

CORE CURRICULUM IN NEPHROLOGY

Disorders of Sodium and Water

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COMPOSITION OF BODY FLUIDS

Total Body Water (TBW)

- Comprises ~60% of body weight
- Two thirds of TBW is inside cells (intracellular fluid [ICF] ≈ 40% of body weight)
- One third of TBW is outside cells (extracellular fluid [ECF] ≈ 20% of body weight)

Solute Composition of Body Water (H₂O)

- Predominant solutes in ECF:
 - Sodium (Na⁺)
 - Chloride (Cl⁻)
 - Bicarbonate (HCO₃⁻)
- Predominant solutes in ICF:
 - Potassium (K⁺)
 - Protein⁻
 - Phosphate⁻
- Normal ECF osmolality, 275 to 290 mOsm/kg H₂O
- ECF and ICF are in osmotic equilibrium, at steady state

PHYSIOLOGY OF Na BALANCE

Background

- Definition: Na balance is difference between intake (usually oral or intravenous) and excretion (usually renal, gastrointestinal, and perspiratory)

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- Na intake controlled by Na appetite, dietary access, habit, and physicians
- Typical Western diets contain 2 to 6 g of Na (43 mEq/g Na)
- Na elimination regulated by factors that adjust renal excretion and by nonrenal losses (usually gastrointestinal and perspiratory)

Mechanisms of Renal Na Excretion

- Na freely filtered (~25 mol/d in healthy humans)
- >99% reabsorbed; normal fractional Na excretion is <1%
- About 65% reabsorbed along proximal tubule (PT), 25% along loop of Henle, 6% along distal convoluted tubule (DCT), and 3% along collecting duct (CD)
- Primary energetic driving force for Na (and other solute) reabsorption is Na/K adenosine triphosphatase in basolateral membrane of renal tubules
- Na reabsorption along PT is mediated partly by apical Na/H exchange (NHE3)
- H₂O, but not solute, removed from thin descending limb of Henle loop, increasing luminal Na concentration as fluid approaches tip
- Na, but not H₂O, reabsorbed along thin and thick ascending limbs of Henle loop, thereby diluting tubule fluid; along thick ascending limb, Na traverses an apical Na-K-2Cl cotransport pathway (NKCC2)
- Na, but not H₂O, reabsorbed along DCT, predominantly via an apical Na-Cl cotransporter (NCC or NCCT)
- Na reabsorbed along connecting tubule and CD, largely via an apical Na channel (ENaC)

Regulation of Renal Na Homeostasis

- Renal Na homeostasis responds to “effective arterial blood volume” (EABV), a virtual volume that reflects “fullness” of arterial tree
- Na reabsorption varies inversely with arterial pressure, a phenomenon called “pressure natriuresis”

- Na reabsorption along PT regulated by peritubular protein concentration and other “physical factors”; increase in filtration fraction (glomerular filtration rate/renal plasma flow) causes peritubular oncotic pressure to increase, stimulating reabsorption
- This link between filtration and reabsorption called glomerulotubular balance
- Proximal Na reabsorption (largely NHE3) also stimulated by hormones, including angiotensin II; circulating angiotensin II levels are regulated by renin, secreted by juxtaglomerular apparatus in response to EABV contraction or low luminal thick ascending limbs of Henle loop NaCl concentration
- Na reabsorption along second half of DCT, the connecting tubule and CD (collectively termed the “aldosterone-sensitive distal nephron”), regulated by aldosterone, which stimulates ENaC (abundance and/or activity) and NCC; aldosterone secretion regulated directly by angiotensin II, and by serum K concentration
- Natriuretic peptides stimulate guanylyl cyclase along CD, generating cyclic guanosine monophosphate and inhibiting apical cation channels; natriuretic peptides also increase glomerular filtration rate; atrial natriuretic peptide secretion stimulated by atrial stretch
- About 67% reabsorbed along PT, about 10% along loops of Henle, and about 22% along collecting duct, under typical conditions
- Proximal reabsorption is isosmotic, so rates determined by solute reabsorption
- H₂O reabsorbed along descending limb of loop of Henle, driven by medullary hypertonicity
- Solute, not H₂O, reabsorbed along ascending limbs; ascending limb thus dilutes urine
- Solute, not H₂O, reabsorbed along DCT; the DCT dilutes urine
- H₂O variably reabsorbed along cortical and medullary collecting ducts, via a regulated apical H₂O channel (aquaporin 2)

