Ho Medical ANAESTHESIA

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Fluid & Electrolyte Physiology

Physiol-09A11/01A1 Outline the determinants and regulation of extracellular fluid volume.

1. ECF volume is the volume of fluid in the extracellular compartments: interstitial, intravascular and transcellular fluid compartments.
    a. Normal value: 33% total body water, 20% total body weight = 15L.

2. Determinants of ECF: The ECF is separated from the ICF by the cell membrane. Generally, this is permeable to water, but impermeable to many solutes. Thus, the main determinants of ECF are:
    a. the total amount of osmotically active solute present in the ECF compartment (tonicity)
    b. the total body water (hydration)

    Na (cation) and Cl (anion) are the major osmotically active solutes in the ECF compartment. Na accounts for 86% of ECG osmolality and 93% ECF tonicity. Thus, the distribution of TBW can be considered as being effectively determined by the [Na^+] of ECF.
    c. Normal [Na+] = 135-145mmol/L
    d. Normal daily intake 1-2mmol/L = excretion (kidney, sweat, faeces)

3. Regulation of ECF: important for maintaining ECF fluid volume when fluid depletion occurs. The regulation involves the regulation of sodium excretion and reabsorption.

System	Sensor	Effector
ADH	Osmoreceptors: hypothalamic cells OVLT/SFO, detect 1-2% change osmolality >280mosm/L → linear firing increase. Low baroreceptors: great veins, R atria. Detect 10% ↓CVP/blood volume → linear firing increase. Less sensitive, more potent than osmoreceptors. High baroreceptors: carotid sinus, aortic arch detect rise pulse pressure and MAP.	↑osmolality, ↓ blood volume → release of ADH from SO and PV nuclei → axonal transport into posterior pituitary → Released into circulation. Acts on: V_1 (vessels) – vasoconstriction renal vessels V_2 (P cells of DCT/CD) – G_sPCR → ↑cAMP → insertion aquaporin-2 channels → ↑ water reabsorption from CD → ↓urine output. Also ↑ADH-urea transport in DCT/CD → ↑medullary tonicity. V_3: stimulate thirst
RAS	High baroreceptors: ↓ firing with low MAP → ↑SNS → β_1 renin stimulation. Renal: ↓MAP → ↓renal perfusion → ↓afferent arteriolar P → ↓stretch internal baroreceptors JG cells → ↑renin release	Renin: cleaves angiotensinogen → Ang I → Ang II Ang II: Stimulation aldosterone from adrenal Stimulation thirst → ↑ water intake → ↑ECF volume Vasoconstriction ↑ Na reabsorption from PCT Constriction eff > aff arteriole → ↓GFR → ↓Na loss
Aldosterone	Stimulated by: Renin ACTH Hyperkalaemia	Steroid hormone: intracellular receptors → ↑basolateral Na/K ATPase activity, ↑ insertion of Na, K channels in P cells of CD → ↑Na reabsorption.
ANP	Stretch receptors in the RA → respond to ↑ECF volume	Dilation of afferent arteriole, constriction efferent arteriole → ↑GFR → ↑Na filtration and excretion Direct ↓Na reabsorption ↓ renin, ADH, aldosterone release
Tuboglomerular	↓ECF → ↓RBF → ↓GFR →	↓adenosine, ↑NO → relaxation afferent

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feedback	↓Na delivery macula densa	arteriole → ↑GFR → ↑Na filtration
Glomerulotubular feedback	↑ECF → ↑GFR ↑Na transport with glucose ↑ π peritubular capillaries	↑Na reabsorption (feedback to maintain relatively constant proportion Na reabsorption 65% in PCT).

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Physiol-05A11/01A7Describe how the body detects and responds to a water deficit.
1992 Write short notes on osmoreceptors

1. Total body water is usually 60% of body weight in the adult and is divided into ECF and ICF. The ECF water is the component under regulation, with the ICF dependent as water freely crosses cell membranes.
   The regulation of water balance is a negative feedback system.

