Pharmacokinetic-Pharmacodynamic Modeling of Tolerance to the Prolactin-Secreting Effect of Chlorprothixene after Different Modes of Drug Administration

METIN BAGLI, RICHARD SÜVERKRÜP, RALPH QUADFLIEG, GEREON HÖFLICH, SIEGFRIED KASPER,
HANS-JÜRGEN MÖLLER, MICHAEL LANGER, UWE BARLAGE, and MARIE LUISE RAO
From the Department of Psychiatry and Psychotherapy (M.B., G.H., S.K., H.-J.M., M.L.R.) and Institute for Pharmaceutical Technology (R.S., R.O.), University of Bonn, Bonn, Germany; and Bayer Vital GmbH, Leverkusen, Germany (M.L., U.B.)
Accepted for publication July 15, 1999 This paper is available online at http://www.jpet.org

ABSTRACT
The objective of this study was the construction of a pharmacokinetic-pharmacodynamic model to describe the effects of chlorprothixene on prolactin secretion and the time-dependent alterations in the concentration-effect relationship due to tolerance development. Prolactin and chlorprothixene serum concentrations were determined in eight healthy men for up to 72 h after the intravenous and oral administration of chlorprothixene. An integrated pharmacokinetic model and a physiological indirect pharmacodynamic/tolerance model were applied to describe the prolactin-secreting effect of chlorprothixene. A three-compartment model served as pharmacokinetic model. The pharmacodynamic and tolerance model accounted for the baseline effect, the effect induced by the drug, and the regulatory mechanism that opposes the effect of the drug. This model adequately characterized the prolactin response after intravenous and oral drug administration of each individual by the sensitivity (dissociation constant), the efficacy (maximal prolactin secretion rate), the extent, and the rate of tolerance development. We speculate that this approach improves the quality of neuroendocrine challenge tests to determine the subject’s sensitivity to drugs and the time course of adaptation.

Chlorprothixene is a thioxanthene with antipsychotic properties that is widely used in Europe to treat schizophrenia. Despite long-term use, the pharmacodynamics of antipsychotic drugs are still not totally understood. It is desirable to obtain a detailed pharmacological characterization of these drugs. A pharmacological characterization of dose-effect relationships is primarily confounded by the time delay of several days to weeks between the onset of treatment and the onset of antipsychotic effect.

Typical antipsychotic drugs, such as chlorprothixene, block dopamine D2 receptors in the pituitary (lactotroph), compete with the dopamine-induced reduction in prolactin release and consequently cause an increase in prolactin concentration (Moore, 1987). The relationship between prolactin secretion and pathophysiology of schizophrenia or antipsychotic therapy has been extensively studied (Meltzer et al., 1983; Rubin, 1987; Green and Brown, 1988; Nordstrom and Farde, 1998). The results have not been entirely clear cut, and we assume that the discrepancy is mostly due to insufficient data analysis. In this context, the following aspects should be considered: 1) substantial interindividual variability exists in the disposition kinetics of antipsychotic drugs, particularly in the oral bioavailability and systemic clearance; 2) pharmacological response is best described by concentration-effect relationship, which is characterized by the parameters potency (sensitivity to the drug) and efficacy (maximal achievable effect); and 3) virtually all physiological systems, especially endocrine systems, are subject to adaptive self-regulatory processes.

Received for publication December 15, 1998.

1 Present address: Department of General Psychiatry, University of Vienna, Austria.
2 Present address: Department of Psychiatry, Ludwig-Maximilian University, Munich, Germany.

Pharmacokinetic-Pharmacodynamic Modeling of Tolerance to the Prolactin-Secreting Effect of Chlorprothixene after Different Modes of Drug Administration

Chlorprothixene is a thioxanthene with antipsychotic properties that is widely used in Europe to treat schizophrenia. Despite long-term use, the pharmacodynamics of antipsychotic drugs are still not totally understood. It is desirable to obtain a detailed pharmacological characterization of these drugs. A pharmacological characterization of dose-effect relationships is primarily confounded by the time delay of several days to weeks between the onset of treatment and the onset of antipsychotic effect.

Typical antipsychotic drugs, such as chlorprothixene, block dopamine D2 receptors in the pituitary (lactotroph), compete with the dopamine-induced reduction in prolactin release and consequently cause an increase in prolactin concentration (Moore, 1987). The relationship between prolactin secretion and pathophysiology of schizophrenia or antipsychotic therapy has been extensively studied (Meltzer et al., 1983; Rubin, 1987; Green and Brown, 1988; Nordstrom and Farde, 1998). The results have not been entirely clear cut, and we assume that the discrepancy is mostly due to insufficient data analysis. In this context, the following aspects should be considered: 1) substantial interindividual variability exists in the disposition kinetics of antipsychotic drugs, particularly in the oral bioavailability and systemic clearance; 2) pharmacological response is best described by concentration-effect relationship, which is characterized by the parameters potency (sensitivity to the drug) and efficacy (maximal achievable effect); and 3) virtually all physiological systems, especially endocrine systems, are subject to adaptive self-regulatory processes.

