Imperial College Healthcare NHS
NHS Trust

Polyuria and Polydipsia Syndrome: is it Diabetes Insipidus?

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Objectives for talk

1. to understand the pathophysiology of DI
2. to understand the differential diagnosis
3. to understand how we can differentiate between the different causes
4. to understand treatment strategies

Definition of Polyuria

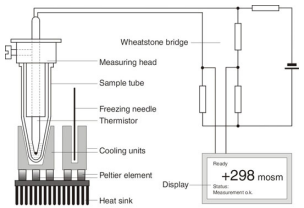
- A urine output exceeding
  - 3 L/day in adults
  - 2 L/m^2 body surface area/day in children.
- Must be differentiated from
  - Frequency of urination
  - Nocturia
  - These are not associated with an increase in the total urine output.

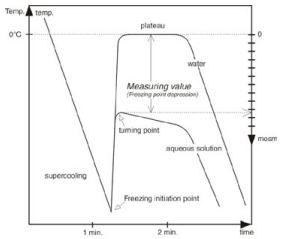
Basic First Line Investigations

- U&E, Ca, Glucose – exclude diabetes mellitus!
- Urinalysis for glucose and S.G.
  - S.G. <1.005 is suspicious
- Paired serum and urine osmolalities
  - Normal serum osmo = 275-295 mOsm/kg
  - Urine osmo ranges from 100 to 1200 mOsm/kg
  - Baseline serum osmo of >295 with urine osmo <200 is diagnostic of DI
- Bladder diary

Osmolality

- Concentration of osmotically active particles in a solution (expressed per kg solvent)
- Measure using freezing point depression (proportional to osmolality)





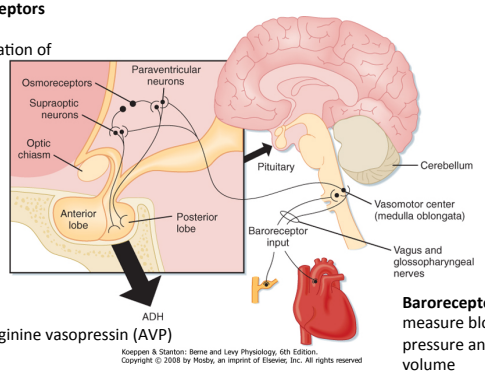
Typical cooling curves of water and aqueous solutions

Bladder diary

Time	In	Out	'Wet'	Urgency rating
0700		300 ml	✔✔	A = felt no need to void but did so for other reasons
0800	Tea 1 cup			B = could postpone voiding as long as necessary without fear of 'wetting'
0900				C = could postpone voiding for a short time without fear of 'wetting'
1000		300 ml		D = could not postpone voiding and had to rush to void in toilet
1100	Water 1 cup			E = leaked before getting to toilet
…				
0400		200 ml		
0500				
0600				

Osmoreceptors vs baroreceptors

Osmoreceptors measure concentration of plasma



ADH = arginine vasopressin (AVP)

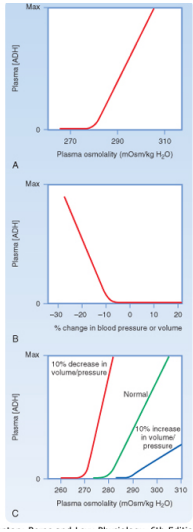
Baroreceptors measure blood pressure and volume

