**Exercice 1**

**Dosage regimen and multiple dosing**

**PART 1: HALF-LIFE**

**Question 1:** Give the definition of terminal half-life

**Time required halving blood concentration when distribution equilibrium is reached**

**Question 2:**

The drug X is administered intravenously. The time profile of plasma X concentrations is shown in the following figure.

Give an estimate of the half-life for this molecule.



**4 h**

**As we cannot check on the graph when distribution equilibrium is reached, we should verify the value of half-life on different parts of the curve**

Half-life time =

**Question 3:**

The drug Y is administered at a dose of 10mg/kg intravenously and blood samples are taken at different times to measure the drug concentration in the plasma.

The concentrations obtained at the different times are presented in the table below:



Try to calculate the half-life time directly by looking at the data in the table:

**Between 40 and 20 µg/ml, the concentration is halved in 1h**

**But between 14 and 8 µg/mL, the concentration is halved in more than 3h**

Half-life =

After typing the table on an Excel sheet, make a graph presenting the concentrations versus time profile.

You can see on the graph that there are 2 distinct phases. Name the phenomena correspond to each phase:

**Distribution + Elimination**

**Elimination**

* phase 1:
* phase 2:

Calculate the half-life of drug Y.

**About 4.5 h**

 Half-life =

**PART 2: CLEARANCE**

**Question 4:** Give the definition of clearance

**Proportionality constant between the rate of elimination and the concentration**



**Question 5:** What is the equation used to calculate the clearance



**PART 3: REPEATED ADMINISTRATIONS**

**Question 6:** Using the excel file "Multiple dosing simulation", simulate the administration of 10 successive doses of the drug YY administered once a day at a dose of 1 mg in a patient A. The half-life of this molecule is 24 hours.

*Data :*

*Dosing interval (e.g. τ = 24 h corresponds to one administration per day)*

*t1/2: half-life*

Can you distinguish 3 characteristics of this profile ?

1. **An accumulation when the rate of elimination is lower than the rate of entry of the drug**
2. **A plateau when the rate of elimination becomes equal to the rate of entry of the drug**
3. **Fluctuations of drug concentration between Min and Max within the dosage interval**

**Question 7:** Explain why plasma concentrations should not be too low or too high. What is the name of the range in which the concentrations should remain?

**Not too low: to reach minimal concentration associated with efficacy**

**Not too high: to avoid concentrations associated with adverse effects**

**This range of concentrations is called Therapeutic window**

**Question 8:** Testing different combinations of t1/2 and tau () on the simulation file, give the influence of changing t1/2 and tau on **the accumulation index**. You can test values of 12 h and 24 h for t1/2 and use the green and red curves to make comparisons.

*Data :*

*Cmin = minimal concentration*

*Cmax = maximal concentration*

*Cmaxeq = maximal concentration at equilibrium (when the plateau is reached)*

*Cmax1= maximal concentration after the first administration*

***Ia = accumulation index = Cmaxeq/Cmax1***

**T1/2 short: Low accumulation**

**T1/2 long : High accumulation**

**Tau short: High accumulation**

**Tau long : Low accumulation**

Influence of T1/2 **:**

Influence of tau :

**Question 9:** Testing different combinations of t1/2 and tau () on the simulation file, give the influence of changing t1/2 and tau on **the amplitude of** the fluctuations at equilibrium. You can test 12 h and 24 h values for t1/2 and use the green and red curves to make comparisons.

*Data :*

*******Cmineq = minimal concentration at equilibrium*

*Cmaxeq = maximal concentration at equilibrium*

***Amplitude = Cmaxeq/Cmineq***

**T1/2 short: High amplitude**

**T1/2 long : Low amplitude**

**Tau short: Low amplitude**

**Tau long : High amplitude**

Influence of T1/2 **:**

Influence of tau :

**Question 10:**

Instead of giving 1 tablet/bolus of 1 mg per day, you want to give a quarter tablet/bolus every 6 hours. Plot together and compare the concentration profiles obtained with the 2 dosing regimens in the simulation file.

