MODELLING THE PHARMACOKINETICS AND PHARMACODYNAMICS OF ANTI-CANCER DRUGS

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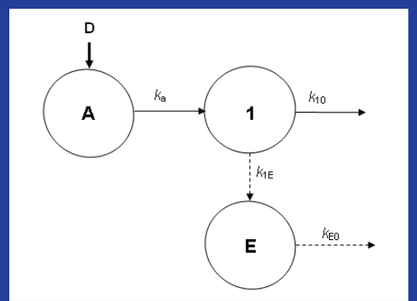
INTRODUCTION

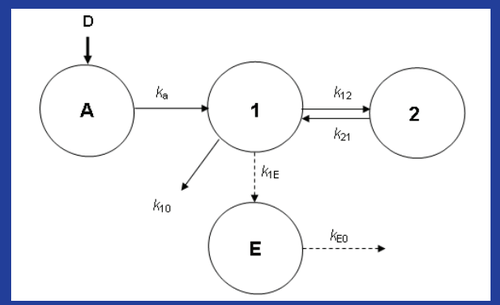
The ideal anti-cancer drug has the quantity of the drug in the blood stream above a certain threshold for as short a time as possible, to reduce the possibility of toxicity, while maintaining the effect above a certain threshold for as long as possible.

MATHEMATICAL MODELS

The pharmacokinetics (concentration of drug in blood) was described by compartmental models with either one or two compartments, plus an absorption compartment to model the appearance of the drug in the blood stream. The pharmacodynamics (the therapeutic effect) was described using the Effect Compartment approach.

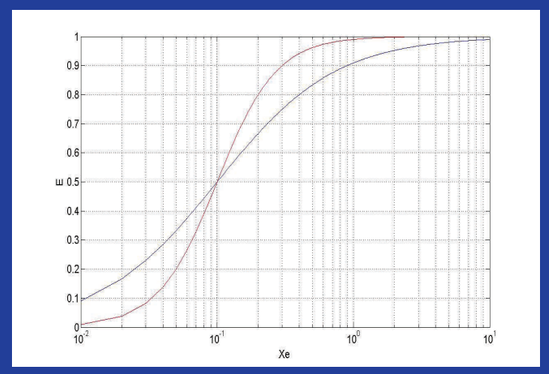


MODEL 1: One compartment absorption, one compartment distribution and elimination model



MODEL 2: One compartment absorption, two compartment distribution and elimination model

The effect E was a nonlinear function of the 'quantity' x_E in the Effect Compartment. Two forms of nonlinearity, both with $E = (K_E)^\alpha/[(K_E)^\alpha+(x_E)^\alpha]$ were used to model the effect. The Michaelis-Menten form has $\alpha = 1$, and the Hill Equation form has $\alpha = 2$.

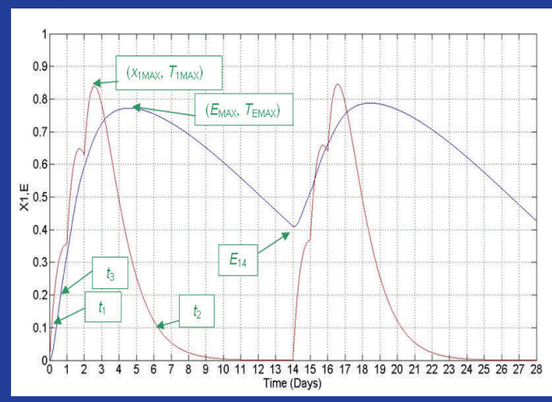


The graph on the left shows Effect E as a function of x_E, with Michaelis-Menten nonlinearity (blue) and Hill Equation nonlinearity (red) for $K_E = 0.1$. The two lines cross at $E = 0.5$ and $x_E = K_E = 0.1$. For small values of x_E, the slope of the Hill Equation curve is much less steep than that of the Michaelis-Menten curve.

RESULTS

Two dosing regimens were considered. Both are based on three doses in alternate weeks, with no doses in the intervening weeks. **Dosing Regimen 1** is for dosing on Monday, Tuesday and Wednesday in alternate weeks, while **Dosing Regimen 2** is for dosing on Monday, Wednesday and Friday in alternate weeks.

Simulations were carried out using the software package *Berkeley Madonna.* The doses on these days were introduced in *Berkeley Madonna* using the SQUAREPULSE function, with amplitude of 1000 and duration of 0.001 days, effectively simulating a bolus dose of size 1.



Pharmacokinetic and Pharmacodynamic Quantities

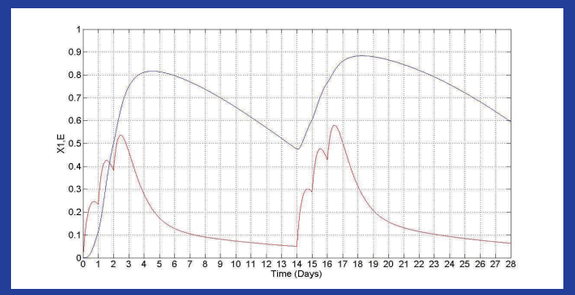
The objective is to keep the (pharmacokinetic) quantity x_1 low while keeping the (pharmacodynamic) effect high for as much of the 14-day dosing cycle as possible. This is illustrated in the figure on the left, in which the following quantities are shown:-

PHARMACOKINETICS

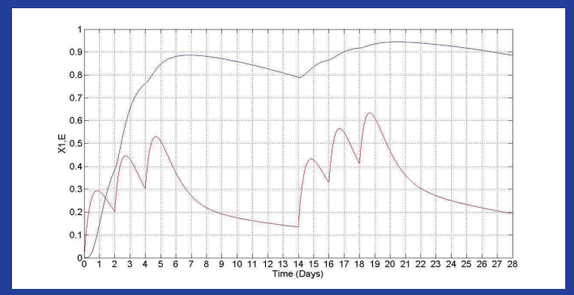
- Maximum value (x_{1MAX}) of x_1 and time (T_{1MAX}) to reach x_{1MAX};
- Times (t_1 and t_2) at which x_1 rises to and falls below 0.1.

PHARMACODYNAMICS

- Maximum value (E_{MAX}) of E and time (T_{EMAX})
- Time (t_3) at which E rises to 0.2;
- Value (E_{14}) of E at the end of the second week.



Model 2, Dosing Regimen 1 with Hill Equation nonlinearity



Model 2, Dosing Regimen 2 with Hill Equation nonlinearity

The red curve on the above graphs represents the quantity of the drug in the blood stream (x_1) and the blue curve represents the effect (E). Times are in Days.

CONCLUSIONS

- It is important to note that, while the quantity of drug in the blood stream falls away rapidly after the administration of the third dose, the effect remains high throughout.
- From the point of view of therapeutic effect, the maximum value of effect (E_{MAX}) and the effect value (E_{14}) at the end of the second week are both higher using **Dosing Regimen 2**, so improving the possibility of therapeutic effects.