2. Detection of water deficit (sensors)
   a. Osmoreceptors: a pure water deficit results relative ↑osmolality of ECF (main solute is Na). Receptors in OVLT and SOF respond to ↑brain ECF tonicity.
      i. Osmolality = 280-295mosm/L
      ii. Detect 1-2% ↑osmolality → linear firing response
      iii. Results in ↑ADH release from SO and PV nuclei of hypothalamus.
   b. Baroreceptors: water deficit → ↓ECF volume → ↓MAP
      i. Low pressure receptors: located atria and great veins. ↓MAP → activation of baroreceptors → ↑ADH release.
         1. Detection begins at 10% volume depletion = 4L water deficit (300mL plasma deficit)
         2. Less sensitive, more potent than osmoreceptors.
      ii. High pressure receptors: located carotid sinus, aortic arch. ↓MAP → ↓activation of stretch receptors → ↓inhibition of SNS, activation PNS (VMS in medulla)
      iii. Intrarenal pressure receptors: baroreceptors in JG cells: ↓MAP → ↓renal BF → ↓afferent arteriole stretch → ↑renin release form JG cells. Enables autoregulation of GFR between MAP 70-170mmHg.

3. Response to water deficit: aim to conserve water (↓ excretion, ↑reabsorption) from kidney.

Effector	**Trigger**	**Mechanism**	**Result**
ADH	↑osm, ↓ECF volume, stress, nausea, Ang II, standing, drugs (carbamezapine)	V_1: (vessels) – vasoconstriction renal vessels V_2: (P cells of DCT/CD) – G_sPCR → ↑cAMP → insertion aquaporin-2 channels → ↑ water reabsorption from CD → ↓urine output. ↑ADH-urea transport in DCT/CD → ↑medullary tonicity. V_3: stimulate thirst	↓GFR → ↓ water filtration ↑water reabsorption → max urine osmolality 1400mosm/L ↑Water intake
Renin	β_1 stimulation JG baroreceptors	Renin: cleaves angiotensinogen → Ang I → Ang II Stimulation aldosterone from adrenal Stimulation thirst Vasoconstriction ↑ Na reabsorption from PCT	↑Na reabsorption ↑ water intake ↑MAP ↑ Na reabsorption
Aldosterone	Angiotensin II ACTH ↑K	Steroid hormone: intracellular receptors → ↑basolateral Na/K ATPase activity, ↑ insertion of Na, K channels in P cells of CD	↑Na reabsorption.
SNS	β_1 stimulation α_1 stimulation	↑renin peripheral vasoconstriction	↑MAP

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Physiol-96A7 In the diagram below indicate how the solvent and solute move across a semipermeable membrane and give a brief explanation of the principles involved.

Blood			
Potassium 6.5mmol/L	Urea 40 mmol/L	Osm 320mosm/kg	Pressure 100mmHg
SEMIPERMEABLE MEMBRANE			
Potassium 3.5mmol/L	Urea 0 mmol/L	Osm 346mosm/kg	Pressure 10mmHg
Dialysate			

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1. The movement of substances across the semi-permeable membrane is dialysis involves the following processes:
    a. Solute: K, urea – both are able to cross cell membranes with relative ease
    b. Solvent: water
    c. Diffusion: the movement of solute from high → low concentration. Important for fluid movement between ICF ⇔ ECF.
    d. Osmosis: the movement of solvent (water) from low → high osmolality. Important for fluid movement between ICF ⇔ ECF.
    e. Filtration: the movement of solvent due to balance of hydrostatic and oncotic pressures. Important for the movement of fluid between plasma ⇔ interstitial fluid.
    f. Solvent drag: the movement of solvent coupled with movement of solute (convection)

2. Diffusion: process is generally slower than osmosis and governed by Fick's law:

$$\textbf{Diffusion} = \frac{\textbf{Sol x A x } \Delta\textbf{P}}{\sqrt{\textbf{MW}}\textbf{xT}}$$

Substance	Direction	Concentration
K	blood → dialysate	Approaches 3.5 mmol/L
Urea	blood → dialysate	Approaches 0 mmol/L

3. Osmosis: process is immediate and rapid.
    a. Water will diffuse into the hypertonic dialysate with a driving gradient 26mosm/L.

