CHEM2024 - Week 20 Lecture 1 - Pharmacokinetic models

T.N. Tozer, M. Rowland, "Introduction to Pharmacokinetics and Pharmacodynamics", Kluwer, 2006.

1. Compartment models

For the purpose of modelling the intake, distribution, action, and elimination of foreign substances, the body is often modelled as a network of compartments (Figure 1).

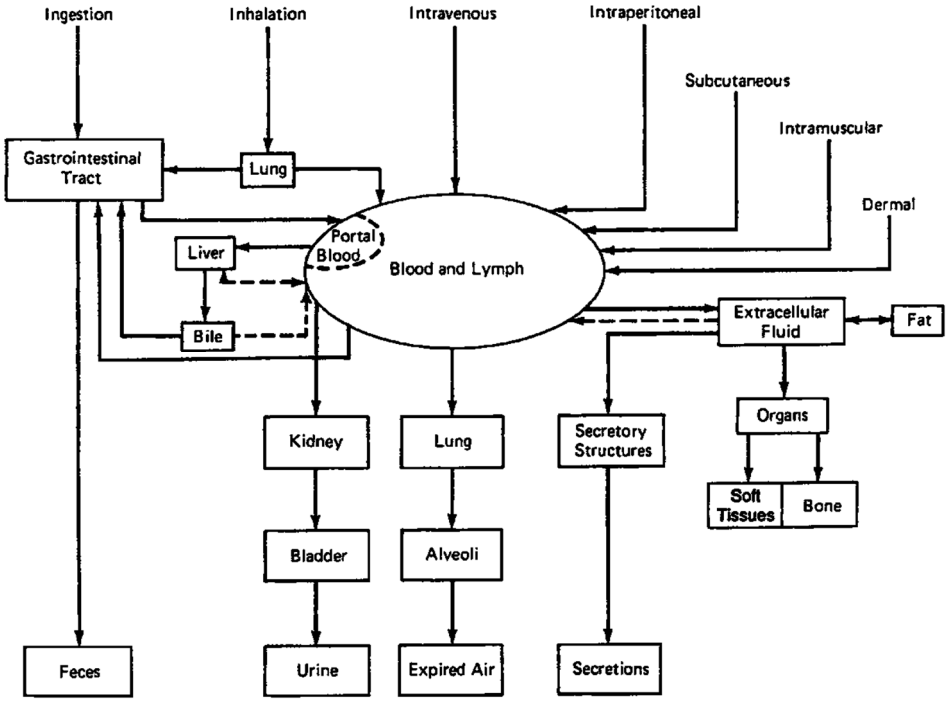


Figure 1. *Schematic diagram of the intake pathways, internal compartmentalisation, and the excretion pathways in a typical mammal. Reproduced from C.D. Klaassen "Toxicology" McGraw-Hill 1996.*

The rate of transport of the substance between compartments is described by simple first order models that only depend on the transport rates and the concentrations. For example, in the absence of chemical reactions, the concentration of a substance S entering the following network of compartments

$$\boxed{\text{Compartment } \mathbf{A}} \underset{k^-_{AB}}{\overset{k^+_{AB}}{\rightleftarrows}} \boxed{\text{Compartment } \mathbf{B}} \underset{k^-_{BC}}{\overset{k^+_{BC}}{\rightleftarrows}} \boxed{\text{Compartment } \mathbf{C}}$$

will obey the following system of differential equations:

$$\begin{cases} \dfrac{dS_A}{dt} = -k^+_{AB} S_A + k^-_{AB} S_B \\ \dfrac{dS_B}{dt} = +k^+_{AB} S_A - \left(k^-_{AB} + k^+_{BC}\right) S_B + k^-_{BC} S_C \\ \dfrac{dS_C}{dt} = +k^+_{BC} S_B - k^-_{BC} S_C \end{cases} \tag{1}$$

where $k^{\pm}_{ABC}$ are the rates of forward and backward transport of the substance S between the corresponding compartments, and S_{ABC} are its concentrations in the corresponding compartments. When chemical reactions happen inside compartments, additional terms appear on the right hand side of Equations (1). For example, if compartment B is liver, and a second order detoxication process happens *via* glutathione conjugation, the second equation would acquire an additional term:

$$\frac{dS_B}{dt} = +k_{AB}^{+}S_A - \left(k_{AB}^{-} + k_{BC}^{+}\right)S_B + k_{BC}^{-}S_C - k_D G S_B \tag{2}$$

where k_D is the detoxication reaction rate constant and G is glutathione concentration.

These pictures and equations illustrate the general principle used for building pharmacokinetic models. At the first stage, the compartment scheme is decided and compartment exchange equations are set up. Chemical reactions are set up inside individual compartments, and the corresponding terms are added to the equations. The intake and the excretion processes may be modelled in the same way. For example, if compartment A receives a steady inflow of the substance S, another rate constant makes an appearance on the right hand side:

$$\frac{dS_A}{dt} = -k_{AB}^{+}S_A + k_{AB}^{-}S_B + k_{in} \tag{3}$$

The resulting system of equations is solved using analytical or numerical methods that will be covered during this course.

