RCPA
The Royal College of Pathologists of Australasia

Faculty of Science
Sample Chemical Pathology Questions and Model Answers

Chemical Pathology Part I Written Examination

Question

a) Describe the regulation of aldosterone in a health individual.
b) How is primary hyperaldosteronism investigated?
c) Describe the effect of of ßeta blockers, ACE inhibitors, renin inhibitors, and the oral contraceptive pill, on the interpretation of aldosterone: renin ratio.

Answer

a)

- Aldosterone is synthesized from cholesterol in the zona glomerulosa of the adrenals
- Aldosterone synthase is the final enzymatic step in aldosterone synthesis
- Potassium and angiotensin II (AII) are primary regulators of aldosterone synthesis
    - AII and/or potassium (high levels) directly stimulate the adrenal to synthesise aldosterone due to a positive influence on aldosterone synthase
- The rate limiting steps in aldosterone synthesis are StAR and Aldosterone Synthase
- ACTH is secondary regulator of aldosterone synthesis

Angiotensin II (AII) levels are regulated by production of renin from the juxtaglomerular apparatus (JGA)

- Sodium depletion; reduced arterial pressure; ECFV contraction all stimulate renin production from the JGA: ANP and BNP have a negative effect on renin production
- Renin converts angiotensinogen (liver) to angiotensin I (AI)
- Angiotensin Converting Enzyme ACE converts AI to angiotensin II(AII)

b)

- Clinical/ case selection for primary aldosteronism (PAL)
- Patients with sustained hypertension; hypertensive patients resistant to therapy and hypertensive patients on 4 or more antihypertensive drugs
- Family history of PAL or CVA at age <40 years
- Adrenal incidentaloma
- Exclusion of other forms of hypertension e.g. renal disease

Screening

- Patients at risk PAL should be screened with an Aldosterone Renin Ratio (ARR)
- In primary aldosteronism the ARR is elevated
- A drug history is required as antihypertensive drug therapy can either increase or decrease the ARR leading to false positive or false negative results. This is dependent on the action of the drug and its influence on aldosterone and renin levels
- The medication may need to be changed prior to ARR measurement
- Aldosterone, renin and ARR results should be reported

- The ARR can be elevated with suppressed/ undetectable renin and “low” aldosterone levels. In PAL aldosterone levels can be as low as ~300 pmol/L and the aldosterone level should be taken into account before proceeding to confirmatory testing

Confirmation of PAL

- Patients with and elevated ARR should be assessed with saline suppression or Fludrocortisone suppression test (FST)
- Lack of Suppression (normal) of aldosterone by Saline infusion or fludrocortisone suppression test (normal suppress to < 150 pmol/L) is used to confirm PAL

It should be determined in patients with confirmed PAL if the patient has unilateral (autonomous) or bilateral (hyperplasia) adrenal aldosterone production.

- Adrenal imaging can be misleading due to incidentalomas
- Adrenal venous sampling is used
- Adrenal vein: peripheral (or IVC) cortisol levels are used to determine if catheters are correctly placed in R and L adrenal veins (R is very difficult);
- Aldosterone/Cortisol Left vein: Aldosterone/Cortisol Right are used to determine nature off secretion (cortisol corrected ratios).
- Ratios for interpretation depend on whether stimulation (synacthen infusion) is used

c)

Abbreviations: Plasma renin activity (PRA); Direct Renin Concentration (DRC)

Beta blockers	increase ARR (false positive) as both PRA and DRC assays are decreased/lowered	
ACE inhibitors	ARR is false negative as ARR decreased due to increase in both PRA and DRC	
Renin inhibitors	ARR (PRA)	False positive ARR due to decreased PRA
	ARR (DR)	False negative ARR due to increased DRC
OCP	ARR (PRA)	No change in ARR or PRA level
	ARR (DR)	False positive / increased ARR due to decreased DRC (increased substrate decreases enzyme levels by negative feedback but enzyme activity remains relatively constant)

Chemical Pathology Part I Oral Examination

Question

a) Why do laboratories measure digoxin levels?
b) What are the causes of an elevated digoxin level?
c) The following results are from an 81-year-old female. She was clinically unwell**.** What is your interpretation of this case?

		Units	Reference
Digoxin	*4.2	nmol/L	(0.6-1.3)
Sodium	**124**	mmol/L	(135-145)
Potassium	4	mmol/L	(3.5-5.5)
Chloride	**79**	mmol/L	(95-110)
Bicarbonate	**16**	mmol/L	(20-32)
Ca (corr)	**2.02**	mmol/L	(2.15-2.55)
Phosphate	**3.5**	mmol/L	(0.8-1.5)
Urea	**77.5**	mmol/L	(2.5-7.0)
Creatinine	**860**	umol/L	(45-85)
eGFR	**4**		(>59)
Gluc R	5.9	mmol/L	(3.6-7.7)

Answer

a) Indications for measurement of Digoxin levels include:
- Clinical concern for toxicity; patients experience cardiac arrhythmias. Toxicity occurs at levels >2.6nmol/L (2.0ug/L)
- To check patient compliance with digoxin treatment
- To optimise efficacy of treatment

b) Elevation of digoxin levels occurs in the following scenarios:
- Specimen sampled at a time too close to the last dose. The optimal time for sampling is at a minimum of 8hrs post dose, and preferably 12 hrs post dose.
- Overdosing
- Renal impairment (80% eliminated by kidney)
- Treatment with other drugs eg quinidine (DIG level x2), verapamil, amiodarone etc
- DLIS/DLIF (associated with salt retention) heart/renal/liver failure, 3rd trimester pregnancy, neonates
- Heterophile Ab's
- Digibind treatment (assay dependent)

c) The results demonstrate renal impairment (elevated urea and creatinine), a factor which predisposes to toxicity. Other biochemical factors to consider include hypokalemia, hypercalcemia and hypomagnesemia (which are not present in this case). A potassium level of >5.0 mmol/L may indicate acute toxicity, while a level of >5.5 is indicative of serious toxicity.