B19 - Diuretics

(a) To outline a physiological basis of classifying diuretics related to their site of action.

See diagram - Sites of action diuretics

(1) Thiazides
(2) Loop
(3) Osmotic
(4) K+ sparring
(5) Aldosterone antagonists
(6) Carbonic anhydrase inhibitors

Thiazides

- ie. bendroflurazide
- used in HT, mobilization of oedema, management of DI, treatment of hypercalcaemia.
- inhibit reabsorption of Na+ & Cl- principally in the cortical portions of the ascending loops of Henle & proximal & distal renal tubules -> increased loss of Na+, Cl- & HCO3- + associated loss of K+ (occurs when ever there is enhanced distal delivery of Na+ & H2O).

Bendroflurazide

Chemical - a thiazide

Uses

(1) HT
(2) oedema
(3) diabetes insipidus
(4) renal tubular acidosis
(5) hypercalcuria
(6) inhibition of lactation

Presentation

- tablets: 2.5mg to 5mg
- other combination drugs

Route - PO

Dose - 2.5mg - 10mg daily

Duration: 16hrs

PK

Absorption - great
Distribution - 94% protein bound, Vd 1.2L/kg
Metabolism -
Elimination - urinary, 30% unchanged, Cl 3.5ml/min/kg, t1/2 = 3hrs

PD

Main action - diurectic & antihypertensive

Mechanism

- inhibit Na+ & Cl- co-transport in DCT -> increased urinary excretion of Na+, K+ & H2O.

CVS

- decrease BP
- slight increase in Q

RESP

- nil

CNS

- in toxic doses -> depression

GU

- decreased RBF
- decreased GFR
- decreased urinary excretion of Ca2+ & increased loss of Na+, K+ & Mg2+

Metabolic

- increase blood glucose
- increase urate, triglyceride & cholesterol concentration.

Toxicity

- CNS depression
- haemopoietic disturbance
- rashes
- impotence
- acute pancreatitis

- gout
- hypokalaema
- hypercalcaemia

Drug interactions

- digoxin -> toxicity
- NDNMBD -> increased duration of blockade
- GA -> increased risk of arrhythmias
- opioids, barbiturates, halothane -> hypotension

Loop

- ie. frusemide, bumetanide, ethcrynic acid
- inhibit Na+ & Cl- reabsorption in medullary portions of the ascending limbs of LOH.

Frusemide

Chemical - an anthranilic acid (sulphonamdie) derivative

Uses

(1) oedema of cardiac, renal or hepatic origin
(2) chronic renal failure
(3) hypertension
(4) raised ICP
(5) symptomatic hypercalcaemia
(6) conversion from oliguric -> polyuric renal failure

Presentation

- injection: clear solution, must be protected from light
- tablets

Route - IV, IM or PO

Doses

- PO: 20 -> 2000mg
- IM: 20 -> 50mg
- IV: 10 -> 1000mg

PK

Absorption

- bioavailability 60%

Distribution

- 96% protein bound
- Vd = 0.1 L/kg

Metabolism

- in kidney to glucuronide

Elimination

- 80% kidney, 20% faeces
- Cl = 2mL/min/kg
- t1/2 = 60min

PD

Main action - diuretic

Mechanism of action

- inhibition of Na+ & Cl- reabsorption in PT & ascending LOH -> reduces tonicity in renal medulla -> diuresis

CVS

- vasodilation (pulmonary & systemic)

RESP

- decrease SOB

GU

- diuresis occurs in 2min and lasts 2hrs
- O2 consumptin in the LOH is reduced

Metabolic

- metabolic alkalosis
- increased in serum urate
- hypkalaemia
- hypocalaemia
- hypomagnesaemia

Other adverse effects

- ototoxicity
- pancreatitis
- skin rashes
- bone marrow depression
- interstitial nephritis

Osmotic

- ie. mannitol & urea
- freely filterable at glomerulus, undergo limited reabosorption, resist metabolism and are pharmacologically inert.
- they thus can be administered in large quantities to alter the osmolarity of the plasma, filtrate & renal tubular fluid -> induce a osmotic diuresis.
- site of action = parts that are highly permeable to H2O -> PCT, descending LOH.

Mannitol

Chemical - an alcohol derived from Dahila tubers (6 carbon sugar)

Uses

(1) reduce CSF volume -> reduce ICP
(2) preserve renal function during perioperative period in jaundice patients under going major vascular surgery.
(3) acute management of glaucoma
(4) bowel prep
(5) initiate diuresis in transplanted kidney
(6) treatment for rhabdomyolysis

Presentation

- sterile solution
- 10-20% in water

Route - IV

Dose

- decrease ICP: 1g/kg over 15min -> 0.5g/kg intermittently
- diuresis: 0.5-1.0 g/kg
- bowel prep: 100mL of 20%

Onset - minutes
Duration - 3 hrs

PK

Absorption - 20% absorbed orally
Distribution - Vd 0.5L/kg
Metabolism - not metabolized
Elimination - Cl = 7mL/min/kg, t1/2 = 72min

PD

Main action - osmotic diuretic

Mechanism

- increases the osmolarity of the glomerular filtrate -> increasing urinary volume
- decreases CSF volume & pressure by

(1) decreasing rate of CSF production
(2) withdrawing brain extracellular water across the BBB into plasma

CVS

- decreases Q
- decreases BP

CNS

- decreases ICP
- preserves preservation of cerebral blood flow

GU

- diuresis
- washes out medullary interstitial gradient -> decreased ability to concentrate urine

Metabolic

- Na+ & K+ plasma levels may fall
- plasma urea increases

Other adverse effects

- irritant to veins & tissues
- may have toxic effect on DCT & CD's
- after cessation of treatment -> may produce rebound increases in ICP.

