Pharmacokinetic Models for the Saturable Distribution of Paclitaxel

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ABSTRACT:

Paclitaxel pharmacokinetics are nonlinear with saturable metabolism and saturable distribution to the tissues. The saturable distribution has in previous pharmacokinetic modeling been described as a saturable transport process, whereas the present study was undertaken to investigate alternative explanations. Using a sparse sampling scheme (on average 3.3 samples per profile), 101 plasma concentration-time profiles in 22 female patients with metastatic cancer of the breast or ovary were monitored. It was found that the observed data could be equally well described by saturable tissue binding as well as by capacity-limited tissue transport. The data were better described by a model where equilibrium was achieved with drug in the central rather than in the peripheral compartment.

Paclitaxel, the first taxan to be used clinically, is now used against a variety of tumors. The pharmacokinetics of paclitaxel was first believed to be linear, but Sonnichsen et al. (1994) reported that pharmacokinetic data obtained from children after a 24-h infusion was best described by a two-compartment model with saturable elimination and saturable transport to the tissues. Gianni et al. (1995) similarly used a three-compartment model with saturable transport to one of the peripheral compartments and saturable elimination to describe the concentration-time profiles after 3- and 24-h infusions of paclitaxel in adults. In both cases, the saturable distribution was clearly indicated from the data and also in both cases the transport was saturated at lower plasma concentrations than the elimination. Although capacity-limited transport of drug to tissues mechanistically can be explained by saturable transport processes across the membrane to the interior of the cell, no such processes have been described for paclitaxel. Saturable tissue distribution of a drug could occur as a result of saturable transport or saturable binding. Whereas only the former has been investigated as a potential explanation for the peculiar pharmacokinetics of paclitaxel, the latter seems to offer a mechanistically more plausible explanation. Wild et al. (1995) reported on extensive and saturable binding of paclitaxel to human platelets, and binding of paclitaxel to its site of action, the microtubule, has also been reported for a number of tissues (Spencer and Faulds, 1994). The present work was undertaken to find out whether saturable tissue binding could describe the pharmacokinetic phenomena of saturable tissue distribution of paclitaxel.

Models where the binding was assumed to be an instantaneous or a noninstantaneous process were tried, but the data did not allow resolution between these two possibilities. The value at which the saturable transport was half-maximal was 0.55 μM. The Km values of the binding models were 0.06 to 0.12 μM. These are close to the values reported as a threshold for drug toxicity of paclitaxel, suggesting a possible connection between the binding sites involved in the pharmacokinetics and the mechanism responsible for the toxicity. For all models, a saturable elimination of paclitaxel was included using the Michaelis-Menten model. Km for the elimination ranged in the different models from 2.5 to 5.6 μM.

Experimental Procedures

Twenty-one female patients treated for metastatic cancer of the breast (n = 15) or ovaries (n = 6) received paclitaxel every third week as a 3- (15 patients) or a 24-h (6 patients) continuous infusion. Either 135 or 175 mg/m² was used as initial dose level for the 3-h infusion, whereas all patients receiving a 24-h infusion were started on 175 mg/m². If called for, dose adjustment was carried out from the second dose and onwards guided by white blood cell count and neutrophil granulocyte nadir levels. The resulting dose range was 90 to 225 mg/m². A total of 101 doses were monitored with a range of 1 to 12 courses per patient, of which four patients were monitored for one course only. Of the 101 doses, 74 and 27 were 3- and 24-h infusions, respectively.

Peripheral venous blood samples were obtained on each dose occasion according to a sparse sampling scheme, with a maximum of four samples taken (average 3.3). Target times for the sampling were 1, 3 (just before stopping the infusion), 6, and 12 h for the short infusion and 1, 6, 24 (just before stopping the infusion), and 25 h for the long infusion. All blood samples were analyzed according to a reversed phase HPLC method described previously (Rizzo et al., 1990; Karlsson et al., 1998).

