Simultaneous Modeling of Abciximab Plasma Concentrations and ex Vivo Pharmacodynamics in Patients Undergoing Coronary Angioplasty

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ABSTRACT

An integrated structural pharmacokinetic/pharmacodynamic (PK/PD) model was developed for the glycoprotein IIb/IIIa antagonist abciximab administered to patients undergoing percutaneous transluminal coronary angioplasty. PK/PD data, in the form of plasma abciximab concentrations and ex vivo platelet aggregation in the presence of 20 μM adenosine diphosphate, were obtained from two previously conducted clinical studies. Study 1 consisted of patients who were given abciximab as a single intravenous injection of 0.25 mg/kg (n = 32). Patients in study 2 received an identical bolus dose, followed by a 36-h infusion at 0.125 μg/kg/min (n = 15). The PK component of the final model included drug-receptor binding, nonspecific distribution, and linear systemic clearance, whereas the PD module assumed that ex vivo dynamics were controlled by free plasma drug concentration. Mean PK/PD data from both studies were fitted simultaneously using nonlinear regression. PK profiles from both studies show rapidly decreasing plasma abciximab concentrations at early time points, but with extended terminal disposition phases. The maximum effect (E_{max} = 83.6%) was achieved rapidly and gradually returned to baseline values, although inhibition could be measured long after abciximab concentrations dropped below the detection limit. The final model well described the resulting PK/PD profiles and allowed for parameter estimation with relatively small coefficients of variation. Simulations were conducted to assess predicted receptor-occupancy and effects of selected parameters on PK/PD profiles. Models such as the one developed in this study demonstrate how drug binding to pharmacological targets may influence the PK of certain drugs and also provide a suitable paradigm for defining the PK/PD relationships of similar compounds.

Activation of the glycoprotein (GP) IIb/IIIa platelet-surface integrin by endogenous agonists (e.g., thrombin, adenosine diphosphate or ADP, and collagen) results in the binding of adhesive proteins such as fibrinogen and von Willebrand factor, thus mediating platelet aggregation (Phillips et al., 1991). Antagonists directed against this receptor represent a family of antiplatelet drugs that are used clinically for the prevention of pathological thromboses (Majerus and Tollefsen, 2001). Abciximab, a monoclonal antibody Fab fragment, was the first approved agent in this class of drugs (Coller, 1997) and has been shown to prevent acute cardiac ischemic complications from percutaneous transluminal coronary angioplasty (PTCA) and atherectomy (EPIC Investigators, 1994). Typical dosing regimens include a weight-normalized i.v. bolus dose of 0.25 mg/kg, followed by an i.v. infusion of 0.125 μg/kg/min (up to a maximum of 10 μg/min) for 12 to 24 h, depending on the indication. This scheme was designed to achieve and sustain greater than 80% receptor occupancy and less than 20% of baseline ex vivo platelet aggregation (induced by 20 μM ADP), which was shown to correspond with the prevention of in vivo thrombus formation in mon-

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ABBREVIATIONS: GP, glycoprotein; PTCA, percutaneous transluminal coronary angioplasty; PK, pharmacokinetic; PD, pharmacodynamic; t-PA, tissue plasminogen activator; D_{iv}, intravenous abciximab dose; E_{iv}, residual ex vivo platelet aggregation in presence of maximum drug concentration; EC_{50}, plasma abciximab concentration producing 50% maximum effect; GP IIb/IIIa, glycoprotein IIb/IIIa platelet-surface receptor; K_{D}, zero-order drug infusion rate constant; k_{f1}, first-order rate constant for drug distribution from central to peripheral compartment; k_{e1}, first-order rate constant for drug distribution from peripheral to central compartment; K_{D}, drug-receptor equilibrium dissociation constant in amount units (nanomoles per kilogram); k_{el}, first-order elimination rate constant; R_{max}, maximum GP IIb/IIIa concentration (nanomolar); T_{inf} time duration of drug infusion; V, composite volume of distribution.
keys (Coller et al., 1989). In addition, combining the bolus dose with an infusion was shown to significantly reduce the need for urgent repeated revascularization procedures in patients compared with the bolus alone (EPIC Investigators, 1994).

