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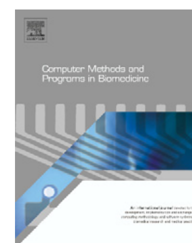

Compartmental modelling of the pharmacokinetics of a breast cancer resistance protein

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ABSTRACT

A mathematical model for the pharmacokinetics of Hoechst 33342 following administration into a culture medium containing a population of transfected cells (HEK293 hBCRP) with a potent breast cancer resistance protein inhibitor, Fumitremorgin C (FTC), present is described. FTC is reported to almost completely annul resistance mediated by BCRP in vitro. This non-linear compartmental model has seven macroscopic sub-units, with 14 rate parameters. It describes the relationship between the concentration of Hoechst 33342 and FTC, initially spiked in the medium, and the observed change in fluorescence due to Hoechst 33342 binding to DNA. Structural identifiability analysis has been performed using two methods, one based on the similarity transformation/exhaustive modelling approach and the other based on the differential algebra approach. The analyses demonstrated that all models derived are uniquely identifiable for the experiments/observations available. A kinetic modelling software package, namely FACSIMILE (MPCA Software, UK), was used for parameter fitting and to obtain numerical solutions for the system equations. Model fits gave very good agreement with in vitro data provided by AstraZeneca across a variety of experimental scenarios.

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1. Introduction

In this paper a mathematical model for the pharmacokinetics of Hoechst 33342 following administration into a culture medium containing a population of transfected cells (HEK293 hBCRP) is described.

Cancer cells develop mechanisms that allow them to resist the action of anti-cancer compounds. This can reduce the exposure of the diseased tissue and so have consequences for the efficacy of a compound. One such important mechanism is efflux transport by the breast cancer resistance protein (BCRP) [1]. It is therefore important to know whether a novel drug is a substrate for BCRP.

The purpose of this work is to produce a mechanistic compartmental model based on mass balance principles, which describes the saturable binding of Hoechst 33342 to BCRP. Rabindran et al. [2] report that Fumitremorgin C (FTC) is a potent BCRP inhibitor, which therefore directly competes with Hoechst 33342 for the limited number of binding sites on BCRP, which in turn will effectively reduce the ability of the efflux transporter to resist the action of the anti-cancer

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compound. The concept is to use the parameterised mathematical model to estimate any unknown rate constants and parameters from *in vitro* data provided by AstraZeneca in order to obtain information on the relative binding affinities to the BCRP transporter.

This article reports the modelling of the kinetics of an assay that uses transfected cells that express BCRP. The assay indirectly measures the binding potential of a drug or similar molecule to BCRP by observing the effects on the kinetics of Hoechst 33342 [3], a BCRP substrate. When Hoechst 33342 binds to DNA the resulting complex fluoresces [3,4,9,10]. This allows the relative levels of Hoechst 33342 bound to DNA to be measured under different experimental conditions. Mathematical modelling of *in vitro* pharmacokinetic assays has proven useful elsewhere [5,6].

With this experimental scenario it is challenging to measure the binding affinity of a drug for BCRP because the only known quantities in the system are the initial extracellular concentrations of Hoechst 33342 and the drug of interest, as well as a fluorescence time series.

This paper describes the modelling of this system along with parameter estimates based upon experimentally obtained data. The intention here is to derive a compartmental model to characterise substrate binding to DNA and in addition account for the effect of transportation of the substrate out of the cell. Such a model, once validated, should permit the prediction of the dosage levels required in order to achieve the levels of absorption desired once bound to DNA.

2. The model

Hoechst 33342 has been shown to be a substrate for BCRP previously [7,8], it is readily taken up into living cells, is non-toxic and binds specifically and quantitatively to DNA whereupon it fluoresces [3,4,9,10]. Hoechst 33342 (and an inhibitor of interest) can be added to the medium in which the cells sit at the beginning of the experiment. The marker compound enters the cell and binds to DNA in the nucleus, resulting in fluorescence. This fluorescence may be measured and is used as a surrogate to measure binding to DNA. The marker compound is a substrate of BCRP and so may be also transported out of the cell actively. In the model, compartments are used to represent different parts of the cell. Based upon what is known about the system a seven-compartment model illustrated in Fig. 1 is used initially to describe the flow of the substrate and inhibitor within and out of the cell.

