AGROTECHNOLOGY & FOOD SCIENCES GROUP
WAGENINGEN UR

DIVISION OF HUMAN NUTRITION

Example EXAM 2011 - HNE-23306 Nutrition & Pharmacology

Date : ********

Place : ********

Explanation : This exam consists of:

- **** open problems on pharmacokinetics (normally 2-3)
- *****series of five propositions where you are also to provide a short motivation (normally 1)
- 1 serie of questions on drug information leaflets (case-studies)
- ****** multiple choice questions (normally 20-25). Normally, the multiple choice questions determine the final mark for approx 50 ± 5 %

In total, 100 points can be earned. The maximum number of points which can be earned per question is indicated.

Notes : This may be subject to slight changes. The set of questions on the information leaflets with their answers will be published on Blackboard. Contribution to the final mark will be (at least) 10 %
For this example exam, the points are indicative, and the total may be more than 100. This is done as I thought you might like to have some more questions to train or test yourself. In particular the pharmacokinetic part is a little more than usual, but most students find these the most difficult type.

The time allowed for this exam is normally 3 hours
A result of 56 points or higher is rounded up to a sufficient note.

PLEASE TAKE NOTICE OF THE FOLLOWING POINTS:

- During the exam pocket calculators may not be shared or passed through
- Answers to open questions may be given in the Dutch language
- Supervisors (surveillanten) are allowed to help you with the English of the question
- Write down your name on every page of the exam

LIST OF FORMULAS: A list of pharmacokinetic formulas is given on the last page.

Part 1: open questions and propositions + motivation

Problem 1 (open question, kinetics) [indication : 15 points]*

** indicative to get an idea about weighing factors. Of course, during a real exam the number of points per question will be mentioned on the form*

A drug has the following pharmacokinetic properties:

- Plasma half-life: 3.3 hours
- Volume of distribution 800 ml/kg bodyweight
- MTC (minimal toxic concentration): 35 µg / ml
- MEC (minimal effective concentration) : 15 µg / ml

Questions :

a. Calculate a suitable dosage schedule (dose and dosing interval), based on intravenous administration
b. Suppose we have an emergency situation, which necessitates a starting dose , aiming to reach effective plasma concentrations already at the first dose. Please calculate this starting dose

Problem 2 (open questions, kinetics [indication : 10 points]

A drug has a half-life of 3.5 hours, and a Vd of 0.6 L/kg.

Questions:

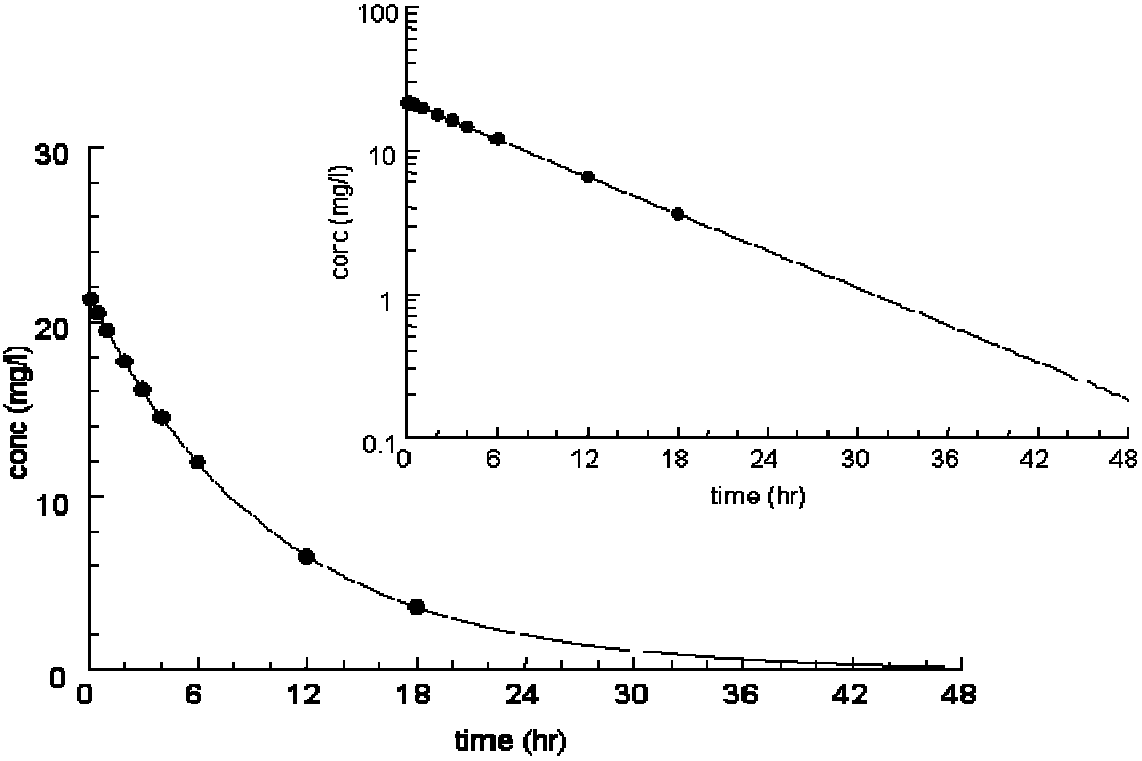
a. If the drug is administered by IV infusion to a 65 kg man at a constant rate of 2 mg/min, what will be the steady-state plasma concentration?
b. How long will it take to reach that concentration?