Identify 2 main characteristics and explain them.

Compare the two regimens in terms of advantages and disadvantages.

1. **mg each 24h versus 0.25 mg each 6h**
2. **Both reach the same average concentration at equilibrium : the daily dose is the same**
3. **The amplitude of concentrations is lower for 0.25mg/6h**

**0.25mg/6h = FRACTIONATING the daily Dose**

**Advantage: safety is increased because higher probability to fluctuate inside a narrower Therapeutic widow**

**Disadvantage: compliance is decreased**

**Question 11:** You will now administer 1/24th of the 1 mg dose (1/24mg) e hour. Compare the concentration profile obtained with this new dosing regimen with the administration of one tablet/bolus (1mg) once a day in the simulation file. How can you describe the evolution of the concentrations? At what type of clinically feasible administration does this concentration profile correspond?

**The more the daily dose fractionated, the lower the amplitude of concentrations**

**The concentrations profile looks like that produced by an intravenous infusion**

**Question 12:** You decide to prescribe the same treatment (1 mg per day of the drug YY) to a patient B who has renal failure (the capacity of his kidneys to eliminate the drug is divided by 2). The drug YY is only eliminated by the kidneys. What influence the real failure will have on the half-life of drug YY in this patient compared to the patient A (who has a normal renal function)?

**The renal clearance of the drug is divided by 2.**

**The body clearance is divided by 2.**

**The terminal half-life is multiplied by 2**

What happens in terms of accumulation of the drug YY in pa tient B compared to patient A? Is it serious for patient B?

**The same dosage regimen double the accumulation in patient B.**

**The concentrations are above the Therapeutic window: high risks of adverse effect**

**Question 13:** Can you propose 2 dosing regimens to solve the problem in patient B? Discuss the consequences of each dosing regimen in terms of accumulation, amplitude, safety and compliance.

**As clearance is divided by 2, we have to divide by 2 the daily dose.**

1. **Halving Dose / Same tau**
2. **Same dose / Doubling tau**

**Accumulation: the Index of accumulation is different BUT the SAME average concentration is reached at equilibrium**

**Amplitude: Llower for dosage 1) / Safety increased**

**Compliance: better for dosage 1)**

**In general, dosage 1) is preferred for dosage adjustment**

**Question 14:** You will now prescribe digoxin, which is a drug used in the treatment of heart failure or **arrhythmia** (digoxin slows, strengthens and regulates heart contractions).

*Data:*

*Therapeutic concentrations: between 2 and 2.5 ng/mL*

*t1/2 = 48h*

Calculate the maximal range of plasma concentrations that are acceptable (for efficacy and safety reasons).

**Acceptable range of concentrations: [2 – 2.5]**

**Max/Min ratio of the Therapeutic window: TW = 1.25**

We consider that the daily dose (DDdigo) is known. Calculate the dosing interval (tau) that allows the amplitude of concentrations to fill the objective.



*Data:*

**Objective: concentrations fluctuate inside the Therapeutic Window**

**Amplitude < TW**

**2^tau/t1/2 < TW**

**Tau < t1/2 x Log(TW)/Log(2)**

**Tau < 48x Log(1.25)/Log(2)**

**Tau < 15.45 h**

What is the dosing regimen that you will prescribe?

**The daily dose is split in 2 times per day**

**One half in the morning, one half in the evening**

**Question 15:**

How long will it take for the concentration profile to reach equilibrium?

*Data: Steady-state condition is reached after 4 times the half-life*

**Time to reach equilibrium = 8 days**

**This time only depends on the half-life.**

**See the Excel file**

What do you think of this duration?

**Question 16:** What solution could you imagine? Discuss this solution in terms of advantages and disadvantages.

**Use a LOADING dose (LD): the first dose**

**And then continue with the “normal” dose, which is called MAINTENANCE dose (MD) because is role is to maintain the equilibrium°**

**LD = \_\_ x MD**

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