2. Pharmacokinetics of ethanol

The early wisdom on ethanol elimination was that it is a zero-order process: in 1919, Lord Mellanby reported a figure of 0.148 grams per kilogram (body mass) per hour, independent of time and the amount of ethanol in the organism. This was later disputed, and various misconceptions persisted until 1958, when Lundquist and Wolthers pointed out that the reaction is enzymatic and must therefore obey some variation of the following general reaction scheme:

$$\mathrm{E} + \mathrm{S} \underset{k_{1-}}{\overset{k_{1+}}{\rightleftarrows}} \mathrm{ES} \xrightarrow{k_2} \mathrm{E} + \mathrm{P} \tag{4}$$

where E stands for enzyme, S for substrate and P for product. This chain of reactions is described by the following system of differential equations:

$$\begin{cases} \dfrac{d[E]}{dt} = -k_{1+}[E][S] + k_{1-}[ES] + k_2[ES] \\ \dfrac{d[S]}{dt} = -k_{1+}[E][S] + k_{1-}[ES] \\ \dfrac{d[ES]}{dt} = +k_{1+}[E][S] - k_{1-}[ES] - k_2[ES] \\ \dfrac{d[P]}{dt} = +k_2[ES] \end{cases} \tag{5}$$

When the concentration of the enzyme is much smaller than the concentration of the substrate, a steady state exists with respect to the substrate-enzyme complex ES, and therefore $d[ES]/dt = 0$. This makes one of the Equations (5) algebraic and leads to the appearance of the pseudo-zero order kinetics that does indeed look like the substrate is being eliminated at a concentration-independent constant rate:

$$\begin{cases} \dfrac{d[S]}{dt} = -k_{1+}[E][S] + k_{1-}[ES] \\ k_{1+}[E][S] - (k_{1-} + k_2)[ES] = 0 \end{cases} \quad \Rightarrow \quad \frac{d[S]}{dt} = -k_2[ES] = const \tag{6}$$

As the concentration of ethanol is reduced, the steady-state approximation would eventually break down, but in Mellanby's case it had happened far below his detection limit. The presence of the linear region on the ethanol elimination profile is illustrated in Figure 2.

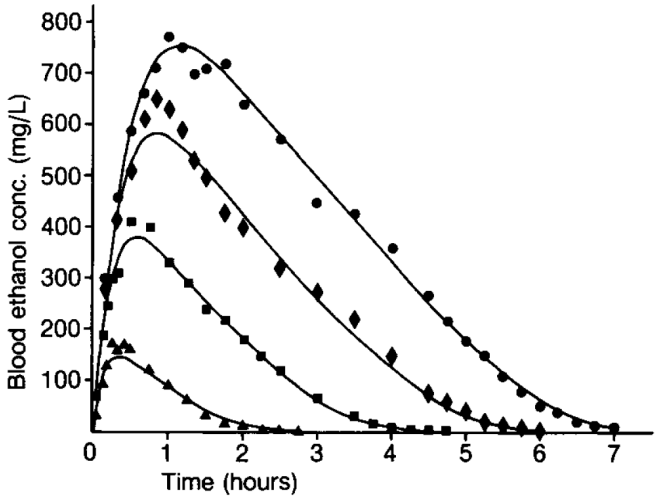
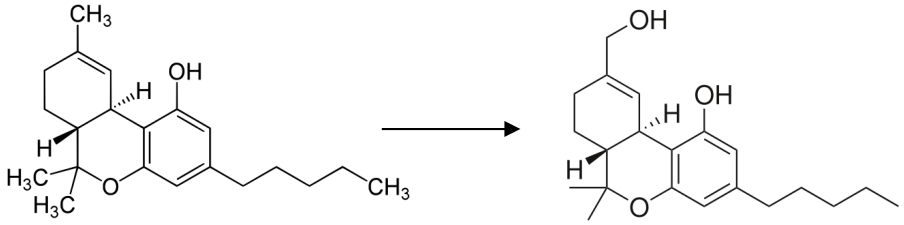


Figure 2. *The effect of increasing ethanol dose on the time course of its blood concentration. Reproduced from N.H.G. Holford, "Clinical Pharmacokinetics of Ethanol", Clinical Pharmacokinetics 13 (1987) 273-292.*

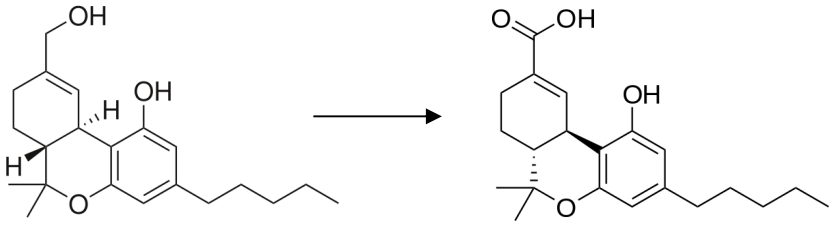
The enzyme in question – alcohol dehydrogenase (AHD) – is a NAD/NADH dependent metalloprotein with a Zn^{2+} ion in the active centre. Its primary locations are the liver and in the lining of the stomach. AHD expression and activity is strongly influenced by genetic and developmental factors.

