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A mechanistic approach to modelling the formation of a drug reservoir in the skin

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ABSTRACT

It has been shown that prolonged systemic presence of a drug can cause a build-up of that drug in the skin. This drug 'reservoir', if properly understood, could provide useful information about recent drug-taking history of the patient. We create a pair of coupled mathematical models which combine to explore the potential for a drug reservoir to establish based on the kinetic properties of the drug. The first compartmental model is used to characterise time-dependent drug concentrations in plasma and tissue following a customisable drug regimen. Outputs from this model provide boundary conditions for the second, spatio-temporal model of drug build-up in the skin. We focus on drugs that are highly bound as this will restrict their potential to move freely into the skin but which are lipophilic so that, in the unbound form, they would demonstrate an affinity to the outer layers of the skin. Buprenorphine, a drug used to treat opiate addiction, is one example of a drug satisfying these properties. In the discussion we highlight how our study might be used to inform future experimental design and data collection to provide relevant parameter estimates for reservoir formation and its potential to contribute to enhanced drug monitoring techniques.

1. Introduction

The reservoir function of the skin is a recognised phenomena in the field of percutaneous absorption [1]. A reservoir in the skin was first identified for the case of topically applied corticosteroids [2,3] after a prolonged therapeutic effect was observed. Presence of a reservoir in the skin has since been demonstrated for many other drugs [1]. Moreover it has been shown, via tape stripping, that the main site of this skin reservoir is the stratum corneum (SC), the layer of dead cells at the skin surface [1,2,4].

Research on the presence of a reservoir in the SC is generally focussed on formation from an external source, specifically topically applied drugs and chemical exposure [1]; drug that comes into contact with the skin surface enters the body via passive diffusion. As only unbound drug diffuses [5] the cause of a reservoir forming in the SC is thought to be high keratin binding and slow desorption kinetics [5]. Binding within the skin is most typical for lipophilic drugs with high molecular weight [6,7].

More recently, detection of a 'reservoir' of drug in the skin as a result of systemic presence of that drug has highlighted the potential of skin to act as a site for noninvasive monitoring [8] both to measure systemic drug levels and to estimate historic usage by exploiting the reservoir.

The existence of such a reservoir in the SC has been demonstrated in the case of lithium [8,9]. Lithium is a small drug which remains unbound and is not metabolised within the body. Mathematical modelling in that case [10], showed how the drug reservoir could be used to assess prescription compliance; but it was a simplest case scenario in many ways given the properties of the drug within the body.

The purpose of this paper is to extend that work to use a mathematical modelling approach to explore the potential for reservoir formation with a more complex drug. In particular, we are interested in a drug that is metabolised within the body; bound to molecules within the body; and lipophilic. These choices reflect the properties of many prescription drugs that are metabolised as well as excreted by the body and which bind to proteins and other molecules within both the plasma and the tissue. The choice of a lipophilic drug reflects the composition of the SC which consists of a lipid matrix together with corneocytes and their connecting structures, desmosomes; by focussing on a drug that is lipophilic, we assume that the drug will have affinity to the SC and poten-

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tially a tendency to accumulate in this outer skin layer. The drug buprenorphine used to treat opiate addiction, where compliance is an essential component of effective treatment, satisfies these three criteria and so acts as a motivation for our choice. Despite being well-established, parameter estimates for buprenorphine in the mechanistic model structure are not readily available from the literature and so we use this example simply as a motivation at this stage for our theoretical modelling work.

Classical modelling approaches to drug absorption, distribution, metabolism and excretion (ADME processes) often use a phenomenological approach in which model compartments represent theoretical spaces to give model predictions that fit well with the data. These are known as pharmacokinetic models. More recently, there has been a move towards more complicated physiologically based pharmacokinetic models (PBPK) which take a mechanistic approach, modelling each component of the body relevant to the passage of a given drug [11]. PBPK models are used as predictive tools in research, drug development and risk assessment. However, these models require large amounts of data to estimate the considerable number of model parameters.

In the following section we build the model structure which consists of two sub-models that couple together to provide a profile of compartmental drug concentrations in the body and spatial distribution within the SC. The compartmental body model is a simplified form of a PBPK model where we restrict the number of body compartments to three, invoking Occams razor. The outputs from this model provide boundary conditions for the spatial distribution model in the SC. Analysis of the models leads to predictions about the effect of bound and unbound plasma drug concentration, drug compliance, binding coefficients and diffusive potential on reservoir size. We conclude with observations about the potential to exploit the SC reservoir as a mechanism for non-invasive drug monitoring.