Received for publication December 15, 1998.

1 Present address: Department of General Psychiatry, University of Vienna, Austria.
2 Present address: Department of Psychiatry, Ludwig-Maximilian University, Munich, Germany.

ABBREVIATIONS: \( r_{\text{in.prl}} \), prolactin secretion rate; \( r_{\text{in.prl.max}} \), maximal prolactin secretion rate; \( r_{\text{ptl.p}} \), prolactin secretion rate without compensatory increase of \( T \); \( r_{\text{in.prl.0}} \), baseline secretion rate of prolactin; \( r_{\text{ptl.50}} \), prolactin secretion rate obtained by 50% inhibition of the prolactin-lowering effects of \( T \); \( r_{\text{in,T}} \), secretion rate of \( T \); \( r_{\text{in,T.0}} \), baseline secretion rate of \( T \); \( c_{\text{cpx}} \), chlorprothixene concentration; \( c_{\text{dop}} \), dopamine concentration; \( c_{\text{prl}} \), prolactin concentration; \( c_{\text{prl.p}} \), prolactin concentration that results from \( r_{\text{in.prl.p}} \); \( c_{\text{prl.0}} \), prolactin concentration at baseline; \( c_{\text{cpx.50}} \), dopamine concentration producing 50% inhibition of \( T \); \( E_{\text{t}} \), extent of tolerance; \( I_{\text{cpx.50}} \), chlorprothixene concentration required to produce 50% inhibition of \( T \); \( I_{\text{cpx.50}} \), \( I_{\text{cpx.50.0}} \), chlorprothixene concentration without compensatory increase of \( T \); \( T_{\text{in.prl.0}} \), prolactin elimination rate constant; \( K_{\text{el.prl}} \), prolactin elimination rate constant; \( K_{\text{INP}} \), chlorprothixene dissociation constant at the dopamine D2 receptor; \( K_{\text{I}} \), rate of tolerance development; \( m_{\text{ptl}} \), mass of prolactin; \( P \), proportionality factor; \( T \), EC50-normalized dopamine concentration; \( T_{\text{ss.50}} \), T at steady state for \( c_{\text{cpx}} = I_{\text{cpx.50.0}} \); \( T_{\text{ss.prl}} \), T at steady state for \( c_{\text{cpx}} = I_{\text{cpx.50}} \); \( T_{\text{ss.0}} \), T at baseline; \( V_{\text{prl}} \), volume of distribution of prolactin.
In brief, the determinants of the response to a drug are the pharmacokinetics of the drug, the pharmacokinetic-pharmacodynamic relationship, and the extent and rate of tolerance development. During the past two decades, there has been tremendous progress in the development of pharmacokinetic-pharmacodynamic models to relate the time course of the pharmacological effect to the systemic drug concentrations for investigation of the quantitative aspects of these determinants (Holford and Sheiner, 1987). The prolactin secretion serves as a continuous, sensitive, and reproducible pharmacodynamic measure of the dopamine D₂ receptor function. Several reports focus on the application of such models in analyzing the effects of drugs on the prolactin secretion (Grevell et al., 1986; Francheteau et al., 1991; Jusko and Ko, 1994; Movin-Osswald and Hammarlund-Udenaes, 1995; Valente et al., 1997).

Despite the importance of homeostatic mechanisms in physiology and pharmacology, limited attention has been paid to the kinetic and dynamic relationship of the tolerance development. Cheng and Paalzow (1990) proposed a tolerance model to describe the time-dependent adaptation of dopaminergic activity during constant infusion of haloperidol to rats. A different concept was used by Movin-Osswald and Hammarlund-Udenaes (1995) to model the time-dependent changes in the prolactin response to remoxipride after two consecutive administrations of the same dose.

We present here a pharmacokinetic-pharmacodynamic model to describe the concentration-effect relationship of chlorprothixene on the prolactin secretion in healthy subjects and to determine how different routes of administration influence this relationship. The model includes the physiological homeostatic mechanism, which is responsible for tolerance development as an integral part of the pharmacodynamic system.

