe pulmonary edema or cerebral edema may occur. Acetazolamide may relieve symptoms by reducing the formation and pH of CSF—it can also be used for prophylaxis.
5. **Epilepsy:** Acetazolamide is used as an adjuvant as it increases the seizure threshold.
6. **Hyperphosphatemia:** When hyperphosphatemia is severe, it can be treated with acetazolamide to increase the urinary phosphate excretion.

OSMOTIC DIURETICS

Mannitol is a pharmacologically inert substance. When given IV (orally not absorbed), mannitol gets filtered by the glomerulus but not reabsorbed. It causes water to be retained in the proximal tubule and descending limb of Henle's loop by osmotic effect resulting in water diuresis. There is also some loss of sodium.

Adverse effects are dehydration, extracellular fluid (ECF) volume expansion, headache and allergic reactions.

Uses:

- To maintain urine volume and prevent oliguria in conditions like massive hemolysis, shock and severe trauma.
- To reduce intracranial and intraocular pressure—following head injury and glaucoma respectively.

Glycerol is effective orally. It reduces intraocular and intracranial pressure.

Newer Agents

Vasopressin antagonists are a new class of drugs found to induce diuresis. They inhibit the effects of ADH in the collecting tubule and cause free water diuresis. **Conivaptan, tolvaptan** and **lixivaptan** are the **vaptans** used in inappropriate ADH secretion syndrome.

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Sodium-glucose cotransporter-2 (SGLT-2) inhibitors: 90% of glucose is reabsorbed through SGLT-2 and inhibition of this transporter increases the excretion of glucose and sodium and causes diuresis. Dapagliflozin and canagliflozin are SGLT-2 inhibitors used in diabetes mellitus.

Drug Interactions with Diuretics

1. Frusemide and ethacrynic acid are highly protein bound and may compete with drugs like warfarin and clofibrate for protein-binding sites.
2. Ototoxic drugs like aminoglycosides should not be used with loop diuretics to avoid enhanced ototoxicity.
3. Hypokalemia induced by diuretics increases digitalis toxicity.
4. NSAIDs blunt the effect of diuretics as they cause salt and water retention.
5. Diuretics increase lithium toxicity by reducing renal excretion of lithium.
6. Other drugs that cause hyperkalemia (ACE inhibitors) and oral K^+ supplements should be avoided with K^+ sparing diuretics because, given together they can cause severe hyperkalemia.

DIURETICS AND DENTISTRY

- When a patient is on medication with anticoagulants like warfarin and diuretics, such as frusemide, profound anticoagulant activity would be present. Minor dental procedures including dental extraction can cause severe bleeding.
- When a patient is already receiving frusemide or other loop diuretics, avoid using aminoglycoside antibiotics as the ototoxicity can get added up.
- It is necessary to be cautious in using NSAIDs to a patient who is receiving diuretics because NSAIDs blunt the diuretic effect. However, one or two days of analgesics does not matter much.

ANTIDIURETICS

Antidiuretics are drugs that reduce urine volume. These include:

- Antidiuretic hormone (vasopressin)
- Thiazide diuretics
- Others
  - Carbamazepine
  - Chlorpropamide.

Antidiuretic hormone (ADH) or vasopressin is secreted by the posterior pituitary along with oxytocin. It is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus, transported along the hypothalamo-hypophyseal tract to the **posterior pituitary** and is stored there.

ADH is released in response to two stimuli—dehydration and rise in plasma osmolarity. ***Diabetes insipidus*** (DI) is chracterized by excretion of large volumes of dilute urine. It could be:

1. ***Neurogenic***—due to decreased secretion of ADH from the pituitary (neurohypophysis)
2. ***Nephrogenic***—due to reduced response from the renal tubules to ADH.

Vasopressin receptors: ADH acts on V1 and V2 receptors. Location:

1. **V1 receptors:**
   - Blood vessels (vasoconstriction)
   - Other smooth muscles— gut (increased peristalsis),
   - Kidneys, uterus and anterior pituitary.
2. **V2 receptors:** Collecting duct in the kidneys, vascular endothelium **(Fig. 10.4)**.

Actions: Antidiuretic hormone (ADH) increases water reabsorption by acting on the collecting duct. ADH activates the V2 receptors present on the cell membrane of the collecting duct and increases the water permeability of these cells.

ADH causes vasoconstriction and raises BP mediated by V1 receptors. It also acts on

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other smooth muscles to increase peristalsis in the gut and contracts the uterus.

Vasopressin is given parenterally as injection—SC/IM/IV or as nasal spray.

Vasopressin Analogs

Desmopressin, terlipressin, felypressin and **lypressin** are selective for V2 receptors and are longer acting. Desmopressin is given as nasal spray. Felypressin is used with local anesthetics to prolong the duration of action because of its vasoconstrictor properties.

Adverse effects: When used intranasally, ADH can cause nasal irritation, allergy, rhinitis and atrophy of the nasal mucosa. Other effects include nausea, abdominal cramps and backache (due to contractions of the uterus).

Uses of vasopressin analogs:

1. ***Central diabetes insipidus*** (DI) of pituitary origin or neurogenic DI—desmopressin is the drug of choice. It should be used life-long (not effective in nephrogenic DI).
2. ***Bleeding esophageal varices***—ADH constricts mesenteric blood vessels (V1 receptors) and reduces pressure on the varices → stops bleeding. Terlipressin is the preferred analog as it is safer.
3. ***Before abdominal radiography***—expels gases from the bowel.
4. ***Hemophilia*** and von Willebrand's disease—ADH may release factor VIII and prevent bleeding—desmopressin is given IV.
5. ***Nocturnal enuresis:*** Desmopressin at bed time may help by reducing the urine formed at night.

Others:

Paradoxically **thiazides** reduce urine volume in diabetes insipidus of both pituitary and renal origin by an unknown mechanism.

Carbamazepine an antiepileptic, stimulates ADH secretion.

Vasopressin antagonists: Conivaptan, tolvaptan and lixivaptan are available for the treatment of inappropriate or elevated ADH secretion.

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