Anti- diuretic Drugs

Disclaimer

All the content material provided here is only made for teaching purpose.

Anti-diuretics

> The drugs that decrease urine volume are called antidiuretics.

> They inhibit water excretion without affecting salt excretion.

> Primary indication of antidiuretics is the treatment of diabetes insipidus(DI).

Anti-diuretic Classification

1. Antidiuretics hormones and its analogues
   - Vasopressin(ADH)
   - Desmopressin
   - Lypressin
   - Terlipressin
1. Natriuretics
   - Thiazides, Amiloride,
3. Miscellaneous
   - Carbamazepine, Chlorpromazine, Indomethacin

Anti-diuretic Hormone (ADH)

> Physiological antidiuretics is 8 arginine vasopressin (AVP) that is synthesized in the hypothalamus and secreted by the posterior pituitary.

> It is secreted in response to increased plasma osmolality or decreased volume of extracellular fluid (ECF).

> ADH acts via 2 receptors V1 and V2

Vasopressin (ADH) Receptors

	V1 receptor	V2 receptor
Location	V1a - vascular and other smooth muscle, platelets and hepatocytes, wider distribution. V1b - anterior pituitary, brain and pancreas. (V1b rec. also called as V3 receptor)	Site- principal cells of collecting ducts(CDs) in the kidney, thick ascending limb of LH. Endothelium of blood vessels,
Mechanism	G protein coupled cell membrane receptor PLC-IP3/DAG pathway	G -protein coupled cell membrane receptor. Adenylyl cyclase c-AMP pathway
Functions	Vasoconstriction, Visceral smooth muscle contraction, platelet aggregation	Antidiuretic action

Actions of ADH

> In the absence of ADH, collecting ducts(CD) of the nephron are impermeable to water.

> ADH increase the permeability of CD by its actions on V2 receptors.

> Stimulation of these receptors elevates cAMP levels that increase aquaporins on the apical membrane of CD(by decreasing endocytosis and increasing exocytosis).

> Activation of vasopressin regulated urea transporter at apical membrane of collecting ducts in the inner medulla.

Contd....

> Translocation of Na K-2Cl cotransporter to the luminal membrane of cells in thick ascending limb of loop of henle.

> Activation of Na+ K+ 2Cl- cotransporter in Thick ascending limb of loop of henle (TAL)cells.

> V1a receptor mediated vasoconstriction of vasa recta.

> All the above effects leads to medullary hypertonicity and maximum concentrated urine.

> Gene mediated increased expression of aquaporin 2 Channels in collecting duct cells.

> Gene mediated increased expression of Na^+ K^+ $2Cl^-$ cotransporter in TAL cells.

Effects on Blood vessels:

> AVP constrict blood vessels through V1 receptors and increases peripheral resistance.

> Rise in BP occurs at higher doses.

> AVP is an effective pressor agent in shock patients.

> Though vasopressor effect is not physiologically important in the healthy state, it may play role in hypotensive state, CHF.

> Most visceral smooth muscles contract.

> Increased peristalsis in gut, results in evacuation of bowels and expulsion of gases.

> Uterus: contracted by AVP acting on oxytocin receptors.

> CNS: exogenously administered AVP does not cross blood brain barrier. AVP may be involved in the regulation of body temperature, systemic circulation, ACTH release and in learning of tasks.

> AVP induces platelet aggregation and hepatic glycogenolysis.

> It releases coagulation factor VIII and von willebrand's factor.

Pharmacokinetics:

> AVP is inactive orally because it is destroyed by proteolytic enzyme.

> It can be given by any parenteral route.

> Plasma half life is 25 min.

Vasopressin analogues

Lypressin:

> less poent than AVP.

> It acts on both V1 and V2 receptor and has longer duration of action.

> it is used in place of AVP for V1 receptor mediated action.

Terlipressin:

> synthetic prodrug of vasopressin is specifically used for bleeding esophageal varices.

