PK34 - Reversible metabolism

Objectives

- To implement a set of differential equations mimicking reversible metabolism
- To estimate the disposition and interconversion parameters of the two compounds

Keywords

Reversible metabolism, cisplatin, monohydrate, multiple compartment kinetics

Problem specification

The aim of this exercise is to demonstrate how to implement a system of differential equations describing reversible metabolism. Data were taken from the literature on cisplatin kinetics (Andersson [1995]) and used to generate synthetic concentration-time values for cisplatin p and its monohydrate m. This information was then used to obtain initial parameter estimates for a model of reversible metabolism. This exercise demonstrates how to implement the equations for this model into a program. In an infusion solution of cisplatin, equilibrium is established between cisplatin and its monohydrate complex. Thus, the input rate can be split into cisplatin infusion rate In_p and monohydrate infusion rate In_m. We have also chosen to describe the equilibrium process *in vivo* between cisplatin and its monohydrate complex by means of two clearance rates Cl_{pd} and Cl_{md}. The experimental data and model for reversible metabolism that takes account of such a split input rate and clearance are shown in Figure 34.1. See also Section 2.4.

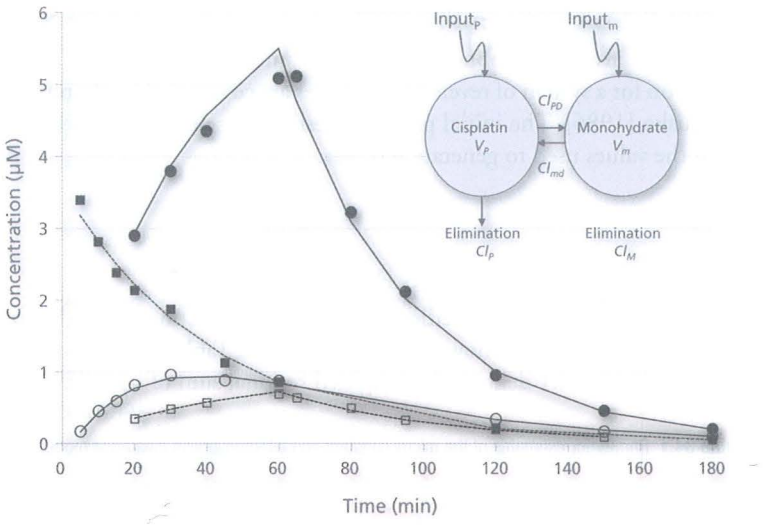

Figure 34.1 Left: Observed (symbols) and predicted (solid lines) concentration-time data of cisplatin and its monohydrate. The symbols correspond to cisplatin (upper curve) and the monohydrate (bottom curve) after infusion of cisplatin which also contains the monohydrate, and cisplatin (second from bottom) and monohydrate (second from top) after monohydrate infusion. **Right:** A two-compartment model mimicking reversible metabolism was used to model the data.

The equation for cisplatin (p) is

$$V_p \cdot \frac{dC_p}{dt} = In_p - Cl_p \cdot C_p - Cl_{pd} \cdot C_p + Cl_{md} \cdot C_m \quad (34:1)$$

Where V_p, C_p, In_p, Cl_p and Cl_{pd} are the volume, concentration, input rate, clearance and inter-conversion clearance of cisplatin respectively. C_m is the concentration of the monohydrate. The conversion of cisplatin to the monohydrate occurs with a rate constant derived according to Equation 34:2

$$k_{12,pd} = Cl_{pd} \cdot V_p \quad (34:2)$$

The reversal rate for conversion of the monohydrate to cisplatin is

$$k_{21,md} = Cl_{md} \cdot V_m \quad (34:3)$$

The equation for the monohydrate (m) is

$$V_m \cdot \frac{dC_m}{dt} = In_m - Cl_m \cdot C_m - Cl_{md} \cdot C_m + Cl_{pd} \cdot C_p \quad (34:4)$$

Where V_m, C_m, In_m, Cl_m and Cl_{md} are the volume, concentration, input rate, clearance and inter-conversion clearance of the monohydrate respectively. C_m is the concentration of the monohydrate.

Initial parameter estimates

Procedures involved in obtaining initial parameter estimates, *AUC*, *MRT*, and so on for a system of reversible processes are covered in depth in Ebling and Jusko [1986]. The initial parameter estimates selected differed a little from the values used to generate the data.

Interpretation of results and conclusions

The observed and model-predicted plasma concentrations, and the final parameter estimates are shown in Figure 34.1 and Table 34.1, respectively. *WRSS* in Table 34.1 denotes the weighted residual sum of squares.

Table 34.1 Parameter estimates of the micro-constant and interconversion clearance models

Microconstant model			Interconversion clearance model		
Parameter	**Estimate**	***CV%***	**Parameter**	**Estimate**	***CV%***
V_c (L)	14.1	3	V_c (L)	14.1	3
Cl_m (L·min^{-1})	0.0085	22	Cl_m (L·min^{-1})	0.0084	22
V_m (μg·L^{-1})	2.96	2	V_m (μg·L^{-1})	2.97	2
Cl_p (L·min^{-1})	0.446	2	Cl_p (L·min^{-1})	0.445	2
k_{12} (min^{-1})	0.00021	34	Cl_{pd} (min^{-1})	0.0031	33
k_{21} (min^{-1})	0.021	3	Cl_{md} (min^{-1})	0.063	5
WRSS	0.0089		*WRSS*	0.0089	