OSMOTIC DIURETICS

- Osmotic diuretics have their major effect in the proximal tubule and the descending limb of Henle's loop. Through osmotic effects, they also oppose the action of ADH in the collecting tubule
- **Osmotic Diuretics Drugs (Mannitol)**

Clinical Indications

- **Reduction of Intracranial and Intraocular Pressure**
  Osmotic diuretics alter Starling forces so that water leaves cells and reduces intracellular volume. This effect is used to reduce intracranial pressure in neurologic conditions and to reduce intraocular pressure before ophthalmologic procedures.

ANTIDIURETIC HORMONE (ADH, VASOPRESSIN) AGONISTS

- **Vasopressin** and **desmopressin** are used in the treatment of central diabetes insipidus. renal action appears to be mediated primarily via V_2 ADH receptors, although V_{1a} receptors may also be involved.
- There are three known vasopressin receptors, V_{1a}, V_{1b}, and V_2. V_1 receptors are expressed in the vasculature and CNS, while V_2 receptors are expressed specifically in the kidney

Clinical Indications

- **Syndrome of Inappropriate ADH Secretion** Antidiuretic hormone antagonists are used to manage SIADH when water restriction has failed to correct the abnormality. This generally occurs in the outpatient seting, where water restriction cannot be enforced, but can occur in the hospital when large quantities of intravenous fluid are needed for other purposes.

SUMMARY Diuretic Agents

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
CARBONIC ANHYDRASE INHIBITORS				
• Acetazolamide, others	Inhibition of the enzyme prevents dehydration of H_2CO_3 and hydration of CO_2 in the proximal convoluted tubule	Reduce reabsorption of HCO_3^-, causing self-limited diuresis • hyperchloremic metabolic acidosis • reduce body pH, • reduce intraocular pressure	Glaucoma, mountain sickness, edema with alkalosis	Oral and topical preparations available • duration of action ~8–12 h • *Toxicity:* Metabolic acidosis, renal stones, hyperammonemia in cirrhotics
• *Brinzolamide, dorzolamide: Topical for glaucoma*				
SGLT2 INHIBITORS				
• Canagliflozin	Inhibition of sodium/glucose cotransporter (SGLT2) in the PCT results in decreased Na^+ and glucose reabsorption	Inhibition of glucose reabsorption lowers serum glucose concentration, and reduced Na^+ reabsorption causes mild diuresis	Diabetes mellitus; approved for the treatment of hyperglycemia, not as a diuretic	Available orally. Half-life 10–12 h • not recommended in severe renal or liver disease
• *Dapagliflozin, empagliflozin: similar to canagliflozin*				

(*continued*)

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
LOOP DIURETICS				
• Furosemide	Inhibition of the Na/K/2Cl transporter in the ascending limb of Henle's loop	Marked increase in NaCl excretion, some K wasting, hypokalemic metabolic alkalosis, increased urine Ca and Mg	Pulmonary edema, peripheral edema, heart failure, hypertension, acute hypercalcemia, anion overdose	Oral and parenteral preparations • duration of action 2–4 h • *Toxicity:* Ototoxicity, hypovolemia, K wasting, hyperuricemia, hypomagnesemia
• *Bumetanide, torsemide: Sulfonamide loop agents like furosemide*				
• *Ethacrynic acid: Not a sulfonamide but has typical loop activity and some uricosuric action*				
THIAZIDES				
• Hydrochlorothiazide	Inhibition of the Na/Cl transporter in the distal convoluted tubule	Modest increase in NaCl excretion • some K wasting • hypokalemic metabolic alkalosis • decreased urine Ca	Hypertension, mild heart failure, nephrolithiasis, nephrogenic diabetes insipidus	Oral • duration 8–12 h • *Toxicity:* Hypokalemic metabolic alkalosis, hyperuricemia, hyperglycemia, hyponatremia
• *Metolazone: Popular for use with loop agents for synergistic effects*				
• *Chlorothiazide: Only parenteral thiazide available (IV)*				
• *Chlorthalidone: Long half-life (50–60 h) due to binding to red blood cells*				
POTASSIUM-SPARING DIURETICS				
• Spironolactone	Pharmacologic antagonist of aldosterone in collecting tubules • weak antagonism of androgen receptors	Reduces Na retention and K wasting in kidney • poorly understood antagonism of aldosterone in heart and vessels	Aldosteronism from any cause • hypokalemia due to other diuretics • postmyocardial infarction	Slow onset and offset of effect • duration 24–48 h • *Toxicity:* Hyperkalemia, gynecomastia (spironolactone, not eplerenone) • additive interaction with other K-retaining drugs
• Amiloride	Blocks epithelial sodium channels in collecting tubules	Reduces Na retention and K wasting • increases lithium clearance	Hypokalemia from other diuretics • reduces lithium-induced polyuria • Liddle's syndrome	Orally active • duration 24 h • *Toxicity:* Hyperkalemic metabolic acidosis
• *Eplerenone: Like spironolactone, more selective for aldosterone receptor*				
• *Triamterene: Mechanism like amiloride, much less potent, more toxic*				

OSMOTIC DIURETICS

• Mannitol	Physical osmotic effect on tissue water distribution because it is retained in the vascular compartment	Marked increase in urine flow, reduced brain volume, decreased intraocular pressure, initial hyponatremia, then hypernatremia	Renal failure due to increased solute load (rhabdomyolysis, chemotherapy), increased intracranial pressure, glaucoma	IV administration • *Toxicity:* Nausea, vomiting, headache

VASOPRESSIN (ADH) ANTAGONISTS

• Conivaptan	Antagonist at V_{1a} and V_2 ADH receptors	Reduces water reabsorption, increases plasma Na concentration, vasodilation	Hyponatremia, congestive heart failure	IV only, usually continuous • *Toxicity:* Infusion site reactions, thirst, polyuria, hypernatremia
• Tolvaptan	Selective antagonist at V_2 ADH receptors	Reduces water reabsorption, increases plasma Na concentration	Hyponatremia, SIADH	Oral • duration 12–24 h • *Toxicity:* Polyuria (frequency), thirst, hypernatremia