Desmopressin:

> It is synthetic selective V2 antagonist.

> 12 times more potent antidiuretic and negligible vasoconstrictor activity.

> Intranasal route is preferred though bioavailability is only 10-20%.

Uses

> Terlipressin stops bleeding in 80% and has been shown to improve survival.

>Simultaneous addition of nitroglycerine with vasopressin reduces the cardiotoxic effects of vasopressin and enhances beneficial splanchnic effects of drug.

> Dose-2mg followed by 1mg every 6hr I.V. until bleeding stops (max. 72 hr)

2). Miscellaneous uses:

> To treat postoperative paralytic ileus and before abdominal radiography.

> Vasopressin or terlipressin can be used during abdominal surgery in patients with portal hypertension to reduce the risk of haemorrhage.

> These drugs can also be used to prevent bleeding in acute haemorrhagic gastritis .

A. based on V2 actions: (Desmopressin is the drug of choice) 1).Diabetes insipidus:

> Only central DI (neurogenic or neurohypophyseal DI) respond to desmopressin because ADH receptors on CD are non functional.

> Dose: oral 100 µg TDS; (nasal) 10-40 µg /day;(IV, IM or SC) 1-4 µg /day.

2).Primary Nocturnal Enuresis:

> Desmopressin is used intranasally with restricted fluid intake and behavioural conditioning.

> Dose: orally 200-400 µg at bed time; (nasal) 20-40 µg at bedtime.

3).To relieve post lumbar puncture Headache:

> Due to its water retention property it facilitates equilibration of fluid osmolarity in CNS.

4). Bleeding disorders in patients of Haemophilia A and von Willebrand's Disease:

> Desmopressin elevates factor VIII and von willebrand factor and shortens bleeding time.

Adverse effects:

V1 receptor mediated adverse effects

> Facial pallor, nausea, abdominal cramps and an urge to defecate(due to increased intestinal motility), and precipitation of angina(due to constriction of coronary arteries).

> More with vasopressin, terlipressin and lypressin.

> It is contraindicated in patients of hypertension and ischaemic heart disease.

V2 receptor mediated Adverse Effects:

> Fluid retention and hyponatraemia.

> Carbamazepine, Indomethacin and chlorpropamide can potentiate the antidiuretic effects of desmopressin.

> Irritation, ulceration and rhinitis due to intranasal administration.

Thiazides

- These drugs are used as diuretics but exert paradoxical effect (decrease urine formation) in DI.
- This paradoxical effect is believed to be due to increased formation of cAMP in the distal tubules.
- Another proposed mechanism is that thiazides cause dehydration that result in compensatory increase in reabsorption of Na and water from the proximal portions of nephron.

> These are low efficacy antidiuretics but beneficial in both central as well as nephrogenic DI.

> hydrochlorothiazide 25-50 mg TDS or equivalent dose of longer acting agent is commonly used.

Amiloride

> It is the agent of choice for the treatment of lithium induced DI.

> Along with blocking entry of Na in the principal cells of CD, it also blocks Li entry.

Indomethacin:

> Also reduce polyuria in renal DI to some extent by reducing renal PG synthesis.

> It can be combined with a thiazides and amiloride in nephrogenic DI.

Chlorpropamide:

> It is long acting sulfonylurea oral hypoglycaemic.

> It reduce urine volume in DI of pituitary origin.

> It sensitizes the kidney to ADH action.

Carbamazepine:

> An antiepileptic drug which reduces urine volume in DI of pituitary origin.

Vasopressin antagonists

Tolvaptan:

> It is an orally active nonpeptide selective V2 receptor antagonist.

> It is used for the treatment of hyponatraemia due to CHF, cirrhosis of liver or syndrome of inappropriate ADH secretion(SIADH).

> It increases the free water clearance by the kidney and helps to correct the low plasma Na levels.

> Mozavaptan (V2 selective antagonist) Conivaptan (V1a+V2 antagonist)

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