Regulation of Renal H₂O Excretion

- Urinary osmolality typically ranges between 50 and 1,200 mOsm (mmol)/kg H₂O
- Countercurrent multiplication generates medullary hypertonicity in part via Na-K-2Cl cotransporter (NKCC2) at apical membrane of thick ascending limb cells
- Countercurrent multiplication along thin limbs requires active transport by other segments and differential solute and H₂O permeability
- Tubule fluid leaving loop of Henle is always dilute compared with plasma
- Arginine vasopressin (AVP), the antidiuretic hormone (ADH = AVP), regulates H₂O excretion:
 - AVP secretion stimulated when serum osmolality increases
 - AVP secretion also stimulated when EABV volume reduced
 - Osmolality is usually predominant regulator of AVP release
- AVP regulates H₂O excretion:
 - When AVP absent, H₂O channels (aquaporin 2) are absent from apical membrane of CD cells; dilute tubule fluid leaves kidney
 - AVP activates V2 receptors on basolateral membrane of CD cells
 - AVP stimulates adenylyl cyclase in CD cells; when AVP present, H₂O channels (aquaporin 2) move into apical membrane, permitting H₂O to be reabsorbed,

PHYSIOLOGY OF H₂O BALANCE

Background

- H₂O balance is difference between intake (usually oral or intravenous) and excretion (usually renal, gastrointestinal, perspiratory, and insensible)
- H₂O intake controlled by thirst, taste, habit, and physicians; thirst regulated partly by serum osmolality and by angiotensin II
- Typical H₂O intake ranges from 1 to 5 L/d
- H₂O excretion regulated by factors that adjust renal excretion and by nonrenal losses (insensible, perspiratory, and gastrointestinal losses)

Mechanisms of Renal H₂O Excretion

- H₂O freely filtered at glomerulus (~150 L/d)

driven by medullary hypertonicity, concentrating urine

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DISORDERS OF Na BALANCE

Background

- Na balance disorders are disorders of ECF *volume*
- Serum Na concentration may be high, low, or normal

Hypovolemia

Causes

- Extrarenal losses:
 - Blood
 - Gastrointestinal
 - Perspiratory
 - “Third space”
- Renal losses (salt wasting):
 - Adrenal steroid deficiency:
 - Inherited:
 - Hypoaldosteronism (eg, aldosterone synthase defect)
 - Addison disease
 - Acquired:
 - Addison disease
 - Kidney tubule diseases:
 - Inherited, with hypokalemia:
 - Bartter syndromes: types I (bumetanide-sensitive Na-Cl cotransporter dysfunction), II (K channel dysfunction), and III (basolateral Cl channel dysfunction), V (activating mutations of calcium sensing receptor)

- Bartter syndrome with sensorineural deafness (resulting from deficiency in Cl channel β subunit, Barttin) (Bartter syndrome type IV)
- Gitelman syndrome: NCC dysfunction
- Inherited, with hyperkalemia:
 - Pseudohypoaldosteronism type I (ENaC dysfunction): autosomal dominant (mineralocorticoid receptor defect) or autosomal recessive (ENaC defect)
 - Acquired:
 - Renal disease, especially interstitial
- Drugs, especially diuretics

Treatment

- Identify and treat underlying disease
- Volume repletion with normal saline
- High-salt diet
- Fludrocortisone (synthetic mineralocorticoid)

Hypervolemia

- Occurs when Na retention is “inappropriate”

Primary Na retention

- Causes hypertension, not edema
- Example: hyperaldosteronism
- Reviewed in Core Curriculum in Nephrology on Hypertension (August 2004 issue)

Secondary Na retention

Causes.