AVP secretion is related to osmolality and blood volume

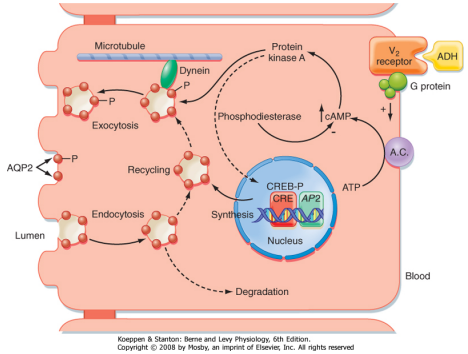
↑osmo → ↑AVP

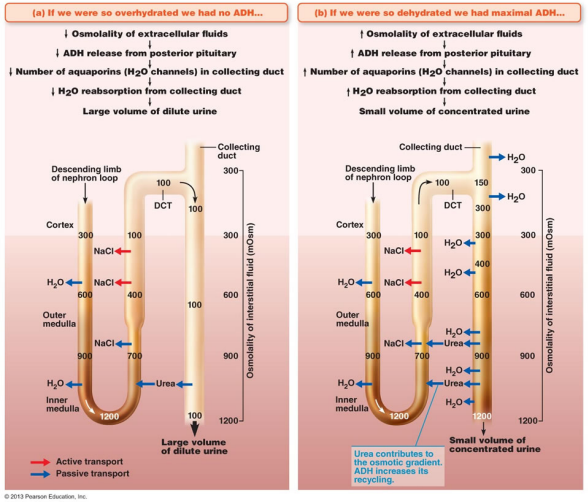
↓volume → ↑AVP

↓volume modifies AVP response to osmolality

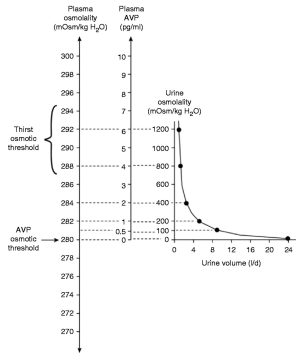


AVP controls aquaporin recruitment in the collecting duct of kidney





Relationship of AVP release to plasma osmolality and urine osmolality



When polyuria proven…

- Exclude uncontrolled diabetes mellitus
- Three major causes of polyuria in the outpatient setting:
  - primary polydipsia
  - central diabetes insipidus (DI)
  - nephrogenic DI

Primary polydipsia

- A primary increase in water intake.
- Most often seen in
  - middle-aged women
  - patients with psychiatric illnesses
  - including those taking a phenothiazine which can lead to the sensation of a dry mouth
- Primary polydipsia can also be induced by
  - hypothalamic lesions that directly affect the thirst center, e.g. sarcoidosis
  - Xerostomia (lack of saliva) leading to excessive drinking

Cranial DI

- Deficient secretion of AVP from posterior pituitary
- Often idiopathic
  - possibly due to autoimmune injury to the ADH-producing cells
- Trauma (head injury)
- Pituitary surgery
- Hypoxic or ischaemic encephalopathy
- Familial: mutations in pro-AVP gene

Nephrogenic DI

- High AVP but kidneys insensitive to this
- Familial
  - Mutations in V2 receptor or aquaporin
- Li toxicity
- Hypercalcaemia
- Hypokalaemia
- Renal disease (e.g. CKD)
- Pregnancy – placental vasopressinase

Case 1

- 40 year old lady
- Bipolar disorder on Lithium carbonate
- Polyuria and polydipsia (up to 10 litres a day)
- Complains of a dry mouth all the time
- What are the possible diagnoses?

Case 1

- Nephrogenic DI
  - Due to chronic Li treatment
  - Li-induced hyperparathyroidism and hyperCa?
- Primary polydipsia
  - Due to underlying psychiatric disorder?
- Cranial DI less likely

Tests

- Baseline
  - Na 145, K 4.5, Ca normal, glucose normal
  - Li undetectable
- Went on to water deprivation test

What is a water deprivation test?

- First stage
  - Serial measurements of serum and urine osmo under conditions of water deprivation
  - **Differentiates** primary polydipsia (urine osmo ↑) from DI (urine osmo fails to ↑ beyond a limit)
- Second stage
  - If DI proven, give DDAVP
  - **Differentiates** cranial DI (urine osmo ↑ to DDAVP) vs nephrogenic DI (urine osmo does not respond)
- Needs to be done under supervision for safety

Interpretation of water deprivation

Pre-test		Water deprived (8h)		Given DDAVP	
Serum	Urine	Serum	Urine	Serum	Urine
295	460	305	605	306	598

- Pre-test
  - **Serum** top end of normal
  - **Urine** can't comment
- Water deprived
  - **Serum** too high
  - **Urine** is inappropriately low (would expect >750)
- DDAVP given
  - **Serum** is still too high
  - **Urine** is still not concentrated enough

➢ Nephrogenic DI

Nephrogenic DI due to Lithium

- 20-40% taking Li have ↑urine vol (2-3 L/d)
- 12% of patients have frank polyuria (>3 L/d)
- **Direct inhibitory effect** of Li on aquaporin expression and recruitment
- **Chronic effect:** Li-induced interstitial nephritis can contribute to DI
- Usually reversible with discontinuation, but can persist long-term
- **In this case** discontinuation led to settling of DI