Pharmacokinetic models were fitted to the data from all individuals simultaneously using the NONMEM program (Beal and Sheiner, 1992). The pharmacokinetic analysis was based on multicompartmental models of up to three compartments with addition of nonlinear processes when indicated. Saturable elimination was modeled using the Michaelis-Menten relationship characterized by the maximal elimination capacity, Vmax, expressed in concentration per unit time, and the concentration at which the elimination rate is half-maximal, denoted Km. Nonlinear distribution was considered to occur either as saturable transport to the tissues or by nonlinear tissue binding. It should be noted that in the context of this model, tissue binding represents the binding to all components outside plasma, i.e., it includes, e.g., red blood cells and platelets. The model for saturable transport was analogous to the saturable elimination.
model, but with using $T_{\text{max}}$ and $T_m$ for the maximal transport capacity and the concentration at which the transport rate is half-maximal, respectively. Saturable tissue binding was modeled using eq. 1:

$$\frac{dB}{dt} = k_1^* C^*(B_{\text{max}} - B) - k_{-1}^* B$$

(1)

where $C$ denotes paclitaxel concentration, $B$ is the concentration of paclitaxel bound, $B_{\text{max}}$ the maximal binding capacity, and $k_1$ and $k_{-1}$ the rate constants for binding and dissociation. The ratio of $k_{-1}$ to $k_1$, denoted $K_d$, is the concentration at which binding is half-maximal. Two options were investigated separately: whether the data were best explained by relating saturable tissue binding to the concentrations in the central or a peripheral compartment. Binding processes can be very rapid compared with other processes or they may occur at a rate of a similar order of magnitude. For very rapid binding processes the different disposition processes (distribution, elimination, and binding) occur at very different rates, the model presents a hard computational task called a stiff problem. Such problems often cannot satisfactorily be estimated using differential equations systems. In the model library of the NONMEM program there is an option called ADVAN9, which allows the specification of models with a combination of processes where equilibrium is attained instantaneously and processes that take place over an appreciable time period. Thus, as an alternative to estimating both $k_1$ and $k_{-1}$, this ADVAN9 option was used to build a model where binding was supposed to be instantaneous and where only the ratio of the binding rate constants, $K_d$, was estimated. For all other models, the ADVAN8 option of the NONMEM program was used.

It is the practice in the modeling of data from many individuals simultaneously to use nonlinear mixed effects models, where the estimated population pharmacokinetic parameters are the typical parameter value in the population together with an estimate of the interindividual variability, usually as its S.D., denoted $\omega$. This is accomplished by allowing each individual’s data to be described by subject-specific parameters $P_i$; this is assumed to come from the distribution of parameters in the population according to eq. 2:

$$P_i = P_{\text{pop}} + \sigma_x \exp(\eta_i)$$

(2)

where $P_{\text{pop}}$ is the parameter value of a typical individual and $\eta$ is a symmetrically distributed zero-mean variable with the S.D. $\omega$. An alternative to nonlinear mixed effect modeling is to treat all data as coming from a single individual. This is usually termed “naive pooling”. Naive pooling has the disadvantage of not providing any estimate of interindividual variability. It has also been reported to provide poor estimates in a number of situations, for example, when unbalanced data sets due to censoring (as may be the case when subjects with short terminal half-lives have less data than others) are analyzed. The method has, however, recently in some situations been shown to provide population parameter estimates as useful as the nonlinear mixed effects models (Katari et al., 1994). Nonlinear mixed effects models and naive pooling were used in parallel when the present data were analyzed. For mixed effects models, the residual error corresponds to the difference between the observed concentration ($C_{\text{obs}}$) and prediction ($C_{\text{pred}}$) by individual parameters ($P_i$), whereas for naive pooling the residual error corresponds to the difference between the observed concentration and prediction by population parameters ($P_{\text{pop}}$). For both types of methods, the residual error contained both a proportional and an additive component according to:

$$C_{\text{obs}} = C_{\text{pred}} (1 + \epsilon_i) + \epsilon_2$$

(3)

where either component could be omitted if it did not provide any improvement of the fit to the data. $\epsilon$ are zero-mean random variables with S.D. $\sigma_1$ and $\sigma_2$.

Model adequacy was evaluated using goodness-of-fit plots, parsimony, and precision of the parameter estimates. For the graphical goodness-of-fit analysis, extensive plotting was available through the use of Xpose (Jonsson and Karlsson, 1999), a purpose-built set of subroutines in S-PLUS (Mathsoft, 1997). In the comparison between models the objective function value (which is $-2\log$ likelihood) provided by NONMEM was used. For hierarchical models, the difference in objective function value is approximately $\chi^2$-squared distributed, and formal testing between models can be performed. A $p$ level of .01 was chosen for accepting a more complex model over a reduced one. For hierarchical models differing by two parameters, the corresponding difference in the objective function value is 9. For nonhierarchical models, the objective function value cannot be used for formal testing, but we considered a difference of 9 units between models of the same number of parameters to represent a real difference in the description of the data.