Extracellular Hoechst 33342 (SO) diffuses into the cell (SI) and may then bind to DNA in the nucleus (NS) resulting in fluorescence. Hoechst 33342 is also transported out of the cell by a BCRP transporter (TS). Similarly extracellular inhibitor FTC (IO) diffuses into the cell (II) and is also transported out by the BCRP transporter (TI).

Although the level of BCRP can conceptually be described by a single compartment, it is represented mathematically by two state variables (compartments) as there are two different complexes present; the substrate Hoechst 33342 and inhibitor FTC, which both compete for the same limited number of binding sites on the BCRP transporter molecules.

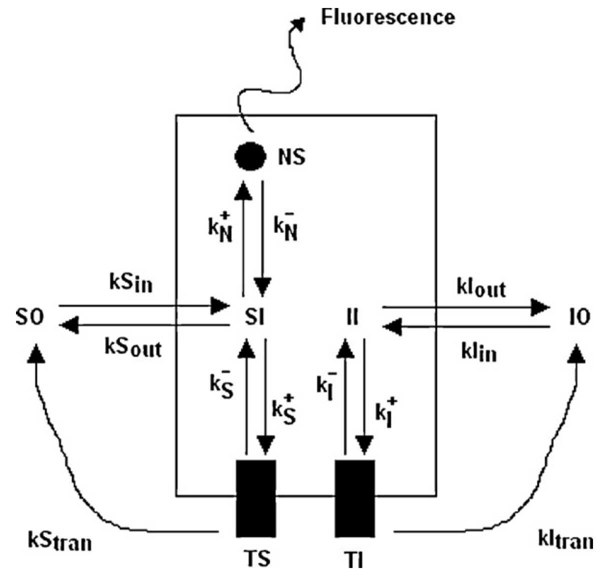

Fig. 1 – Model representation.

The seven compartments used and the inter-compartmental rate transfers are summarised in Table 1 (square brackets denoting quantities represented in terms of relative fluorescence units – RFU).

2.1. System equations

The system of ordinary differential equations describing the model is derived using classical mass-balance principles, as per Jacquez [11]. The first order flow rates give rise to linear terms. Eq. (1) shows the flows to and from the extracellular quantity of marker compound [SO], namely the reversible monomolecular substrate diffusion into the cell, kS_{out} and kS_{in}, and the transporter flow back to marker compound, kS_{tran}.

$$[\mathrm{TS}]\xrightarrow{kS_{tran}}[\mathrm{SO}]\underset{kS_{out}}{\overset{kS_{in}}{\rightleftarrows}}[\mathrm{SI}] \tag{1}$$

The law of mass action gives:

$$\frac{d[\mathrm{SO}]}{dt} = kS_{out}[\mathrm{SI}] - kS_{in}[\mathrm{SO}] + kS_{tran}[\mathrm{TS}] \tag{2}$$

whereas, the second order biological reactions give rise to non-linear terms. Eq. (3) describes the flows to and from the quantity of marker bound to the BCRP transporter [TS], namely the non-linear reversible binding of the marker compound to the BCRP, with association and dissociation rate constants k_S^+ and k_S^-, and the transporter flow back to marker compound, kS_{tran}.

$$[\mathrm{T}] + [\mathrm{SI}]\underset{k_S^-}{\overset{k_S^+}{\rightleftharpoons}}[\mathrm{TS}]\xrightarrow{kS_{tran}}[\mathrm{SO}] \tag{3}$$

where [T] is the quantity of transporter molecules with free binding sites. The law of mass action gives:

$$\frac{d[\mathrm{TS}]}{dt} = k_S^+[\mathrm{SI}][\mathrm{T}] - (k_S^- + kS_{tran})[\mathrm{TS}] \tag{4}$$

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