Problem 3 (open questions, kinetics [indication : 10 points]

If equal volumes of intestinal juice (pH = 5.4) and plasma (pH = 7.4) were separated by an epithelial membrane, what would be the ratio of concentrations (plasma/intestinal juice) achieved by an organic acid (pKa = 6.4)

Problem 4 (open question, kinetics) [indication : 20 points]

A drug is given by IV injection to patient at a dose of 10 mg/kg. The plasma concentrations that were determined have been plotted in the following two graphs (one with normally distributed y-axis, the other with a logarithmic y-axis).



Question 1

a. Please determine the plasma half-life and the distribution volume for this drug in this patient.[5]

b. Determine the clearance of this drug. [4]

c. Suppose this drug is now administered at multiple doses, with a dose interval of 8 hours (in the same dose, so 10 mg/kg). What will be the plasma concentration at 24 hours, immediately after giving the 3rd dose?[5]

The drug is now given to another patient. However, this patient has an impaired (=decreased) kidney function. Due to this, the clearance of this drug is now 50 % lower than the value of the first patient (with a normal kidney function)

d. If the dose regimen (10 mg/kg every 8 hours) would **not** be changed in the second patient, what will be the plasma concentration at 24 hours (immediately after the 3rd dose) [6]

Problem 5 (propositions + motivation, open question) [indication : 10 points]

This problem consists of *** (separate) propositions [NL: stellingen]. Decide for each of them whether you agree or disagree and provide a short motivation (max 5 lines) for your answer (weighing factor: each good answer gives 2 points, provided that motivation is correct).

a. Zero-order elimination means that the amount of drug that is eliminated is proportional to the plasma concentration

b. The isolated guinea pig preparation is particularly suitable to study the action of sympathicolytic drugs

c. When compound A has a greater volume of distribution than compound B, the half-life of compound A will be shorter than that of compound B

d. When two formulations are bio-equivalent, this implicates by definition that the bio-availability of the active ingredient of the formulation is the same for both formulations.

e. Decreasing the pH of the urine can help to reduce the urinary concentration of basic drugs like amphetamine

f. When taken during or after a meal, alcohol is more rapidly metabolized than when taken on an empty stomach

g. Metabolites of drugs are more rapidly eliminated from the body than the original (“parent”) compound

h. Sulfathiazole is an acidic compound with a pK_a value of 7.2. As a result, the compound is better soluble in an acid solution (pH approximately 5) than in a weakly basic solution (pH approx 8)

i. Sublingual administration of a drugs generally leads to a rapid onset of the effects, but does not prevent first-pass metabolism

Part 2 : multiple choice questions

(in general, the MC questions will contribute between 45 and 55 % of the final note; which corresponds to approximately 25 questions)

Only one out of four questions is correct !

1. The Moris water maize test is primarily a test to study

   A. Motor activity
   B. Anxiety
   C. Motor activity and anxiety
   D. Learning and memory

2. When a patient starts to get treated with the drug phenytoin, the dose often needs to be increased after one to two weeks. This is caused by

   A. A gradual inhibition of the enzymes that metabolise phenytoin
   B. A gradual saturation of the tissues, leading to a decrease in the volume of distribution
   C. A gradual induction of the enzymes that metabolise phenytoin
   D. An adaptation of the renal transport mechanisms

3. If the drug itraconazole is given as capsule, there is positive effect of food on the C_{max} of the drug. However, when given as solution, food doesn't have any effect on the absorption of itraconazole.
   This can be explained as follows:

   A. Itraconazole is not stable in the stomach
   B. Itraconazole dissolves better in the stomach than in the duodenum
   C. Itraconazole is more stable when it is dissolved
   D. Itraconazole is transported with the food components

4. A medicinal product carries an RVG notation, This means that this drug

   A .Is an approved phytotherapeutic medicinal product
   B. Is an approved homeopathic medicinal product
   C. Is an approved medicinal product
   D. Is a prescription-only medicinal product

5. Typical first-line / first choice drugs for use in *acute episodes* of angina pectoris include:

   A. Beta adrenergic antagonists
   B. ACE-inhibitors
   C. Ca-antagonists
   D. Organic nitrates

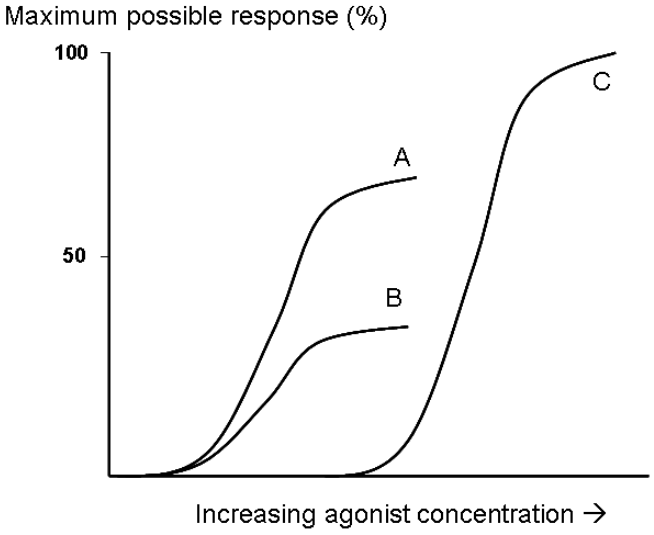
6. Given the following two statements :

Statement I: A reversible competitive antagonist shifts the dose-response curve of an agonist to the right and reduces the size of the maximum response of the agonist
Statement II: An irreversible competitive antagonist does not shift the dose-response curve of an agonist along the x-axis, but reduces the size of the maximum response of the agonist

Which of the following answers is correct regarding statement I and II ?

A. Statement I is true, statement II is false
B. Statement I is false, statement II is true
C. Statements I en II are true
D. Statements I en II are false

The following **two** questions refer to the dose-response curves for the agonists A, B and C in the figure below.



7. Which agonist has the lowest intrinsic activity?
   A. A
   B. B

C. C
D. A and B

8. Which agonist has the lowest affinity ?
   A. A
   B. B
   C. C
   D. A and B

9. Parasympathetic postganglionic neurons secrete:

   A. epinephrine
   B. acetylcholine
   C. nicotine
   D. muscarine

10. Acetylcholine causes the production of action potentials in nerve cells. Lignocaine (=lidocaine) reduces this response by blocking sodium channels in the nerve fibre, thus preventing action potential propagation. What type of antagonist is lignocaine?

    A. Reversible competitive antagonist
    B. Non-competitive antagonist
    C. Physiological antagonist
    D. Irreversible competitive antagonist

11. Which of the following statements are correct ?
    A. Drugs are applied to the skin surface only for local surface action
    B. With the right sort of pharmaceutical formulation, most drugs are well absorbed when applied to the skin for systemic action
    C. Some drugs used clinically are given into the nose for systemic action
    D. Some drugs used clinically are given as eye drops for systemic action

12. The melanocortin receptor in the brain shows constitutive activity. As a consequence,

    A. Full antagonists will decrease the activity mediated by the receptor
    B. Full antagonists will not affect the activity mediated by the receptor
    C. Agonists are not able to stimulate the receptor
    D. Inverse agonists will increase the activity of the receptor

13. Which one of the following statements is true about leptin ?

A. Leptin induces appetite and food-intake
B. Leptin is secreted by entero-endocrine cells in the GI tract
C. Leptin is formed in adipose (fat) tissue
D. People that have a deficient leptin receptor show a decreased appetite

14. Which of the following statements is true for the clinically used calcium channel blockers?

A. They block calcium efflux into the vascular smooth muscle cells
B. In presynaptic nerve terminals they block the calcium influx, which is necessary for transmitter release
C. The can block calcium influx into skeletal muscle cells
D. They block calcium influx into cardiac muscle cells