**Results**

The observed paclitaxel concentration-time profiles are shown in Fig. 1. In the description of these data, entering a saturable distribution component, either as saturable transport or saturable binding, offered significant improvement over assuming linear distribution models. Saturable elimination also increased the goodness-of-fit significantly over assuming a linear elimination. Assuming saturable transport to a peripheral compartment, a three-compartment model best described the data, whereas for the binding models no improvement was obtained when going from two- to three-compartment models.

The best model assuming saturable transport (as opposed to nonlinear binding) and using a mixed effects model is shown in Table 1 (denoted Model 1). The nonlinear distribution appears to be saturated at considerably lower concentrations, $T_{\text{MM}}$ is 0.61 $\mu$M, than the elimination, for which $K_m$ is 3.1 $\mu$M. Clearance of paclitaxel at low concentrations compared with $K_m$, which can be obtained as $\frac{V_{\text{max}}}{K_m}$, is estimated to be 25 liters/h. Interindividual variability estimates for three parameters, $T_{\text{max}}, T_m$, and $K_m$, were in the range of 30 to 40%. For the other parameters, inclusion of interindividual variability did not improve the fit. This should not be interpreted as an absence of interindividual variability in these parameters, but only that the data do not contain sufficient information to estimate these. The naive pooling analysis of the same model resulted in similar parameter estimates (Table 1; Model 2).

The best model assuming a noninstantaneous, saturable binding component and using a nonlinear mixed effects model resulted in a similar objective function value (Table 1; Model 3) and similar goodness-of-fit as the best model assuming saturable transport. Assuming that the binding was driven by the concentration in the central compartment provided a considerably better fit than assuming it was driven by the concentration in a peripheral compartment. As for the model with saturable transport, the nonlinear distribution in this model appears to be saturated at considerably lower concentrations ($K_d = 1.24 \mu$M) than the elimination, for which $K_m$ is 5.6 $\mu$M. Clearance of paclitaxel at concentrations that are lower than the $K_m$ is estimated to be 24 liters/h. Interindividual variability estimates for three parameters, $K_{\text{MM}}, K_{12}$, and $k_{-1}$, were 20, 31, and 53%, respectively. For the other parameters, inclusion of interindividual variability did not improve the fit. The dissociation half-life was estimated to 10 h, but the uncertainty, expressed as relative S.E., in the estimate of $k_{-1}$ was high, 64%. This indicates that the data do not contain much information about the temporal aspect of the binding component. The parameter estimates are similar for the noninstantaneous binding model when the two methods, mixed effects modeling and naive pooling, are used (Table 1; Models 3 and 4).

If data only contain little information about the temporal aspects of the binding process, models where the binding processes are modeled as instantaneous or noninstantaneous should provide similar fits. Unfortunately, it was not possible to obtain a successful termination with a mixed effects model with instantaneous binding equilibrium. Instead, the comparison is made on the fit using the naive pooling analysis. The objective function values of the naive pooling analyses of the models with noninstantaneous and instantaneous binding were

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1 Abbreviations used are: $T_{\text{max}}$, maximal transport capacity; $T_m$, concentration at which the transport rate is half-maximal.
similar, −374 and −370, respectively. The latter is another indication that the data do not contain information about the temporal aspects of the binding process.

The estimates of comparable parameters for Models 1 to 5 presented in Table 1 are all quite similar. Although there is some difference in the estimate of $K_m$, the estimates of CL in the linear range are similar, and because the majority of the elimination of taxol for both the 3- and 24-h infusion takes place at such concentrations, this can be considered the most important elimination parameter. The volume of the central compartment is showing little variability between the models and so are the rate constants for distribution to the linear peripheral compartment. Also, the values for the parameter indicating at which concentration the saturable distribution becomes important range from 0.55 to 1.24 $\mu$M.

