**Exercice 2**

**Determination of the pharmacokinetic properties of a drug**

**Development of a new antibiotic in dogs.**

A 20 kg dog received the antibiotic intravenously at the dose of 20 mg/kg. Plasma concentrations (μg/mL) were measured at different times (min) after administration (Table 1).

**TABLE 1: Plasma concentrations (μg/mL) measured after IV administration (20 mg/kg**

|  |  |
| --- | --- |
| **Time (min)** | **Concentration (μg/mL)** |
| 1 | 4.97 |
| 5 | 4.84 |
| 10 | 4.68 |
| 20 | 4.38 |
| 30 | 4.09 |
| 60 | 3.35 |
| 120 | 2.25 |
| 240 | 1.01 |
| 360 | 0.45 |
| 480 | 0.20 |
| 720 | 0.0412 |

Question 1:

After copying the table on an Excel sheet, make a graph presenting the concentrations versus time. By changing the scale of the Y-axis, you can display the graph in arithmetic or logarithmic scale.

Give the equation of the curve: **C(t) =**

Question 2: **Calculation of the area under the curve (AUC)**

Calculate the area under the curve, and provide the units of AUC

a) between t=1min and the last sampling time (tlast) by the trapezoidal method: **AUC1-last =**

## Calculation using the "trapezoidal rule".

The AUC between two concentrations is calculated using the following equation:

$$AUC\_{t1-t2}= C\_{mean over t1-t2} x (t\_{2}-t\_{1})$$

b) between t=tlast and infinity: **AUCtlast-∞ =**

***Help for extrapolation to infinity***

*The extrapolation is performed by mathematical integration of the curve between the last measured concentration (Clast) and infinity:*

**

*with Clast, the last measured concentration, and lambda (), the slope.*

c) between t=1 min and infinity: **AUC1-∞ = 768**

And don't forget the units.

Very important for the following questions: we need the units of the calculated parameters.

Question 3: **Body clearance**

Calculate the plasma clearance. **Cltot =**

How does this clearance value relate to the maximal capacity of drug elimination in the dog?

Question 4: **Renal clearance**

*The urine was collected and the total amount of the drug eliminated in the urine was measured: 10 mg.*

Calculate the renal clearance: **Clr=**

*The drug is at 84% bound to albumin.*

Name the 3 biological mechanisms that may be involved in the urinary excretion of the drug. Determine which mechanism(s) is (are) predominantly involved in the renal clearance of this antibiotic.

What do you think about the dose required for a dog with renal failure?

Question 5: **Hepatic clearance**

*It is assumed that the antibiotic is eliminated only by the kidneys and the liver (biotransformation into an inactive metabolite):*

Calculate the hepatic clearance: **ClH=**

What do you think about the dose required for a dog with liver failure?

Question 6: **Bioavailability of the oral route**

When administered orally, what are the 3 main stages the antibiotic will go through before reaching the general circulation?

Can you deduce an expression for the oral bioavailability (**Foral**).

Can you estimate the oral bioavailability from available informations? **Foral =**

What could be the dose of the antibiotic if administered by oral dose? Can you identify problems?

Question 7: V**olume of distribution**

Calculate the half-life (t1/2) of the antibiotic from the equation identified in question 1. **T1/2=**

Calculate the volume of distribution (Vd). Are you comfortable with this value? **Vd=**

***Help for calculating the volume of distributions***

*You will use the equation :*

$$t\_{1/2}= \frac{Ln(2)×V\_{D}}{Cl}$$

Give the definition of volume of distribution.

What is the amount of the antibitoic which is present in the body when the plasma concentration is equal to 0.45 μg/mL?

**Xtot =**

What is the amount of the antibitoic which is present in the plasma when the plasma concentration is equal to 0.45 μg/mL?

**Xtot =**

What is the percentage of the antibiotic present in the general circulation?

**Xplasma/Xtot=**

If we consider now a toxic compound that have the same volume of distribution, do you think that an emergency doctor will implement a blood dialysis on an intoxicated patient? Why?

Question 8: **Dose calculation**

Calculate the intravenous dose maintaining an **average** antibiotic **concentration equal to 1.0 μg/mL** over a 12-hour dosing interval.

**D =**

Calculate the dose to ensure that the antibiotic concentrations will always be **greater than 1.0 μg/mL** over a 12 hour dosing interval.

*Data : *

**D =**

Is this second dose underestimated or overestimated?

Question 9: **Subcutaneous bioavailability**

*The pharmaceutical company decided to develop a formulation for the subcutaneous (SC) route.*

*After SC administration of a 30 mg/kg dose,* the AUC is 900 μg.min.mL-1. Calculate the bioavailability of this formulation. **FSC =**

Calculate the dose that must be administered subcutaneously to maintain an **average concentration of** the antibiotic **equal to 1.0 μg/mL** over a 12-hour dosing interval.

**D =**

Question 10:

*The plasma half-life after subcutaneous administration is 6 hours.*

Compare this value to the half-life after IV. Discuss the origin of this phenomenon and its consequences for the equilibrium concentration profile.