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West Midlands Training Course in Clinical Biochemistry

Course Assessment – Spring 2010

Short Answer Questions. **<u>Answer all questions</u>.**
Time allowed 1 hour.

1. A screening test for a disease has a diagnostic sensitivity of 99% and a diagnostic specificity of 95%. Calculate the positive predictive value of the test, and the population prevalence of the disease, given that testing of a randomly selected sample of 100,000 subjects gave 10 false negative results. **(5 marks each)**

	Diseased	Non-diseased	Totals
Test Positive	990 (TP)	4950 (FP)	5940 (TP + FP)
Test Negative	10 (FN)	94050 (TN)	94060 (TN + FN)
Totals	1000 (TP + FN)	99000 (FP + TN)	100000 (TP+FP+TN+FN)

Where TP = true positives TN = true negatives
FP = false positives FN = false negatives

Predictive value of a positive test = TP/(TP + FP) = 990/5940 = **0.167**

Population prevalence of disease = (TP + FN)/(TP + TN + FP + FN)

= 1000/100000 = **0.01**

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2. Assuming the salt XCl_2 is completely dissociated in water and a 19g/L solution of the salt gives an osmolality of 600 mmol/kg calculate the molecular weight of XCl_2 **(10 marks)**

XCl_2 is fully dissociated so it generates 3 osmotically active species:

X^+ + Cl^- + Cl^-

The measured osmolality = 600 mmol/kg which equates to an approximate concentration of osmotically active species of 600 mmol/L of solution

The molar concentration of XCl_2 must therefore =

600/3 = 200 mmol/L

A 19g/L solution of XCl_2 = 200 mmol/L

So for a 1M solution require:

1000/200 * 19 = 95 g/L

Molecular weight of XCl_2 = **95 Da**

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3. A plasma sample contains 140 mmol/L of sodium and 95% water by volume. Ignoring sodium binding by plasma proteins, calculate the apparent plasma sodium concentration determined from measurements with an electrode system that responds to water sodium a) in undiluted plasma b) in plasma diluted 1 in 20 with water. **(5 marks each)**

a) The plasma sodium concentration is 140 mmol/L of plasma

Only 95% of the plasma is water and the sodium is restricted to this fraction

The water sodium concentration must be >140 mmol/L

140 mmol/L of sodium are restricted to 950 mL of plasma water

The concentration of sodium in plasma water =

Amt Na(mmol)/vol of plasma water(L) = 140/0.95 = **147.4mmol/L**

b) Diluting the sample 1 in 20 reduces the plasma protein concentration to $1/20^{th}$ of its original value = 5/20 = 0.25%

140/20 mmol/L of sodium are found in 997.5 mL of water

The concentration of sodium in the diluted sample =

7/0.9975 = 7.0175 mmol/L

So multiplying by 20, Sodium = **140.4 mmol/L**

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4. Define the term isoenzyme and briefly describe a single example of the application of an isoenzyme measurement in clinical practice. (**5 marks each**)

a) Isoenzymes are multiple forms of an enzyme arising from genetically determined differences in the primary structure that catalyse the same reaction.

b) CK isoenzymes to differentiate cardiac from skeletal muscle damage
ALP isoenzymes to differentiate primarily between liver and bone sources but also placental, intestinal and malignancy related forms

5. A subject was infused with a drug at the rate of 100 μmol/min until a steady state plasma concentration of 200 μmol/L was reached. What is the clearance of the drug? **(10 marks)**

Clearance (mL/min) = (U (μmol/L) * V (mL/min)) / P (μmol/L)

U = urine concentration
P = plasma concentration
V = urine formation rate

Under steady state conditions:

Rate of excretion (U*V) = rate of infusion = 100 μmol/min

So Clearance (ml/min) = Rate of infusion (μmol/min)/ P (μmol/**mL**)

P = 200 μmol/L = 200/1000 = 0.2 μmol/**mL**

Clearance = 100/0.2 = **500 mL/min**

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6. A 19 year-old male was admitted to hospital via A&E from an army camp where he had been undertaking basic training that included strenuous physical exercise. The previous day he had undertaken a 30 mile hike on Bodmin Moor. He was unwell, had generalized muscle pain, complained of feeling weak and was passing brown urine. The urine tested positive for blood (4+) by urine dipstick, but urine microscopy was negative for haematuria. The note from the camp medical officer indicated that the patient had no previous medical history of note and was not taking any medication. His serum biochemistry results were:

Sodium	140 mmol/L
Potassium	5.2 mmol/L
Urea	6.0 mmol/L
Creatinine	110 μmol/L
Phosphate	1.40 mmol/L
Adj Calcium	2.29 mmol/L
CK	58,800 U/L

a) Comment on the results (**2 marks**)