3. Pharmacokinetics of THC

Over 100 metabolites of tetrahydrocannabinol have been identified, but the principal stages are the oxidation of THC into 11-hydroxy-THC, which is also psychoactive:



followed by further oxidation of the hydroxymethyl moiety into a carboxylic group, producing 9-carboxy-THC, which is not psychoactive:



The characteristic time of both processes is measured in hours. However, the carboxyl derivative is eliminated very slowly – its half-life in the blood is approximately one week. If the three substances are labelled A, B, and C, the following reaction scheme describes the process:

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C \xrightarrow{k_3} \ldots$$

Unlike the non-linear system of ODEs describing the elimination of ethanol, the ODEs describing THC elimination are linear (its much lower concentration does not overwhelm the detoxication enzymes):

$$\begin{cases} \dfrac{dA}{dt} = -k_1 A \\ \dfrac{dB}{dt} = +k_1 A - k_2 B \\ \dfrac{dC}{dt} = +k_2 B - k_3 C \end{cases} \tag{7}$$

with the initial condition of $A(0) = A_0$, $B(0) = 0$ and $C(0) = 0$. The matrix form of Equation (7) is:

$$\frac{d}{dt}\begin{bmatrix} A \\ B \\ C \end{bmatrix} = \begin{bmatrix} -k_1 & 0 & 0 \\ +k_1 & -k_2 & 0 \\ 0 & +k_2 & -k_3 \end{bmatrix}\begin{bmatrix} A \\ B \\ C \end{bmatrix} \tag{8}$$

We will learn how to solve such equations in a few lectures' time. This solution is plotted in Figure 3 for the case when $k_1 = k_2 = 1.0$ hour^{-1}, and $k_3 = 1.0$ week^{-1}.

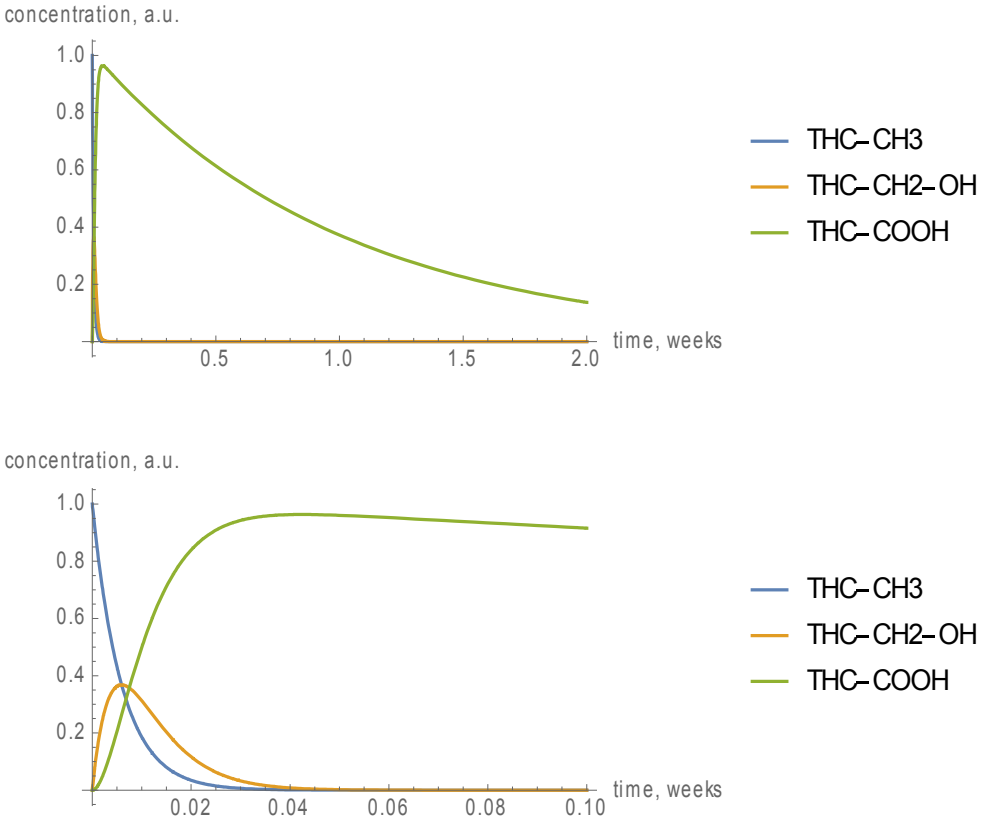


Figure 3. *Pharmacokinetics of THC and its metabolites, based on the solutions of Equations* (7) with k_1 and k_2 set to 1.0 hour^{-1} and k_3 set to 1.0 week^{-1}. **Top diagram:** long-term dynamics. **Bottom diagram:** short-term dynamics.

Even though the psychoactive substances are eliminated in hours, the carboxylic acid metabolite persists for weeks. This fact allows cannabinoid intake to be detected for a very long time after the event.