The pharmacokinetics (PK) and pharmacodynamics (PD) of abciximab, along with several other drugs in this class, have been reviewed (Kleiman, 1999; Scarborough et al., 1999; Coller, 2001). In general, PK profiles show rapidly decreasing plasma abciximab concentrations at early time points (half-life ~10–30 min), presumably as a result of drug binding to free receptor and the elimination of free drug. However, after or in the absence of an i.v. infusion, drug concentrations decline very slowly with an extended terminal disposition phase (half-life ~7 h). The primary mechanism of drug elimination is unknown but is suggested to be catabolism or proteolytic degradation with negligible renal excretion of the parent compound. The maximum ex vivo percent inhibition of platelet aggregation (in the presence of 20 μM ADP) is rapidly achieved and the effect gradually returns to baseline values, although inhibition can be measured long after abciximab is no longer detectable in plasma. This ex vivo effect seems to recover faster than the decay in receptor occupancy (Tcheng et al., 1994), suggesting a threshold value of receptor occupancy and/or that ex vivo effects may be controlled by free drug concentrations.

Abciximab is a drug with a narrow therapeutic index, with serious complications resulting from undertreatment (lack of antithrombotic effect) or overtreatment (e.g., bleeding episodes). The standard administration regimen results in substantial interpatient variability in dose-concentration and concentration-effect relationships (Steinhubl et al., 1999). These observations suggest a role for the individualization of abciximab pharmacotherapy as well as the potential for therapeutic drug monitoring. However, despite a readily accessible biophase (plasma), there is considerable debate as to whether such an approach would be feasible or which method of platelet function monitoring would yield clinically meaningful data (Coller, 1998). Regardless, efforts continue to be made to identify key patient characteristics that contribute to the variability in patient response to abciximab therapy, such as the role of the PI factors in altering the sensitivity to inhibition of aggregation by antiplatelet drugs (Michelson et al., 2000; O’Connor et al., 2001; Wheeler et al., 2002). We hypothesize that a mechanistic structural PK/PD model may provide additional insights into the determinants of such variability, as well as a basic model upon which future population pharmaco-statistical models may be developed to identify covariates in a quantitative manner. The purpose of the present study is to establish such a model in patients undergoing coronary angioplasty, which to our knowledge has not been reported for abciximab.

Heparin was continued for at least 6 h after the procedure as repeated bolus doses required to maintain an activated partial thromboplastin time of 300 to 400 s. Abciximab was given to each patient as a single i.v. bolus of 0.25 mg/kg, at least 15 min after the first dose of heparin and 2 to 60 min before angioplasty balloon inflation. Blood samples were collected at various times, and the measurements acquired for the present analysis included plasma abciximab concentration, GP IIb/IIIa receptor occupancy (percentage of receptor sites per platelet relative to baseline values), and ex vivo platelet aggregation in the presence of 20 μM ADP. Plasma drug concentrations were determined using an enzyme immunoassay (Abernetly et al., 2002), the number of receptors per platelet was measured by a radiometric method (Wagner et al., 1996), and inhibition of platelet aggregation was quantified by a turbidometric method (Mascelli et al., 1997).

Materials and Methods

Study 1. This study was conducted at St. James’s Hospital, Dublin, Ireland, the details of which have been published previously (Quinn et al., 2001). Within 18 to 24 h before the procedure, 15 patients aged 21 to 70 years undergoing elective PTCA were given abciximab as an i.v. bolus (0.25 mg/kg) followed by a 36-h infusion at 0.125 μg/kg/min (up to a maximum of 10 μg/min). Similar to study 1, all patients received oral aspirin (300 mg 4 h before angioplasty) and unfractionated heparin (50–70 U/kg i.v. bolus up to a maximum of 7000 U to achieve an activated partial thromboplastin time greater than 200 s). However, those patients who had a coronary stent inserted also were given either ticlopidine (250 mg twice daily) or clopidogrel (75 mg once daily) for 4 weeks starting immediately after the procedure. The identical PK/PD measurements listed under study 1 were obtained from study 2. Plasma abciximab concentrations were measured by immunoassay (Quinn et al., 2001). Receptor number and occupancy were determined using the GP IIb/IIIa receptor occupancy kit (Biodex, Marseilles, France) and inhibition of platelet aggregation by a turbidometric assay, both as described previously (Quinn et al., 1999).