K+ sparring

- ie. amiloride, triamterine
- act on renal tubular transport mechanism in DCT -> increase in urinary excretion of Na+, Cl- & HCO3-.

Amiloride

Chemical - pyrazinoylguanidine

Uses

(1) oedema of all causes
(2) HT

Presentation

- 5mg tablets
- in fixed dose combinations

Route - PO

Doses

- 10 to 20mg/day

Onset - 2 hrs
Duration - 24hrs

PK

Absorption - bioavailability = 50%
Distribution - <5% protein bound, Vd = 5L/kg
Metabolism - no metabolism
Elimination

- 50% unchanged in urine
- 50% in faeces
- Cl = 300mL/min/kg
- t1/2 = 20hrs

PD

Main action - diuretic

Mechanism

- selective block of Na+ reabsorption in DCT -> electrical potential across tubular epithelium decreases -> K+ exretion inhibited.

CVS

- decrease in Na+ content in arteriolar smooth muscle -> decrease in BP

GU

- diuresis
- increased Na+ & HCO3- loss
- decreased K+, Ca2+, ammonium & H+ loss

Metabolic

- inhibition of H+ ion excretion -> alkalinisation of urine
- increase in serum uric acid levels

Other adverse effects

- hyperkalaemia
- nausea
- abdominal pain
- diarrhoea
- rashes
- cramps
- impotence
- interstitial nephritis

Drug interactions

- digoxin -> accumulation of dig
- NSAIDS -> amiloride activity obtunded

Aldosterone Antagonists

- ie. spirnolactone

Spirinolactone

Chemical - synthetic steroid

Uses

(1) congestive heart failure

(2) hepatic cirrhosis with ascites & oedema
(3) refractory oedema
(4) hypertension
(5) nephrotic syndrome
(6) diagnosis & treatment of Conn's sydrome

Presentation

- tablets: 25 to 100mg

Route - PO

Doses

- 100 - 400mg/day (onset = 4 days)

PK

Absorption

- bioavailability 70%

Distribution

- >90% protein bound

Metabolism

- rapidly & extensively hepatically metabolised

Elimination

- urinary & biliary
- t1/2 = 2hrs

PD

Main action - diuretic

Mechanism of action

- competitive antagonism of ALD at its receptor site (cytoplasmic mineralocorticoid receptor) in DCT -> Na+ reabsorption inhibited & K+ ion reabsorbed

CVS

- decrease BP

CNS

- sedation
- weakness

GI

- n & v

GU

- diuresis
- mentrual disturbances

Metabolic

- inhibition of ovarian androgen secretion -> antiandrogenic effect
- increase in renal Ca2+ excretion -> hypercholraemic metabolic acidosis
- increase plasma urea concentration
- hyperkalaemia
- gynaecomastia in men

Drug interactions

- decreased response to pressors & anaesthetic agents

Carbonic anhydrase inhibitors

- ie. acetalzolamide
- non-competitive inhibition of CA in proximal renal tubules -> diminished loss of H+ & increased loss of HCO3-.

Acetazolamide

Chemical - a sulphonamide

Uses

(1) glaucoma
(2) pet mal epilepsy
(3) Meinere's disease
(4) familial periodic paralysis
(5) prophylaxis & treatment of mountain sickness.
(6) reversal of metabolic acidosis in critically ill

Presentation

- 250mg tablets
- 500mg vials for reconstitution with H2O

Route - IV, PO

Dose - 250 to 1000mg Q4hrly

PK

Absorption - 100% bioavailability
Distribution - 80% protein bound
Metabolism - not metabolized in man
Elimination - urinary, Cl 2.7mL/min/kg, t1/2 = 4hrs

PD

Main action - diuretic & decrease in intraocular pressure

Mechanism

- reversible, non-competitive inhibition of CA within cell cytosol and on brush border of the PCT.
- enzyme catalyses the conversion of HCO3- + H+ -> carbonic acid -> CO2 + H2O
- decreases the availability of H+ ions therefore Na+ & HCO3- remain in the tubule as Na+ usually transported with H+.

RESP

- produces a compensatory increase in ventilation in response to the metabolic acidosis & increased tissue CO2

CNS

- anticonvulsant
- decreased IOP
- decrease in CSF formation

GI

- inhibits pancreatic & gastric secretion

GU

- mild diuresis (alkaline urine)

Metabolic

- hyperchloraemic metabolic acidosis
- interfers with iodide uptake in thyroid gland

Other adverse effects

- GI & haemopoietic disturbances
- rashes
- renal stones
- hypokalaemia

Drug interactions

- renal or hepatic failure -> contraindicated

Chemical

(b) To describe the actions of mannitol, frusemide, thiazides, aldosterone antagonists & carbonic anhydrase inhibitors.

See above

(c) To describe the side-effects of the diuretics.

See above

(d) To describe the major applications & toxicities of thiazides, loop diuretics & K+ sparring diuretics.

See above