Treatment of Nephrogenic DI

- IV fluids (if patient very hypovolaemic)
  - Need to use fluid of similar osmo to urine otherwise instability of [Na] may ensue
- Low protein/Na diet
  - ↓amount of solute that needs to be excreted and therefore ↓urine volume needed
- Thiazide diuretics
  - Causes mild volume depletion
  - ↑resorption of Na and water in proximal tubule

Treatment of Nephrogenic DI

- NSAIDs (e.g. indomethacin)
  - Prostaglandins antagonise effect of AVP
  - Therefore inhibiting production of PG causes increased water reabsorption
- High dose DDAVP
  - Most patients with non-familial nephrogenic DI have partial defects that may respond to DDAVP

Case 2

- 25 year old woman
- "Always drunk lots and passed lots"
- No other relevant past history
- Baselines
  - Na 136, K 3.6, Ca and Glucose normal
  - Serum osmo 277, urine osmo 100

Interpretation of water deprivation

Pre-test		Water deprived (8h)	
Serum	Urine	Serum	Urine
275	100	280	850

- Pre-test
  - **Serum** low end of normal
  - **Urine** is dilute
- Water deprived
  - **Serum** rises to normal range
  - **Urine** rises to >750
  - **Note** would expect Urine osmo to rise to >1000 in a young person
  - Chronic polydipsia causes 'washout' of medullary concentration and therefore some reduction in ability to concentrate urine

➢ Primary polydipsia

Treatment of primary polydipsia

- Fluid restriction
- Consider artificial saliva if problem driven by dryness of buccal mucosa (e.g. with xerostomia)

Case 3

- 24 y.o. man, RTA last year, polyuric
- Baselines
  - Na 145, K 4.0, Ca normal, glucose normal
- Went on to water deprivation test

Case 3 intepretation

Pre-test		Water deprived (8h)		Given DDAVP	
Serum	Urine	Serum	Urine	Serum	Urine
295	300	302	295	285	1154

- Baseline
  - **Serum** top end of normal
  - **Urine** not interpretable
- Water deprived
  - **Serum** clearly high
  - **Urine** inappropriately dilute (should be >750 at least or even >1000 in young person)
- DDAVP given
  - Sharp rise in **urine** osmo seen
  - Recovery of **serum** osmo to normal

➢ Cranial DI

Cranial DI due to head injury

- Acutely after head injury in 1 in 5 patients
- Seen chronically in 1 in 12 patients
- Associated with other pituitary problems or can be isolated
- DDAVP Rx:


Tablets


Nasal spray


Sublingual melts

Other causes of cranial DI

- Pituitary tumours
  - Not common in pituitary adenoma
  - More common with other types of tumours (e.g. craniopharyngioma, metastasis)
- Pituitary surgery
- Infiltrative disease
  - Sarcoidosis, histiocytosis X
- Infection
  - Meningitis, encephalitis
- Hereditary (rare)

How to monitor a Patient on DDAVP

- DDAVP has different doses depending on preparation, e.g.
  - Tablets: 100 µg nocte to 200 µg TDS
  - Nasal spray: 10-20 µg (1-2 sprays) OD-TDS
  - Melts: 60, 120, 240 µg OD-TDS
  - Subcutaneous injection: 0.5-1 µg OD-BD
- Different durations of action
  - Tablets ~4-6 h
  - Nasal Spray ~8 h
  - Injection ~12 h

DDAVP is a vital drug

Patients must receive steady supplies of DDAVP

Classification: Official

NHS England

Patient Safety Alert

Stage One: Warning

Risk of severe harm or death when desmopressin is omitted or delayed in patients with cranial diabetes insipidus

8 February 2016

Alert reference number: NHS/PSA/W/2016/001

Alert stage: One - Warning

Actions

Patients are entitled to exemption from prescription charges

How to monitor a Patient on DDAVP

- Two key parameters for monitoring:
  - Body weight (reflects body water)
  - Na^+
- Warning signs:
  - Tiredness
  - Confusion
  - Ataxia
  - Nausea and vomiting
  - Headaches
  - Acute change of >2 kg from baseline body weight
- CHECK U&E URGENTLY

Some common questions

- Blockage of nasal passages in patients using spray (e.g. URTI)
  - Consider Rx tablets
- Pregnancy
  - May require increased dose: placental vasopressinase breaks down AVP/DDAVP
- Travelling
  - Patients may require a letter for airport security to carry medication through screening
  - Patients should take doses according to local time