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Comparison of two types of population pharmacokinetic model structures of paclitaxel

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ABSTRACT

Two main types of model structures have been proposed for the pharmacokinetics of paclitaxel; an empirical model structure based on total plasma concentrations of paclitaxel, and a mechanism-based model structure derived from both total and unbound paclitaxel concentrations and concentrations of the formulation vehicle Cremophor EL. The purpose was to compare the two pharmacokinetic model structures when only total paclitaxel concentrations are available. To support the mechanism-based model structure with Cremophor EL concentrations, *in silico* concentrations were obtained from simulations of a pharmacokinetic model available in the literature. Local algebraic observability was tested on both model structures; the mechanism-based model structure was found, with high probability, not to be algebraically observable if total paclitaxel concentration is considered to be the only model output, and if no kind of prior information is used. Sensitivity analysis was performed to reveal which parameter should be fixed in order to make it locally observable. Parameter estimation was then performed on both model structures using nonlinear mixed effects and data from a clinical study. The estimated mechanism-based model turned out to have a somewhat better fit to data than the corresponding empirical model, $\Delta AIC = -31$, where AIC is the Akaike Information Criterion. Hold-out validation was performed on three patients, but did not favour any of the models. In conclusion, since the mechanism-based model structure behaved at least as good as the empirical model structure, it is suggested that the former model structure should be used since it offers a more accurate description of the disposition.

1. Introduction

The drug paclitaxel is used in chemotherapy for treatment of various forms of cancer, for instance ovarian cancer. Since paclitaxel is insoluble in water, the drug (Taxol) is administrated with the formulation vehicle Cremophor EL. A number of similar model structures representing the metabolism and disposition of the drug have been proposed from population pharmacokinetic studies of total plasma concentrations of paclitaxel. Sonnichsen et al. (1994) first suggested a two-compartment model structure with both saturable elimination and saturable transport, while Gianni et al. (1995) found that an extended version of this model structure with an additional linear peripheral compartment best fitted experimental data. Variants of the three-compartment model structure were investigated by Karlsson et al. (1999)

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who concluded that the saturable transport mechanism could be equally well described by saturable binding. The three-compartment model structure was also found to best fit data in Joerger et al. (2006). In Henningsson et al. (2001) the nonlinear mechanisms for metabolism and disposition observed for total plasma concentrations were explained as plasma protein binding and binding to Cremophor EL micelles. A linear three-compartment model structure was found to best fit unbound plasma concentrations of paclitaxel where a complementary nonlinear static equation described the relations between total plasma and unbound plasma concentrations of paclitaxel and plasma concentrations of Cremophor EL. van den Bongard et al. (2002) proposed that the kinetics of Cremophor EL itself can be explained by a three-compartment model structure with saturable elimination and linear disposition. Henningsson et al. (2005) confirmed this model structure for 1 and 3 h infusions.

If the model structure described by Henningsson et al. (2001) is to be considered more mechanistically correct, it should be preferred when performing population analysis of paclitaxel administrated with Cremophor EL. If, however, only total plasma concentrations of paclitaxel are available, the linear three-compartment model structure might not be possible to use straight off. By investigating if it is possible to use only concentrations of total paclitaxel and *in silico* Cremophor EL concentrations, data from previous studies could be revaluated using the mechanism-based model structure.

In this work we investigate the two major model structures suggested from previous works, the empirical model structure with saturable elimination and saturable transport and the mechanism-based model structure. For each model structure we test the local algebraic observability, perform a population pharmacokinetic analysis with paclitaxel data from a clinical study and compare the outcome using hold-out validation. Since not all the information required for using covariate relationships developed for previous paclitaxel models was available in the current study, only non-covariate model structures will be regarded. It was also suspected that covariate relationships could be too specific for the different populations.

2. Materials and methods

2.1. Model structures

The model structure presented by Henningsson et al. (2001) is claimed to have a more mechanistically accurate structure and is for this reason denoted by $\mathcal{M}_{\mathrm{M}}$. The more empirical model structure used in Gianni et al. (1995), Karlsson et al. (1999) and Joerger et al. (2006) will in a similar fashion be denoted by $\mathcal{M}_{\mathrm{E}}$. The mechanism-based model structure, $\mathcal{M}_{\mathrm{M}}$, also requires measurements of Cremophor EL concentrations. Since such data is not available from most studies, including this one, the model structure proposed by van den Bongard et al. (2002) and Henningsson et al. (2005), here denoted by $\mathcal{M}_{\mathrm{CrEL}}$, will also be used. For convenience, all model structures are presented here in their full state-space form, without considering any interindividual effects, without any effects of covariates and with undisturbed outputs.

