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Mixture dynamics: Dual action of inhibition and stimulation

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ABSTRACT

The impact of a drug, or of multiple drugs, on different receptors usually results in a combination of responses. They may be either opposing or reinforcing one another and can lead to complex response versus drug-concentration relations. In this paper, complexity and synergy of multiple drug actions are studied on the basis of four data sets: two involving opposing actions and two resulting from synergistic actions. It is shown that turnover models can be successfully fitted to these data, offer a mechanism for dissecting complex response versus drug-concentration curves, for understanding and quantifying amplification of dual drug actions and elucidate the role of potencies and other parameters related to the different drugs.

1. Introduction

In this paper we study the impact of a single drug or multiple drugs acting on different receptors resulting in a combination of responses, which may be opposing or reinforcing one another. Typical examples where they are opposite are Apomorphine, Clonidine and Sulpiride (cf. Bredberg and Paalzow, 1991; Cheng and Paalzow, 1990; Gabrielsson and Weiner, 2000; Lundström et al., 1992; Paalzow and Edlund, 1979, 1983, 1986). Synergistic actions have been discussed from a drug discovery perspective in PPAR (peroxisome proliferator-activated receptor α/γ agonist) action in TG (triglycerides) turnover (Oakes et al., 2005) and amylin-mediated restoration of leptin responsiveness in diet-induced obesity (Trevaskis et al., 2008). Racemic drug mixtures are other examples of dual composite action displaying different potencies and efficacies of the respective enantiomers on pharmacological response in a clinical setting (Schüttler et al., 1987).

Exposure to two or more compounds involving different mechanism of action has become increasingly common. For instance in the oncology and anti-infectives therapeutic areas a mixture of actions is often used to reduce drug-resistance or the occurrence of tolerance.

We investigate the flexibility of turnover models in describing the dynamics caused by such multiple mechanisms (Mixture Dynamics) by studying in detail four therapeutic cases. In two of them the drug actions are opposite, and in two cases the actions reinforce one another.

- *Composite opposing actions* are studied on the basis of data sets due to Siemers et al. (2007), Fleisher et al. (2008) and Gabrielsson and Weiner (Case Study PD18) (2010).
- *Composite synergistic actions* are studied employing data sets of Gabrielsson and Weiner (Case Study PD39) (2010) and Oakes et al. (2005).

Opposite actions, combining inhibition and stimulation, may lead to very complex response versus time courses. We show how suitably chosen turnover models may be fitted to the data, and how different characteristics of such complex data are reflected in the kinetic parameters, such as the potencies and the maximal values.

Synergistic actions, in which a single drug (single compound) or a combination of drugs (combination of compounds including racemic mixtures, enantiomers) result in multiple actions which reinforce each other and may cause the combined action to have a stronger effect than individual actions generated by the equivalent drug exposure. Specifically, mixed action can be used when a drug has a very good effect but also carries some side effects at higher concentrations that we may want to stay away from. Combining it with a second drug, which is weak but does not have the unwanted side effects, one may utilise synergistic behaviour in order to use the first drug at a lower dose (as in leptin and amylin (cf.

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Trevaskis et al., 2008)). This situation is seen in the data of Case Study PD39, which involves two drugs. There we show how best to optimise the exposure to the individual drugs in order to achieve maximal effect for a given total drug dose.

Whereas previous studies of turnover models involving multiple drug actions have usually been restricted to the study of steady-state response-concentration relations, the impact of the dynamics of the drug concentration can be very relevant (cf. Bredberg and Paalzow, 1991; Cheng and Paalzow, 1990; Lundström et al., 1992; Paalzow and Edlund, 1979, 1983, 1986). Analysis of the relation between response and concentration at steady-state gives considerable insight in the kinetic quantities that are critical. Obtaining criteria which ensure that the results of such an analysis are valid when the drug concentration varies with time requires the study of dynamic properties of the process.

This paper is based on the premise that the underlying dynamic model is a turnover model. In some cases it is possible to reduce the complexity by making the quasi-steady-state (QSS) assumption i.e., to assume that during most of the time course, at any given time the response is almost in equilibrium with its steady-state value for the drug concentration at that time. This is justified when drug is administered through a constant rate infusion, but also when turnover of the response is significantly faster than turnover of the drug in plasma, i.e., half-life of response is much shorter than half-life of drug in plasma.

The analysis in this paper extends earlier studies by Gabrielsson and Weiner (2000) and Earp et al. (2004) which include the models discussed here. In this paper we focus on the following issues:

(i) We show that turnover models involving the kinetics of multiple mechanisms, can be fitted successfully to four therapeutic data sets.
(ii) We discuss strategies for incorporating different drug effects into the classical turnover model, which involves questions such as: "What is the optimal place of impact: the production or the loss term?", and: "Is the drug impact *additive* or *multiplicative* ?".
(iii) We identify and quantify the impact of different parameters. For example, we gain insight in the effect of the potencies involved in the drug mechanism functions and theoretically confirm the observation of Dutta and Ebling (1997), that for the purpose of fitting it is important that the potencies have very different values.
(iv) When multiple drugs act synergistically, we determine dosing ratio's for which optimal effect is achieved.