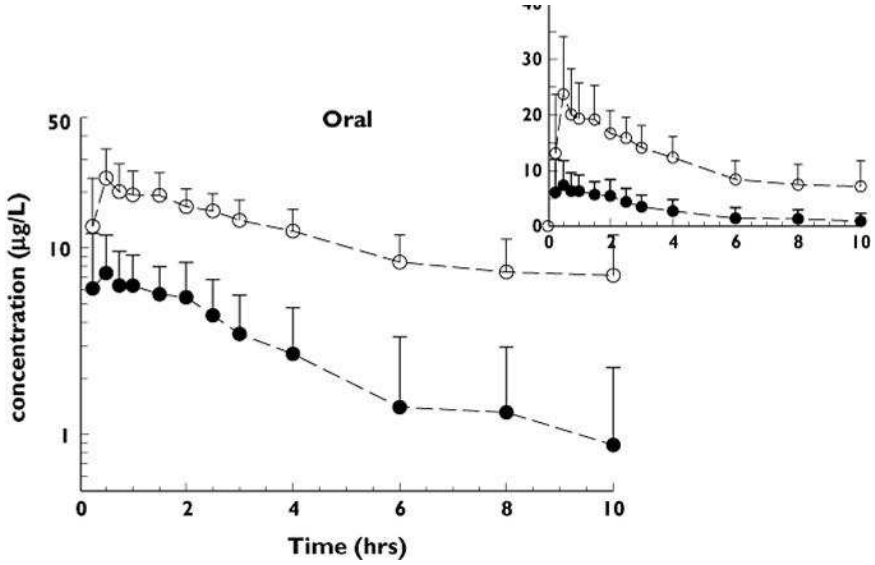
15. Which of the following statements is <u>not</u> true:

A. Receptors may be liked to enzymes via G proteins
B. Receptors may have an integral ion channel
C. Receptors may be linked to ion channels by G proteins
D. Receptors may be linked to DNA by G proteins

16. Which statement correctly describes the main events in acetylcholine synthesis and breakdown in the cholinergic nerve terminals ?

A. Choline is synthesized within the cell body and migrates to the nerve terminal
B. Acetylcholine is synthesized from choline by acetylcholinesterase
C. Acetylcholine is packaged in vesicles within the nerve terminal
D. The neurotransmitter action is terminated by reuptake of acetylcholine into the terminal

17. The drug midazolam (a benzodiazepine mainly used for sleeping problems) was given (orally) to a group of persons before (●) and during (○) treatment with another drug, the antibacterial clarithromycin. The plasma concentrations of midazolam are given in the graphs (log and linear distribution) below. Which of the following statements gives the *best* explanation for the effect of clarithromycin on the kinetics of midazolam ?



A. Clarithromycin increases the absorption of midazolam;
B. Clarithromycin inhibits the biotransformation of midazolam;
C. Clarithromycin inhibits the renal elimination of midazolam;
D. Clarithromycin decreases the absorption of midazolam.

18. A drug is found to have a volume of distribution of 10 L/kg.
Which of the following statements gives the best description of the real distribution of this compound?

A. This compound is extensively distributed throughout the body;
B. This compound is likely to accumulate somewhere in the body;
C. This compound is likely to be distributed over the total body water;
D. This compound will probably not leave the blood circulation.

19. Which of the following statements is true about *Myastenia gravis* ?

A. Myastenia gravis is caused by an decreased number of postsynaptic receptors for acetylcholine.
B. Myastenia gravis is diagnosed by the response to atropine
C. Cholinesterase inhibitors will worsen the symptoms of myasthenia gravis
D. Myastenia gravis is caused by a decreased release of acetylcholine in the synaptic cleft.

20. Which of the following approaches can provide good targets for pharmacological modulation of appetite and/or food-intake ?

A. Stimulation of pancreatic lipase in the gut
B. The use of GLP-1 analogues
C. The use of CCK-analogues
D. Stimulation of leptin release

Addendum

List of Pharmacokinetic formulas

$$\ln C_t = \ln C_0 - \ln 2 * \frac{t}{t_{1/2}}$$

$$Vd_{\beta} = Vd_{area} = \frac{Cl}{\beta} = \frac{D}{AUC * \beta}$$

$$V_d = \frac{D * f}{C_0}$$

$$Cl = \frac{D * f}{AUC}$$

$$Cl = k_{el} * V_d$$

$$C_{ss} = \frac{R_{\text{inf } uus}}{Cl}$$

$$pH = pKa + \log \frac{[B]}{[A]}$$