2. Model

The mathematical model is built in two stages: firstly, a compartmental system of coupled ODEs is used to model time-dependent drug concentrations within the body in response to a regularly administered drug. The outputs from this model provide boundary conditions for the second stage model which explores the spatial distribution of drug molecules within the SC; in turn, this is used to calculate the total amount of drug (the reservoir) within the SC as a function of key, critical parameters. It should be noted that whilst Model 1 feeds into Model 2, the converse is not true. We assume that any drug which enters the SC is not reabsorbed into the blood. We assume that active drug is administered and it is the administered drug that we are interested in modelling. A single daily dose is administered in the fully compliant case. For simplicity we will not consider drug–drug interactions.

2.1. Model 1

This model comprises six time-dependent state variables: unbound drug molar concentration in plasma, $P_u(t)$; bound drug concentration in plasma, $P_b(t)$; unbound drug concentration in well perfused tissues, $Q_u(t)$; bound drug concentration in well perfused tissues, $Q_b(t)$;unbound drug concentration in poorly perfused tissues, $R_u(t)$ and bound drug concentration in poorly perfused tissues, $R_b(t)$ at time t. Noting that only unbound drug is able to move between plasma and tissue, we create a mathematical model based on the schematic shown in Fig. 1. The model equations are built from conservation principles on the amount of drug in the

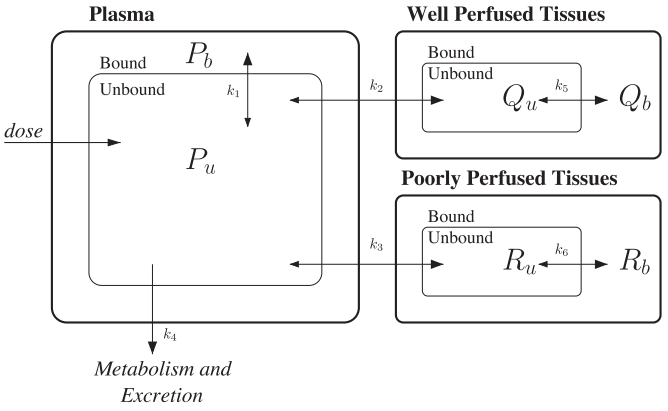

Fig. 1. Schematic demonstrating the flow of drug within a simplified body compartmental structure. Parameters k_i $(i = 1 \ldots 6)$ are described in the text.

system. For unbound drug in the plasma we have:

$$\begin{aligned}&\text{Change in amount of unbound drug in plasma (over time)}\\ &\quad = -\text{ net binding of drug to plasma proteins}\\ &\qquad -\text{ net movement of drug into well perfused tissues}\\ &\qquad -\text{ net movement of drug into poorly perfused tissues}\\ &\qquad -\text{ drug metabolised and excreted}\\ &\qquad +\text{ administered drug.}\end{aligned} \tag{1}$$

As we are considering a fixed plasma volume, V_p, the amount of drug in the plasma is $P_u(t)V_p$.

(Net) binding. Binding in the plasma is a reversible process where, at equilibrium, unbound drug will be a fraction, f_{up}, of the total drug in the plasma, $(P_u + P_b)$. We assume that the rate at which this equilibrium is approached is directly proportional to the difference between the amount of unbound drug at time t, $P_u(t)$, and the amount that will be unbound at equilibrium, $f_{up}(P_u + P_b)$. This gives rise to a binding rate

$$-k_1(P_u - f_{up}(P_u + P_b)),$$

where k_1 is a positive rate constant. The effect of this term on the amount of unbound drug will be positive if P_u is below its equilibrium level and negative if above.

(Net) movement into tissue. Again, this process is reversible. Only unbound drug moves between plasma and tissue which we exploit to give the rate of movement into tissue from the plasma as

$$-k_2(P_u - f_2Q_u) - k_3(P_u - f_3R_u).$$

The parameters k_2, k_3 are the rates at which movement occurs and are dependent on a number of variables such as blood flow to tissues and partitioning coefficients.

Tissues are assigned to well perfused or poorly perfused tissue compartments according to blood perfusion values given in [12]. It therefore follows that $k_2 > k_3$. The remaining two parameters, f_2 and f_3 represent the ratio between concentration of drug in plasma and well perfused tissue, and plasma and poorly perfused tissue at equilibrium, respectively. According to the allocation of tissues to each compartment, poorly perfused tissues have a much higher fat percentage than well perfused tissues [12]. As we are considering lipophilic drugs we can also expect $f_2 > f_3$ (higher affinity for fatty tissue).