2. Materials and methods

We begin with a brief overview of the class of turnover models we fit to the data and introduce some notation. Then we discuss the four case studies in which such models have proven successful. The four data sets are not equally rich. Those of Siemers et al. (2007) and Case Study PD39 involve data of the drug concentration and the response over time. Case Study PD18 only contains response versus drug concentration data, and the results of Oakes et al. (2005) consist of response versus time data for a single fixed drug concentration.

2.1. General mathematical and analytical methods and description of the turnover system with dual action

Point of departure of our analysis is the well-known and extensively studied class of turnover models, or indirect response models (cf. Rescigno and Segre, 1966; Dayneka et al., 1993; Earp et al., 2004; Peletier et al., 2005). For a single drug, with plasma concentration $C = C(t)$, they take the form:

$$\frac{dR}{dt} = k_{\text{in}} H_1(C) - k_{\text{out}} H_2(C) R \tag{2.1}$$

in which $H_1(C)$ and $H_2(C)$ denote drug mechanism functions acting on, respectively, the production and the loss term. For a given *fixed* drug concentration C, the steady state response R_{ss} is then given by

$$R_{\text{ss}}(C) = R_0 \frac{H_1(C)}{H_2(C)} \qquad \text{where} \qquad R_0 = \frac{k_{\text{in}}}{k_{\text{out}}} \tag{2.2}$$

The drug mechanism functions $H(C)$ can be inhibiting ($H(C) = I(C)$) or stimulating ($H(C) = S(C)$), or a combination thereof. Typical examples of such functions $I(C)$ and $S(C)$ are

$$I(C) = 1 - I_{\max} \frac{C^{n_1}}{IC_{50}^{n_1} + C^{n_1}} \qquad \text{and} \qquad S(C) = 1 + S_{\max} \frac{C^{n_2}}{SC_{50}^{n_2} + C^{n_2}} \tag{2.3}$$

in which $I_{\max}$, $S_{\max}$, IC_{50}, SC_{50} and n_1 and n_2 denote the maximal inhibition or stimulation, the two concentrations necessary to reach 50% maximum effect, and the two Hill coefficients.

In some instances two different drugs, A and B, are involved. The drug mechanism functions H_1 and H_2 may then depend on the concentration of both drugs, C_A and C_B.

The effect of drug action on the response depends on

(a) the type of drug mechanism function (whether it is inhibitory or stimulatory), and
(b) the location of the action (on the production or on the loss term).

Thus, the function $I(C)$ will have an inhibitory effect on the response if it acts on the production term but a stimulatory effect if it acts on the loss term. For $S(C)$ the effects are reversed.

We make a distinction between two different situations: in the first the two drug actions – by the same or by different drugs – have *opposite* effects on the response and in the second they have *synergistic* effects on the response. In Fig. 1 we show schematically four models in which the drug actions have opposite effects and in Fig. 2 we show two models in which they have synergetic effects.

The dual-action schemes shown in Fig. 1 result in four turnover models of the form (2.1) in which $H_1(C)$ and $H_2(C)$ are given by

$$\begin{array}{lllll} \text{Model 1}: & H_1(C) = I(C)S(C) & \text{and} & H_2(C) = 1 \\ \text{Model 2}: & H_1(C) = 1 & \text{and} & H_2(C) = I(C)S(C) \\ \text{Model 3}: & H_1(C) = I_1(C) & \text{and} & H_2(C) = I_2(C) \\ \text{Model 4}: & H_1(C) = S_1(C) & \text{and} & H_2(C) = S_2(C) \end{array} \tag{2.4}$$

These synergistic models correspond to the models (i), (j), (k) and (l) discussed in Earp et al. (2004). They are also discussed in Gabrielsson and Weiner (2000).

When the actions reinforce one another, i.e., act in a synergistic manner, the resulting response versus concentration curve may not exhibit the same complexity as with opposing actions. However, synergistic effects may occur which are therapeutically very interesting.

The synergistic models shown schematically in Fig. 2 yield turnover models of the form (2.1) with

$$\begin{array}{lllll} \text{Model5}: & H_1(C) = I(C) & \text{and} & H_2(C) = S(C) \\ \text{Model6}: & H_1(C) = S(C) & \text{and} & H_2(C) = I(C) \end{array} \tag{2.5}$$

These models correspond to the models (m) and (n) in Earp et al. (2004) and are also discussed in Gabrielsson and Weiner (2000).

The six turnover models shown in Figs. 1 and 2 are fitted to the four data sets described in the following two sub-sections.