The objective function values are clearly increased for this model. Predicted versus observed concentrations for the four models using naive pooling (Fig. 2) show that, although there is a marked difference between models with and without saturable distribution, the three models with saturable distribution describe the observed data similarly well. Predicted time courses of paclitaxel after 3- and 24-h infusions for the three models are virtually superimposable (not shown).

Discussion

For any given data set there may be a large number of models that, given sufficient complexity, will be able to adequately describe the data. The selection of basic model type is usually based on tradition, physiological relevance, and parsimony. For linear disposition processes, compartmental models have shown to provide relevant descriptions for a vast number of substances; this has its roots in the laws of diffusion, convection, and partitioning. Likewise, saturable elimination has proven a useful description for a large number of drugs, and it has its basis in the theory of bimolecular interaction between enzyme and substrate. Observable saturable distribution is a much

![Fig. 1. Observed paclitaxel concentrations for all 3- and 24-h infusions.](image)

Observed concentrations are connected by straight lines.

![Table 1. Parameter estimates](table)

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MODELS FOR THE SATURABLE DISTRIBUTION OF PACLITAXEL

rarer phenomenon. Both saturable binding and saturable transport, as general phenomena, have a sound basis in physiology. For paclitaxel, on the other hand, saturable binding, but not saturable transport, agree with the knowledge about the processes involved in its tissue distribution. The saturable binding of paclitaxel to platelets, described by Wild et al. (1995), displayed an apparent binding constant ($K_D$) of 0.8 ± 0.1 μM, which is higher than the $K_D$ values, 0.06 to 0.12 μM, estimated in this study for the models containing saturable binding components (Models 3–5). The difference may depend on other sites than platelets being involved in vivo or different binding environment in vitro than in vivo. Studies of the hematological toxicity of paclitaxel have shown that a plasma concentration of 0.05 to 0.1 μM is a threshold value for toxicity (Sonnichsen et al., 1994; Kearns et al., 1995; Karlsson et al., 1998). If the binding sites characterized by this pharmacokinetic binding model are the same as those exerting the pharmacological effect, it appears as if paclitaxel is one of the few substances where the pharmacological target structure influences the pharmacokinetics of the drug. Nonlinear transport, presumably by $p$-glycoprotein, has also been reported for paclitaxel (Greenberger et al., 1988), but with a $T_{\infty}$ value considerably higher (16.5 mM; Walle and Walle, 1998) than the value estimated from models with saturable transport (Models 1 and 2), which were about 0.6 mM. Even more importantly, the active transport systems provided by $p$-glycoprotein will be directed from within the cell to the outside. Thus, if this transport is saturated, volume of distribution will increase, not decrease, with plasma concentration, as was seen for paclitaxel.

Despite extensive modeling, no discrimination between the models with saturable distribution was possible. The pharmacokinetic data were not collected for the purpose of model discrimination and observations would normally be more frequent for such a purpose. In this case, however, it is doubtful if even rich sampling could have succeeded in discriminating between the models, because they have sufficient flexibility to take on very similar curve shapes over the range of doses and infusion times that are clinically used. To discriminate between the models, some additional information would most likely be needed, such as sampling at a site affected by the nonlinear distribution. Thus, if the purpose of pharmacokinetic modeling is only to interpolate the concentration-time profile under normal therapeutic doses, any of the saturable distribution models will suffice. The use of mechanistically important models may lie in yet untested situations. Some examples, admittedly speculative, of situations where a binding model, if correct, could be of use are: 1) if the platelet-binding capacity is correlated with the $B_{\text{max}}$ for the binding models, 2) if another tubulin-binding drug affects the pharmacokinetics of paclitaxel, this could be incorporated in the model as affecting the binding terms, and 3) if some effect of paclitaxel is shown to correlate with the area-under-curve for the binding component.

In this work we used both nonlinear mixed effects modeling and naive pooling. Although this choice was mainly a result of the inability to obtain satisfactory termination for one of the models, the one with an instantaneous binding related to the concentration in the central compartment, it is encouraging to see that the two methods provide similar parameter estimates.

In summary, this work indicates that pharmacokinetic models based on saturable transport, which are standard for describing paclitaxel disposition, can be exchanged for physiologically more plausible models using saturable binding, without any loss of goodness-of-fit.

Fig. 2. Predicted versus observed paclitaxel concentrations for Models 2, 4, 5, and 6.

References