2.1.1. Empirical model structure for paclitaxel, $\mathcal{M}_{\mathrm{E}}$

The empirical model structure (Gianni et al., 1995), is expressed by the following equations:

$$\dot{x}_{t1}(t) = -\left(\frac{V_{\max}}{V_{t1}K_{\mathrm{MV}} + x_{t1}(t)} + \frac{T_{\max}}{V_{t1}K_{\mathrm{MT}} + x_{t1}(t)} + \frac{Q_{t3}}{V_{t1}}\right) x_{t1}(t) + k_{21}x_{t2}(t) + \frac{Q_{t3}}{V_{t3}}x_{t3}(t) + D_{\mathrm{pac}}(t) \tag{1a}$$

$$\dot{x}_{t2}(t) = \frac{T_{\max}}{V_{t1}K_{\mathrm{MT}} + x_{t1}(t)}x_{t1}(t) - k_{21}x_{t2}(t) \tag{1b}$$

$$\dot{x}_{t3}(t) = \frac{Q_{t3}}{V_{t1}}x_{t1}(t) - \frac{Q_{t3}}{V_{t3}}x_{t3}(t) \tag{1c}$$

$$c_{\mathrm{Ep}}(t) = \frac{x_{t1}(t)}{V_{t1}} \tag{1d}$$

where $x_{ti}(t)$ is the state variable representing the amount of *total* paclitaxel in the ith compartment. $D_{\mathrm{pac}}(t)$ is the rate of the paclitaxel dose given as an infusion and $c_{\mathrm{Ep}}(t)$ is the concentration of total paclitaxel in the plasma compartment derived from $\mathcal{M}_{\mathrm{E}}$. V_{t1} and V_{t3} are the volumes of distribution of the central and second peripheral compartment and Q is the intercompartmental clearance in between. $V_{\max}$ is the maximum elimination rate and K_{MV} the total plasma concentration at half $V_{\max}$. $T_{\max}$ is the maximum transport rate from the central to the first peripheral compartment, K_{MT} the total plasma concentration at half $T_{\max}$ and k_{21} the rate constant governing the linear transport rate from the first peripheral to the central compartment.

2.1.2. Mechanism-based model structure for paclitaxel, $\mathcal{M}_{\mathrm{M}}$

The mechanism-based model structure (Henningsson et al., 2001), is expressed by the following equations:

$$\dot{x}_{u1}(t) = -\frac{\mathrm{CL} + Q_{u2} + Q_{u3}}{V_{u1}}x_{u1}(t) + \frac{Q_{u2}}{V_{u2}}x_{u2}(t) + \frac{Q_{u3}}{V_{u3}}x_{u3}(t) + D_{\mathrm{pac}}(t) \tag{2a}$$

$$\dot{x}_{u2}(t) = \frac{Q_{u2}}{V_{u1}}x_{u1}(t) - \frac{Q_{u2}}{V_{u2}}x_{u2}(t) \tag{2b}$$

$$\dot{x}_{u3}(t) = \frac{Q_{u3}}{V_{u1}}x_{u1}(t) - \frac{Q_{u3}}{V_{u3}}x_{u3}(t) \tag{2c}$$

$$c_{u1}(t) = \frac{x_{u1}(t)}{V_{u1}} \tag{2d}$$

$$c_{\mathrm{Mp}}(t) = c_{u1}(t) + B_{\mathrm{CrEL}}c_{\mathrm{CrEL}}(t)c_{u1}(t) + B_{\mathrm{lin}}c_{u1}(t) + \frac{B_{\max}c_{u1}(t)}{K_{\mathrm{MB}} + c_{u1}(t)} \tag{2e}$$

where $x_{ui}(t)$ is the state variable representing the amount of *unbound* paclitaxel in the ith compartment, $D_{\mathrm{pac}}(t)$ is the rate of the paclitaxel dose given as an infusion and $c_{u1}(t)$ is the concentration of unbound paclitaxel in the plasma compartment. $c_{\mathrm{CrEL}}(t)$ is the concentration of Cremophor EL in the