4. Filtration: the oncotic pressure of blood (holds water in) opposes the hydrostatic pressure of blood (100mmHg). The balance of forces dictates direction and rate of movement and is given by Starling's forces:

$$\textbf{NFP} = \textbf{k}[(\textbf{P}_\textbf{c} - \textbf{P}_\textbf{i}) - \boldsymbol{\sigma}(\boldsymbol{\pi}_\textbf{c} - \boldsymbol{\pi}_\textbf{i})]$$

Generally, the oncotic pressure is approximately 25mmHg, such that:
NFP= 90 – 25 = 65mmHg

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Physiol-95B5 Outline the effects of IV administration of 500 mls of 20% mannitol, and the potential problems associated with its use.

1. Mannitol is an osmotic diuretic. It is a low molecular weight (MW = 182) charged polysaccharide which does not cross cell membranes (especially the BBB) and is freely filtered at the renal glomerulus.
    a. 20% mannitol = 200mg/mL
    b. Osmolality = 1100mosm/L (hypertonic compared to plasma 285mosm/L)

2. Physiological Effects:

Effect	**Description**
Mechanism	Hypertonic and hyperosmotic and distributed Draws water out of ICF
Use	↓CSF pressure / volume Peri-operative diuresis in renal impairment, transplanted kidneys
Cardiovascular	Does not cross cell membranes (reflection co-efficient 0.9) ↑ intravascular volume ↓haematocrit and blood viscosity
Renal	Osmotic diuresis Role in renoprotective diuresis
Cerebral	Draws out water from CSF (does not cross BBB) ↑ cerebral perfusion pressure (↓ICP and ↑IV volume)

3. Adverse Effects:
    a. Initial intravascular overload: due to ↑IV volume → ANP system activation
        i. CCF, acute pulmonary oedema
        ii. Water intoxication
        iii. Hypertension
    b. Delayed Diuresis and dehydration: following osmotic diuresis
        i. Hypotension
        ii. Hyperosmolality → activation of ADH
        iii. ↓CPP → exacerbation of cerebral ischaemia
    c. Electrolyte abnormalities:
        i. ↑ANP → ↓ Na
        ii. ↓ aldosterone / Ang II → ↓Na, ↑K
    d. Venous Irritation
    e. Allergy

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MAKE-UP: Compare the distribution of a 1L infusion of normal saline, 5% dextrose and iso-osmotic albumin.

1. Normal saline, 5% dextrose and albumin are all iso-osmotic solutions used in various clinical settings.

2. Fluid compartments: assuming the exclusion of slowly equilibrating fluids (dense CT and bone fluid – 15% of TBW)
    a. Intracellular fluid – 55% TBW, 23 litres
    b. Interstitial fluid – 20% TBW, 8.4L
    c. Intravascular fluid – 7.5% TBW, 3.2L plasma + RCV 1.8L

3. Assumptions:
    a. TBW is one-third ECF & two-thirds ICF
    b. ECF is one-quarter plasma & three-quarters ISF
    c. The threshold of the volume receptors is 7-10% change in blood volume
    d. The osmoreceptors are sensitive to a 1-2% change in osmolality.
    e. Plasma osmolality is normal prior to the transfusion (i.e. 287-290 mosm/kg)

Property	**Normal Saline**	**5% Dextrose**	**5% Albumin**
Constituents	NaCl MW = 58.4mg 0.9% NS = 9g/L	Dextrose MW = 180mg 5% Dextrose = 50g/L	Albumin
Osmolality	Osm = 154 x 2 = 308 mosm/L Iso-osmotic (approx)	Osm = 278mosm/L Iso-osmotic (approx)	Iso-osmotic (approx)
Tonicity	Isotonic	Hypotonic	
Distribution	Na, Cl does not cross cell membrane –distribution limited to ECF. ISF 750mLs Plasma 250mLs	Rapidly taken up by cells and metabolised → distributed to total body water. ↓ oncotic pressure → fluid loss into ISF ICF 670mls ECF 330mls ISF 250mls Plasma 80mls	Does not cross vessels – limited distribution intravascular. Plasma 1000mLs ↓blood viscosity and [Hb]
IV volume	↑5250mols (5%) Not sensed by volume receptors	↑ 5080mls (2%) Not sensed by volume receptors	↑6000mls (20%) Sensed by volume receptors → ↓ADH
Plasma tonicity	Unchanged as solution is isotonic	↓287 x 3.2/3.28 = 7osm/L ↓ 2.5% → ↓ADH → diuresis	Unaltered
Excretion	2 other mechanisms: ↓oncotic pressure → fluids moves into ISF ↓oncotic pressure → ↑GFR → ↑ Na and water excretion	Diuresis	Delayed diuresis ↑plasma oncotic P → fluid moves from ISF into plasma.
Duration	Rapid	Delayed diuresis (1 hour) ADH requires $3xT_{1/2}$ to reach new steady state	Prolonged and slow excretion phase
Use	Replenish ICF Not good as intravascular volume replacement	Replenish ECF Cheap and used for volume replacement → require 3-4x volume blood lost.	Replenish intravascular volume. Expensive Slow excretion