Pharmacokinetic/Pharmacodynamic Model. The classical description of abciximab pharmacokinetics, including a rapid distribution phase, a prolonged terminal phase, and high-affinity binding to its pharmacological receptor, is consistent with that of target-mediated drug disposition (Levy, 1994), where drug-target interactions may impact the pharmacokinetics of the drug in just such a manner. A general approach to modeling this phenomenon has been developed (Mager and Jusko, 2001) that uses drug binding microconstants (k_{on}, second-order rate constant for drug-target formation, and k_{off}, first-order dissociation rate constant) coupled with a maximum receptor density (R_{max}) to describe the time course of the drug-target complex (RC). For example,

\[
\frac{dR_C}{dt} = k_{on} \cdot C_1 \cdot (R_T - RC) - k_{off} \cdot RC
\]

assuming no degradation of RC and where C_1 is the drug concentration in the central compartment. Although a PK/PD model for the present abciximab data was developed successfully using this modeling scheme, simulations of the time course of RC revealed a significant time-lag of about 2 h for peak values to occur (data not shown). This is in contrast to the literature where it has been shown that drug-receptor binding is rapid and on the order of several minutes (Coller, 2001).

As an alternative, we assumed that eq. 1 was near equilibrium conditions (dRC/dt ~ 0). In doing so, the model collapses into one of the nonlinear pharmacokinetic models [model II(b)] outlined by Wagner (1971). The schematic of the model is shown in Fig. 1 and the differential equations that define it are as follows:

\[
\frac{dC_1}{dt} = \frac{K_dV + k_{21} \cdot C_2 - (k_{12} + k_{a1}) \cdot C_1}{1 + \frac{R_T - C_1}{(k_{21} + K_0)^{1/2}}}
\]
maximum receptor density \( (R_p) \) was fixed to 40 nM, in accord with previous estimates (Pleniaszek et al., 2002) and can be calculated from traditional fibrinogen binding experiments (Bennett et al., 1983). Therefore, the unknown model parameters to be estimated from nonlinear regression analysis included \( k_{12}, k_{21}, k_{31}, V, K_D, E_{50}, \) and the Hill coefficient \( (\gamma) \). A preliminary fit of the pharmacokinetic data using a standard two-compartment model was used to obtain initial estimates of \( k_{12}, k_{21}, k_{31}, \) and \( V \), whereas initial values for \( K_D \) and the pharmacodynamic parameters were used as described previously (Abernethy et al., 2002). Parameter estimation was conducted using the maximum likelihood estimator in the ADAPT II software program (D’Argenio and Schumitzky, 1997), and the variance model was defined as follows:

\[
\text{Var}(C \text{ or } E) = (\sigma_C \text{ or } \sigma_E)^2 \cdot Y^2
\]

where \( \sigma_C \) and \( \sigma_E \) are the variance model parameters for the concentration and effect data and \( Y \) is the PK/PD model predicted value. Goodness-of-fit criteria included program convergence, Akaike Information and Schwarz Criteria, estimator criterion value for the maximum likelihood method in ADAPT II, examination of residuals, and visual inspection. The performance of the final model was compared with that of a standard linear two-compartment model (i.e., eqs. 2–4 with the denominator in eq. 2 set equal to 1 and eq. 4 set equal to \( D_v/V \)) linked to eq. 5 also using the sum of squared residuals, mean prediction error (bias), and mean squared prediction error (precision) (Sheiner and Beal, 1981).