- Congestive heart failure; secondary to inadequate cardiac output or diastolic dysfunction
- Cirrhosis of liver; secondary to systemic vasodilation
- Nephrotic syndrome; mixed, resulting from intrinsic stimulation of renal NaCl reabsorption and hypoproteinemia

Diagnosis.

- History
- Physical examination (edema, ascites, jugular pressure, pulmonary crackles, S_3 , others)
- Laboratory (brain natriuretic peptide concentration, urine Na, urine protein-

creatinine ratio, serum albumin and creatinine)

Treatment

- Treat underlying disease process
- Restrict Na intake (keep intake <100 mEq/d, restrict H₂O only if hyponatremia develops)
- Diuretics:
 - Loop diuretics usually first line for edema:
 - Start with low dose and double until diuretic threshold reached (noticeable increase in urine output)
 - Usually administer twice daily
 - Common side effects are hypokalemia, prerenal azotemia, and metabolic alkalosis
 - DCT diuretics (thiazides):
 - Sometimes useful alone
 - Commonly combined with loop diuretics to treat resistance
 - Common side effects are hypokalemia, prerenal azotemia, and metabolic alkalosis
 - CD diuretics (spironolactone, eplerenone, triamterene, amiloride):
 - First-line treatment for cirrhotic ascites
 - Commonly combined with loop or DCT diuretics to prevent hypokalemia
 - Common side effects include hyperkalemia and metabolic acidosis
 - Proximal tubule diuretics (carbonic anhydrase inhibitors):
 - Rarely used except combined with loop and DCT diuretics, to treat resistance or metabolic alkalosis
 - Common side effects include hypokalemia and metabolic acidosis
 - Natriuretic peptides:
 - Nesiritide (brain natriuretic peptide) infusion
 - Combine diuretic classes if resistance develops; usually combine a loop and a DCT diuretic
- Ultrafiltration or hemodialysis

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DISORDERS OF H₂O BALANCE

Background

- Are manifested by changes in serum osmolality and/or Na concentration
- Are classified on the basis of ECF volume

Hyponatremia

Factitious (normotonic) hyponatremia

- Results from laboratory artifact (high concentrations of proteins or lipids)

Hypertonic hyponatremia

- Results from non-Na osmoles in serum (often glucose or mannitol) drawing Na-free H₂O from cells ([Na] declines by ~1.6 mEq/L for each 100-mg/dL [5.6-mmol/L] increase in glucose)

Hypotonic hyponatremia

Dilutional. Urine is dilute (<100 mOsm/kg H₂O):

- H₂O intake exceeds dilutional capacity ("psychogenic polydipsia," requires as much as 12 L/d in normals); treatment is to reduce H₂O intake

- Dilutional capacity limited by low solute intake (“beer drinkers potomania”); treatment is to reduce intake and increase solute intake

Hypovolemic. Urine is concentrated:

- Urine [Na] is usually <20 mEq/L, except with diuretic drugs and salt wasting, where it is inappropriately elevated; urine [Cl] concentration is low, even if urine [Na] concentration is not, when volume depletion results from vomiting
- Losses of Na and H_2O stimulate AVP appropriately (eg, sweat or gastrointestinal); losses replaced with hypotonic fluids, owing to thirst
- Diagnosis: by history, physical examination (orthostatic hypotension, low jugular venous pressure, tachycardia, low arterial pressure, dry mucous membranes), and laboratory (high hematocrit and serum protein)
- Treatment is normal saline

Euvolemic. Urine is concentrated; urine [Na] usually >20 mEq/L:

- Syndrome of inappropriate ADH secretion (SIADH):
 - Tumors
 - Central nervous disorder
 - Drugs (eg, antidepressants)
 - Others
 - Idiopathic
- Hypothyroidism or glucocorticoid insufficiency
- Diagnosis: by history, absence of signs of volume depletion or overload, and laboratory (low plasma uric acid)
- Treatment:
 - Some causes reversible (eg, nausea, drugs, glucocorticoid insufficiency)
 - Aggressiveness of treatment depends on severity, chronicity, and symptoms
 - “Rapid” treatment for symptomatic and acute:
 - Raise serum Na by 1 to 2 mEq/L/h until symptoms resolve; generally aim to increase no more than 12 mEq/L in first 24 h
 - Hypertonic saline (3%) at 1 to 2 mL/h/kg body weight
 - Furosemide can be used simultaneously to block concentrating capac-

ity and increase Na excretion to match input

- Reduce correction rate once symptoms resolve or $[Na] >125$ mEq/L
- Urine may become dilute during therapy; careful monitoring needed to avoid excess correction
- “Chronic” treatment:
 - H_2O restriction always appropriate
 - Aquaretics, when necessary:
 - Demeclocycline
 - AVP V2 receptor antagonists (investigational)
 - Oral urea
 - Loop diuretics plus NaCl

Hypervolemic. Urine concentrated, Na often <20 mEq/L, except in renal failure:

- AVP secreted because “effective arterial blood volume” reduced (ECF volume deficits, when severe, overcome AVP inhibition by hypotonicity)
- Causes include congestive heart failure, cirrhosis, nephrotic syndrome, kidney failure
- Treatment includes oral H_2O restriction (and continued Na restriction)
- Angiotensin-converting enzyme inhibitors and loop diuretics can help increase Na, when cause is congestive heart failure
- Aquaretics (V2 receptor antagonists, currently investigational drugs) may be useful
- Dialysis

Hypertatremia

Hypervolemic

- Hypertonic infusion (eg, $NaHCO_3$)
- Tube feeding

Hypodyspic

- Usually only when it occurs with other factors:
 - Elderly or very young
 - Altered mental status
 - Prolonged exertion

H_2O loss

- Extrarenal (urine Na <20 mEq/L):
 - Insensible and perspiratory
 - Gastrointestinal
- Renal:

- >Osmotic diuresis (osmotic diuresis, post-obstruction; urine Na >20 mEq/L)
- Diabetes insipidus (dilute urine, urine Na variable):
 - Nephrogenic (ADH resistance):
 - Hereditary: X-linked (V2 receptor), autosomal recessive (aquaporin-2)
 - Acquired: hypercalcemia, hypokalemia, chronic kidney disease, drugs (lithium most common), many others
 - Central (ADH insufficiency):
 - Idiopathic (50%)
 - Autoimmune
 - Tumors
 - Trauma
 - Autosomal dominant
 - Others

Diagnosis

- History; history of exertion, fever, thirst, diarrhea, polyuria, access to H₂O, drugs
- Physical examination: signs of EABV depletion, neurological deficits
- Laboratory tests:
 - Measure urinary osmolality, Na and K
 - Calculate electrolyte-free H₂O reabsorption:

$$TeC_{H_2O} = V \cdot \left(\frac{U_{Na} + U_K}{P_{Na}} - 1 \right)$$

where TeC_{H_2O} is the electrolyte-free water reabsorption, V is urine volume, U_{Na} is urine Na concentration, U_K is urine K concentration, and P_{Na} is plasma Na concentration

If this value has negative sign, it represents ongoing H₂O losses that must be replaced

- H₂O deprivation test for hypernatremia associated with dilute urine (restrict H₂O until 3% to 5% body weight loss or 3 consecutive urine osmolalities within 10%; serum Na must exceed 144 mEq/L); follow patient for signs of excess volume depletion; interpretation:
 - Urine osmolality >800 mOsm/kg H₂O = normal
 - Urine osmolality <300 mOsm/kg H₂O = complete diabetes insipidus
 - Urine osmolality 300 to 800 mOsm/kg H₂O = partial diabetes insipidus
 - Response to exogenous vasopressin defines central versus nephrogenic
- Plasma vasopressin levels correlated with plasma and urinary osmolality often needed in equivocal cases

Treatment

- Hypovolemic hypernatremia, with saline
- Euvolemic hypernatremia, with D5W
- Deficit \approx current body H₂O \times (actual plasma Na concentration/desired plasma Na concentration)
- Aim to correct at <0.5 mEq/L/h and usually \leq 10 mEq/d
- Note that ongoing free H₂O excretion both insensible and renal must be replaced

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