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MAKE-UP: Compare the body response to a 1L Hypertonic Saline (3N) infusion with 1L hypertonic mannitol infusion?

1. Fluid compartments: assuming the exclusion of slowly equilibrating fluids (dense CT and bone fluid – 15% of TBW)
    a. Intracellular fluid – 55% TBW, 23 litres
    b. Interstitial fluid – 20% TBW, 8.4L
    c. Intravascular fluid – 7.5% TBW, 3.2L plasma + RCV 1.8L

2. Assumptions:
    a. TBW is one-third ECF & two-thirds ICF
    b. ECF is one-quarter plasma & three-quarters ISF
    c. The threshold of the volume receptors is 7-10% change in blood volume
    d. The osmoreceptors are sensitive to a 1-2% change in osmolality.
    e. Plasma osmolality is normal prior to the transfusion (290 mosm/kg)

Property	**Hypertonic Saline 3%**	**Hypertonic Mannitol 20%**
Constituents	NaCl MW = 58.4mg 3% NS = 30g/L	Mannitol MW = 180mg 20% Mannitol = 200g/L
Osmolality	Osm = 1028mosm/L (approx 1000) Hyperosmotic	Osm = 1111mosm/L (approx 1000) Hyperosmotic
Tonicity	Hypertonic	Hypertonic
Distribution	Water distributes via osmosis across membranes from low → high osmolality. Na/Cl stay in ECF due to higher osmolality (do not distribute to ICF) Overall: Water moves ICF → ECF	Water distributes via osmosis across membranes from low → high osmolality. Mannitol does not cross BBB → sucks water out of ICF → ECF Overall: Water moves ICF → ECF
Osmoles	Total solute = (42x290) + 1000 = 13180 mosm ICF solute = 23x290 = 6670 (unchanged) mosm ECF solute = (19x290) + 1000 = 6510 mosm	Total solute = (42x290) + 1000 = 13180 mosm
Tonicity	Total tonicity = 13180/43 = 306mosm/L ↑osm 5.5% → activation osmoreceptors → ↑ADH	Total tonicity = 13180/42.8 = 308mosm/L ↑osm 6.2% → activation osmoreceptors → ↑ADH
Volume	TBW = 42 + 1 = 43L ECF Volume = 6510/306 = 21.2L (↑2.2L) ICF Volumes = 6670/306 = 21.8L (↓1.2L) IV volume ↑ 2.2L/4 = 550mLs (↑10%) Activation volume receptors → ↓ADH	TBW = 42 + 0.8 = 42.8L ICF volume = 290/308 x 23L = 21.6L ECF volume = 42.8-21.6 = 21.2L (↑2.2L) IV volume ↑ 2.2L/4 = 550mLs (↑10%) Activation volume receptors → ↓ADH
Excretion	Volume receptors are **less sensitive but more potent** than osmoreceptors. In this case, they override → ↑ADH → naturesis and diuresis	Volume receptors are **less sensitive but more potent** than osmoreceptors. In this case, they override → ↑ADH → naturesis and diuresis
Clinical	↑osmolality worsened by diuresis → cerebral cell dehydration → confusion	Initial: ↑intravascular volume → precipitates HTN, fluid overload, CCF. ↓ blood viscosity, hyponatraemia Delayed: diuresis → dehydration, hypernatraemia
Use	Severe hyponatraemia	↓ICP head trauma Renoprotective diuresis (rhabdomyolysis → washes myoglobin out of tubules)