Once model parameters were determined, several simulations were conducted to assess the implications of the model. First, apparent receptor occupancy was simulated using the following equation for fractional binding \( (F_b)^{1,2,3} \):

\[
F_b = \left( 1 - \frac{C_1}{K_D V + C_1} \right) \cdot 100\%
\]

These profiles were compared with experimentally determined values. Second, PK/PD profiles were simulated for the 36-h infusion regimen via fixing most of the model parameters while allowing several values of \( K_D, R_p, \) and \( EC_{50} \) to be evaluated. All simulations were executed using ADAPT II.

**Results**

Patient demographics and baseline measures of platelet count and receptor number per platelet are listed in Table 1. These details from the original studies are reshown to demonstrate that patients were fairly exclusively selected for these studies and that patient groups were relatively well matched. Although not part of the inclusion/exclusion criteria, individual study populations were not balanced for sex and ethnicity. Initial platelet counts were similar between studies and these values were stable for the duration of each study (data not shown).

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Patient demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1 (n = 32)</td>
<td>Study 2 (n = 15)</td>
</tr>
<tr>
<td>Age ± S.D. (years)</td>
<td>58.3 ± 8.4</td>
</tr>
<tr>
<td>Weight ± S.D. (kg)</td>
<td>84.5 ± 17.7</td>
</tr>
<tr>
<td>Sex (%male)</td>
<td>62.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>22</td>
</tr>
<tr>
<td>Black</td>
<td>5</td>
</tr>
<tr>
<td>Other(^a)</td>
<td>5</td>
</tr>
<tr>
<td>Platelet count (10^3/μl) ± S.D.(^b)</td>
<td>239 ± 41</td>
</tr>
<tr>
<td>Receptor number/platelet ± S.D.(^b)</td>
<td>75,300 ± 22,100</td>
</tr>
</tbody>
</table>

\(^a\) Four Hispanic, one Asian Indian.  
\(^b\) Baseline measurements.
The temporal patterns of mean plasma abciximab concentrations and ex vivo platelet aggregation for both studies are shown in Fig. 2. In accordance with previous reports, free drug concentrations decrease rapidly at early time points but exhibit extended terminal disposition phases. The i.v. infusion administered in the second study maintains slightly higher drug concentrations during the infusion (time \(< T_{inf}\)). However, abciximab concentrations continue a rapid decline once the infusion is stopped and a relatively long terminal phase was confirmed with plasma concentrations detectable at 120 h after initiating treatment. The maximum inhibition of ex vivo platelet aggregation was quickly achieved in both studies. The single i.v. bolus given in study 1 resulted in a gradual return of the drug effect toward the baseline value, measuring 86.1 ± 20.4% at 48 h postdose. In contrast, the response was maintained at lower levels during the abciximab infusion in study 2. The return of the effect to the baseline value after terminating the infusion also was attenuated and inhibition of aggregation could be measured at 360 h after starting therapy (90.6 ± 23.0%).

The lines in Fig. 2 represent model fitted profiles resulting from the simultaneous fitting of the final model (eqs. 2–5) to all of the mean PK/PD data shown in the figure and seem to be in good agreement with measured values. Final model parameters are listed in Table 2 and, with the exception of the \(K_D\) parameter, were estimated with relatively small coefficients of variation (<30%). The estimated volume of distribution (0.118 l/kg) is slightly greater than blood volume but still relatively small, as would be expected for a large molecular weight protein. An apparent equilibrium dissociation constant for the drug-receptor complex can be calculated from the model parameters \(K_D/V = 0.348\) nM and is about 10-fold lower than the 1 to 5 nM concentration reported in the literature (Kleiman, 1999; Scarborough et al., 1999; Coller, 2001). The relative predictive performance of the model was compared with a standard two-compartment model and the results are listed in Table 3. The sum of squared residuals was lower markedly for the PD measures of both studies. However, mean prediction errors (bias) and mean squared prediction errors (precision) were not significantly different between the applied models. The proposed model seemed to better represent the data visually and overall model fitting criteria were improved (Table 3). More importantly, the final model embodies a mechanistic basis that provides the opportunity to assess the role receptor-binding parameters may have in the PK/PD properties of abciximab.