Grossly raised CK
Raised or 'high normal' Potassium, Urea, Creatinine, Phosphate
Low or 'low normal' Adjusted Calcium

b) What condition is the patient likely to have? (**2 marks**)
Exercise induced rhabdomyolysis

c) What is the cause of the brown discolouration in the urine? (**2 marks**)
Myoglobin

d) Why is it important to monitor the biochemistry over the next 24 hours? (**2 marks**)

Rhabdomyolysis can give rise to acute renal failure

e) Name two other enzymes that you may expect to be elevated **(2 marks)**

AST, LDH, ALT

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7. a) Briefly describe what is meant by the term ‘secondary hypertension’ **(3 marks)**

Secondary hypertension is hypertension that has an identifiable cause.

b) Give seven endocrine causes of secondary hypertension (**7 marks**)

Phaeochromocytoma
Conn’s syndrome
Bilateral adrenal hyperplasia syndrome
11 β hydroxy steroid dehydrogenase deficiency
Glucocorticoid remediable hyperaldosteronism
Liddle’s
Cushing’s syndrome
Renin secreting tumour
Acromegaly
Hyperparathyroidism
Hypo and Hyperthyroidism

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8. Plasma lactate concentration is usually measured by a spectrophotometric assay described by the following formula:

$$\text{L-lactate} + NAD^+ \rightleftharpoons \text{Pyruvate} + NADH + H^+$$

The formation of NADH is monitored, and this is usually configured as an 'end point' assay.

a) At what wavelength is the reaction monitored, and why? **(2 marks)**

340nm. Absorbance maximum of NADH, which is produced in proportion to the amount of lactate present

b) Which direction must the equilibrium lie in if the assay is to measure lactate concentration? (**1 mark**)

Right

c) State three ways in which the reaction conditions could be adjusted so that the reaction is optimised to ensure that this is the case. (**3 marks**)

High pH, excess NAD and trap (remove) pyruvate

d) What two factors could you change to enable the reaction to proceed more rapidly? (**2 marks**)

Temperature, LDH concentration

e) What would constitute a reagent blank and why is blanking necessary? (**2 marks**)

Substituting saline or water blank for the sample.
To correct for the background absorbance of reagents

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9. One serum and one urine sample collected from a patient for the measurement of creatinine clearance were each assayed 10 times with the following results:-

Urine Creatinine mmol/L	Serum Creatinine µmol/L
11.1	102
11.5	108
11.9	107
10.9	112
12.1	103
11.2	105
11.8	109
11.7	114
11.6	110
12.1	100

The urine was a 24 hour collection and had a volume of 1250 mL. What is the analytical imprecision in the creatinine clearance determination? **(10 marks)**

Approach 1

%CV = (SD/mean) *100

SD = sq route of $\Sigma(x-\mu)^2/n-1$ where x = individual value
µ = mean

However should be able to work out standard deviation on scientific calculator – suggest familiarise yourself with how to do this since it will save time

CV overall = square route of $(CV_{serum}{}^2 + CV_{urine}{}^2)$

Urine Creatinine mmol/L   Serum Creatinine umol/L

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Mean	11.59	107
SD	0.415	4.50
%CV	3.58	4.2

CV overall = square route of $(4.2^2 + 3.58^2)$ = **5.52%**

Approach 2

Calculate the variable part of the creatinine clearance for each point

Creatinine clearance = UV/ST = constant * (V/S)

where U = urine creatinine
S = serum creatinine
V = volume
T = time

Urine creat mmol/L	Serum creat umol/L	Urine creat/Serum creat mmol/umol
11.1	102	0.109
11.5	108	0.106
11.9	107	0.111
10.9	112	0.097
12.1	103	0.117
11.2	105	0.107
11.8	109	0.108
11.7	114	0.103
11.6	110	0.105
12.1	100	0.121
	mean	0.108
	SD	0.0068
	%CV	**6.3**

10. A 70 kg lady is given an oral dose of carbamazepine of 400 mg. What is the plasma carbamazepine concentration 24 hours later assuming a volume of distribution of 1.0 L/kg a clearance of 0.05 L/h/kg, salt factor of 1 and bioavailability of 0.75? **(10 marks)**

First calculate the theoretical initial drug concentration (I_o)

I_o = (Dose * S * F)/Vd

Where S = salt factor
F = bioavailability
Vd = volume of distribution

Vd = 1.0 L/kg = 1.0*70 = 70L for patients weight

I_o = (400*1*0.75)/70 = 4.29 mg/L

$I = I_o e^{-kt}$

Where I = drug concentration 24 hours post dose
t = time since dose = 24h
k = elimination rate constant = Clearance/Vd = 0.05/1
k = $0.05h^{-1}$

lnI = lnIo –kt

lnI = ln 4.29 – (0.05 *24)

lnI = 1.46 – 1.2 = 0.26

I = **1.3 mg/L**