Several simulations using the final PK/PD model were conducted. Despite an approximate 10-fold lower estimated equilibrium dissociation constant, predicted values of fractional receptor-binding (eq. 7) were significantly correlated with the observed percentage of receptor sites per platelet relative to baseline values (Fig. 3). Simulated PK/PD profiles using a 100-fold range of \(K_D\) values (10-fold above and below the estimated value) showed only slight changes compared with the profiles in Fig. 2 (data not shown), which most likely accounts for the higher CV% of its estimate (Table 2). On the contrary, small perturbations in the maximum receptor density \(R_T\) altered the time course of plasma abciximab concentrations and ex vivo dynamics (Fig. 4). An increase in \(R_T\)

![Fig. 2](image)

**Table 2**

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Final Estimate</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(k_{12}) (h(^{-1}))</td>
<td>1.21</td>
<td>18</td>
</tr>
<tr>
<td>(k_{21}) (h(^{-1}))</td>
<td>0.0326</td>
<td>26</td>
</tr>
<tr>
<td>(k_{12}) (h(^{-1}))</td>
<td>0.583</td>
<td>16</td>
</tr>
<tr>
<td>(V) (l/kg)</td>
<td>0.118</td>
<td>1.0</td>
</tr>
<tr>
<td>(K_D) (nmol/kg)</td>
<td>0.0411</td>
<td>48</td>
</tr>
<tr>
<td>(E_\infty) (%)</td>
<td>16.5</td>
<td>7.2</td>
</tr>
<tr>
<td>(EC_{50}) (ng/ml)</td>
<td>30.4</td>
<td>13</td>
</tr>
<tr>
<td>(\gamma)</td>
<td>2.10</td>
<td>19</td>
</tr>
<tr>
<td>(\sigma_c)</td>
<td>0.25</td>
<td>15</td>
</tr>
<tr>
<td>(\sigma_R)</td>
<td>0.18</td>
<td>16</td>
</tr>
</tbody>
</table>

*Coefficient of variation of the estimate, not reflective of interpatient variability.*
resulted in lower free drug concentrations and a left-shift in the PD profile. The opposite effect on PK/PD profiles was predicted for a lower \( R_T \) value. Such changes might be interpreted as variability in drug efficacy and clearance and/or volume of distribution, although the model parameters associated with these properties \( (k_{el}, V, \text{ and } EC_{50}) \) were kept constant for the simulations in Fig. 4. The effect of changing \( EC_{50} \) on the pharmacodynamics of the system is illustrated in Fig. 5. As would be expected, a lower \( EC_{50} \) produces a right-shift in the effect-time profile because drug concentrations are maintained above the \( EC_{50} \) concentration for longer times and vice versa.

**Discussion**

The impact of nonlinear tissue and plasma protein binding on drug pharmacokinetics has been appreciated for some time, although capacity-limited drug elimination generally receives greater attention (Gibaldi and Perrier, 1982). The recognition that a pharmacological target may represent this high-affinity capacity-limited binding site for some drugs was not formally made until relatively recently (Levy, 1994). In this study, an integrated PK/PD model based on the principles of target-mediated drug disposition was applied successfully to free plasma abciximab concentrations and subsequent ex vivo pharmacodynamics collected from a patient population. The modeling technique used in this study allows for the simultaneous fitting of PK/PD data and uses both to infer the apparent time course of the drug-receptor complex. This approach also provides the unique opportunity to explore the influence of apparent in vivo receptor-binding parameters on the PK/PD properties of the system.

The final model predicts an ability of the maximum receptor density \( (R_T) \) to modify the kinetics and dynamics of abciximab (Fig. 4) and represents a potentially significant clinical implication. Clinical evidence of this phenomenon may already be at hand. Kereiakes et al. (2000) examined the effect of platelet count in platelet-rich plasma on the level of ex vivo platelet aggregation (via abciximab and two other GP IIb/IIIa antagonists) in 30 patients with unstable angina pectoris scheduled for percutaneous coronary intervention.

**TABLE 3**

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonlinear ( \times 10^b )</td>
<td>Linear ( \times 10^b )</td>
<td>Nonlinear</td>
</tr>
<tr>
<td>SSR</td>
<td>1.47</td>
<td>1.16</td>
</tr>
<tr>
<td>MPE</td>
<td>(-151 \pm 87)</td>
<td>(-139 \pm 76)</td>
</tr>
<tr>
<td>MSE ( \times 10^6 )</td>
<td>11.3 ( \pm 7.3)</td>
<td>8.95 ( \pm 5.77)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacodynamics</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonlinear</td>
<td>Linear</td>
<td></td>
</tr>
<tr>
<td>SSR</td>
<td>414</td>
<td>1120</td>
</tr>
<tr>
<td>MPE</td>
<td>4.00 ( \pm 3.26)</td>
<td>1.62 ( \pm 6.08)</td>
</tr>
<tr>
<td>MSE</td>
<td>69.0 ( \pm 30.7)</td>
<td>187 ( \pm 85)</td>
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</table>

Overall criteria

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
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<tbody>
<tr>
<td>Nonlinear</td>
<td>Linear</td>
<td></td>
</tr>
<tr>
<td>ECV</td>
<td>199</td>
<td>206</td>
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<tr>
<td>AIC</td>
<td>419</td>
<td>431</td>
</tr>
<tr>
<td>SC</td>
<td>437</td>
<td>447</td>
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</tbody>
</table>

SSR, sum of squared residuals; MPE, mean prediction error (bias); MSE, mean squared prediction error (precision); ECV, estimator criterion value; AIC, Akaike information criterion; SC, Schwartz criterion.

* Final nonlinear PK/PD model (eqs. 2–5).
* Standard linear two-compartment model linked to eq. 5 (see text).
They found that an elevated platelet count (>350 K/μl) was associated with reduced platelet inhibition produced by abciximab. Although receptor density was not directly measured, platelet count may represent a suitable indirect biomarker for this capacity term, and its use in designing abciximab dosing regimes remains to be further validated. Normal platelet counts vary significantly within the population (130–400 K/μl), as does GP IIb/IIIa receptor density (70,000–100,000 sites/platelet) (Wagner et al., 1996), suggesting that platelet counts would represent a suitable covariate for inclusion in population analyses. Interestingly, Fussler et al. (2002) have reported recently that platelet count was a significant patient covariate for explaining the intersubject variability in both the clearance and EC$_{50}$ of XV459, another potent GP IIb/IIIa inhibitor. The authors acknowledge that XV459 exhibits “pharmacodynamically mediated” pharmacokinetics, referring to the unusual pharmacokinetic characteristics that are associated with target-mediated drug disposition. Platelet count was linearly related to the EC$_{50}$ of XV459, with larger EC$_{50}$ values occurring with increasing platelet count. This would manifest in pharmacodynamic changes similar to those shown in Figs. 4 (bottom) and 5.

The effect of the binding capacity on abciximab pharmacokinetics underlies the attenuated pharmacodynamic effect, because the model predicts that less free drug would be available at higher $R_T$ values (Fig. 4, top). Similar pharmacokinetic findings were reported by Kemme et al. (2003), who applied a three-compartment circulatory model that incorporated reversible and concentration-dependent endothelial binding to characterize the pharmacokinetics of recombinant tissue plasminogen activator (t-PA). t-PA is a relatively large peptide (mol. wt. ~68,000) that exhibits a nonspecific circulatory-delay at early time points during a low dose i.v. infusion, an additional property of target-mediated kinetics (Levy, 1994). Simulations of their final PK model using various $K_D$ and capacity values (Fig. 6 in Kemme et al., 2003) were qualitatively similar to those conducted for this study. Larger values of the binding capacity resulted in lower t-PA plasma concentrations in a manner consistent with an increase in the apparent volume of distribution, as can be seen for abciximab in Fig. 4 (top) as lower initial plasma concentrations and lower peak concentrations at 36 h. Similarly, a 100-fold variation in the $K_D$ parameter for t-PA resulted in less modulation of the concentration-time profile.

In addition to the apparent efficacy changes imparted by receptor density, direct differences in the EC$_{50}$ parameter may lead to significant shifts in abciximab pharmacodynamics (Fig. 5). The EC$_{50}$ may be regarded as a hybrid parameter, reflective of various conditions of the system, including the status of platelet function. Although there is a lack of a definitive explanation for what platelet functional status is, specific patient covariates may indirectly relate to platelet status and thus influence EC$_{50}$. This point is made clear in a population PK/PD analysis of the GP IIb/IIIa antagonist lotrafiban (Mould et al., 2001). Lotrafiban does not seem to exhibit target-mediated kinetics. However, the EC$_{50}$ of inhibition of ex vivo platelet aggregation by lotrafiban was found to differ for smokers and those subjects with a qualifying diagnosis of a recent myocardial infarction. Patients who smoked were less sensitive to the drug effect, whereas patients with a recent myocardial infarction had lower EC$_{50}$ values that might be attributed to previous medications that were administered to those patients. For this abciximab study, patients in study 2 did receive additional drugs that may alter binding affinity and platelet function (ticlopidine and clopidogrel), and this may explain the slight underprediction of the last two pharmacodynamic time points for patients in study 1 (Fig. 2, bottom) given that a single EC$_{50}$ parameter was used for model fitting. Currently, almost all patients who receive abciximab also are given a thienopyridine because most undergo a stenting procedure. Therefore, the PK/PD properties of abciximab should be studied in the presence of these drugs, and data from the second study.
clearly are more clinically relevant. The aspirin and heparin regimens were slightly different between the two studies, and this may have also contributed to any pharmacodynamic differences.

The final PK/PD model also provides details into the transient fall and rise of ex vivo platelet aggregation during the continuous i.v. infusion administered in the second study (Fig. 2, bottom). Investigators from the original study postulate that this phenomenon is not the result of abciximab redistributing from the cell surface to intracellular pools (Quinn et al., 2001). Although alternative hypotheses cannot be excluded, one explanation of these data would be that the slight recovery of drug effect during the infusion results from the rapid elimination of free drug coupled with the slow rise to a steady-state plasma abciximab concentration. This delay in achieving a free steady-state drug concentration is expected because slowly infused drug is rapidly taken up by free receptor sites (Levy, 1994). As an example, computer simulations of a physiologically based target-mediated pharmacokinetic model of S-warfarin in rats showed that rapid infusions reach steady-state concentrations sooner than slower rate infusions (Levy et al., 2003). Future clinical studies are needed to verify whether a varying abciximab infusion rate, such as a fast initial rate followed by a gradual decline, represents an improved dosing scheme for this drug.

In conclusion, a nonlinear simultaneous PK/PD model of abciximab has been presented that showed improved fitting over a traditional model and approach. The combined PK/PD properties of the drug are used to infer the kinetics of drug-receptor binding and allow for an effective separation of variables that may have a role in controlling the time course of abciximab plasma concentrations and ex vivo effects. The final model predicts that binding capacity ($R_T$) and drug sensitivity ($EC_{50}$) are important parameters of interest and may contribute significantly to the intersubject variability in abciximab PK/PD. Future large-scale population analyses are needed to establish the clinical utility of the model and to determine the degree of variability explained by specific patient covariates in a quantitative manner.

References


Fig. 5. Simulated abciximab pharmacodynamics for the i.v. bolus and 36-h infusion regimen using the final model (eqs. 2–5) and parameters (Table 2) allowing for three different values of drug sensitivity ($EC_{50}$).

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