**Materials and Methods**

**Human Study**

The human study protocol was described in detail by Bagli et al. (1996a). In brief, eight healthy male volunteers with a mean age of 28 years (range, 24–32 years) and body weight of 76 kg (range, 63–89 kg) were enrolled in the study. The study protocol was approved by the Ethics Committee of the Faculty of Medicine of the University of Bonn and was carried out according to the Declaration of Helsinki. After receiving detailed information, the volunteers gave their written consent to participate in the study. The subjects fasted overnight for a minimum of 8 h before and 4 h after the administration of the drug between 9 and 10 AM. The subjects were hospitalized for 24 h and received single doses of 100 mg of chlorprothixene i.v. in solution (infusion over 60 min), as well as orally in a randomized cross-over design with a washout phase of at least 2 weeks. The preparations were provided by Bayer AG (Leverkusen, Germany). Up to 8 h after drug administration, blood samples were withdrawn with a indwelling catheter (contralateral during the i.v. infusion) and thereafter via venous puncture. Samples were collected immediately before drug administration and thereafter at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60, and 72 h. During infusion, additional samples were withdrawn at 0.25 and 0.75 h. After 30-min coagulation, the blood was centrifuged and serum was aspirated and stored at 20°C.

Analytical Procedures

Chlorprothixene serum concentrations were determined by a reversed phase HPLC method and electrochemical detection (Bagli et al., 1984). The intra-assay and interassay coefficients of variation were 3 and 8%, respectively. The sensitivity of the method was 0.3 nM. Serum prolactin was measured by a commercially available radioimmunoassay with monoclonal antibodies (PRL-IRMA; Medgenix Diagnostics, Nivelles, Belgium). The intra-assay and interassay coefficients of variation were 5 and 8%, respectively. The sensitivity of the assay was 0.06 nM.

**Pharmacokinetic and Pharmacodynamic Models**

The plot of the observed chlorprothixene concentrations versus the corresponding prolactin concentrations revealed a hysteresis that indicated a temporal delay in the rise and fall of the chlorprothixene and prolactin serum concentrations (Fig. 1). This plot also showed a shift to the right of the concentration-response curve after infusion compared with that after oral administration. This indicated a time-dependent change in the pharmacological response (tolerance); that is, after i.v. infusion, higher chlorprothixene concentrations were required to produce the same effect than after oral administration.

Both observations conform with the pharmacological mechanism of drug action. The corresponding schematic presentation of the chlorprothixene effects on the prolactin secretion derived from in vitro and in vivo observations is given in Fig. 2. Prolactin is a peptide hormone synthesized and released by the anterior pituitary and predominantly regulated by dopamine-sensitive cells in the hypothalamus and pituitary (Moore, 1987). Dopamine is released from the tuberoinfundibular tract and transported through the portal system to the lactotroph of the anterior pituitary; it exerts a tonic inhibitory control over prolactin release. Chlorprothixene, a dopamine D₂ receptor antagonist, blocks these receptors and competes for the tonic inhibitory effect of dopamine on the prolactin release. The circulating level of prolactin increases and feeds back to activate the tuberoinfundibular dopamine neurons (Perkins et al., 1979). Thus, prolactin regulates its own release via a hormonal-neuronal feedback loop (Moore, 1987).

In contrast to other antipsychotics (e.g., thioridazine) that possess active metabolites, the effect of chlorprothixene on prolactin secretion was solely attributable to the mother compound and does not require consideration in the model (Jørgensen, 1986). Our model consisted of three parts: a pharmacokinetic model, a pharmacodynamic model, and a tolerance model.

**Pharmacokinetic Model**

A three compartment model served as pharmacokinetic model for the disposition kinetics of chlorprothixene. The drug absorption rate after oral administration were estimated by deconvolution. A comprehensive description of the pharmacokinetic model and data analysis, especially that of the deconvolution, is given by Bagli et al. (1996b).

**Fig. 1.** Prolactin versus chlorprothixene serum concentration in subject 3 after i.v. infusion (■) and after oral administration (●).
PK/PD Modeling of Chlorprothixene on Prolactin

![Fig. 2. Schematic presentation of the effects of dopamine and chlorprothixene on the prolactin secretion and the hormonal-neuronal feedback loop.](image)

**Pharmacodynamic Model.** The effect of chlorprothixene on the prolactin concentration is mediated by indirect mechanisms, therefore an indirect response model was used to account for the delay in the onset of the prolactin increase relative to the serum concentration-time profile of chlorprothixene (Dayneka et al., 1993; Jusko and Ko, 1994). The rate change of prolactin in blood over time was described by the following differential equation:

\[
\frac{dm_{prl}}{dt} = r_{in.prl} - k_{el.prl} \cdot m_{prl}
\]  

(1)

where \( r_{in.prl} \) is the prolactin secretion rate, \( k_{el.prl} \) is the prolactin elimination rate constant, and \( m_{prl} \) is the mass of prolactin. Because the volume of distribution of prolactin (\( V_{prl} \)) could not be determined independently of \( r_{in.prl} \), the volume was set to unity; hence, \( m_{prl} \) equals the concentration of prolactin (\( c_{prl} \)).

The stimulatory effect of chlorprothixene was produced by competitive inhibition of the prolactin-lowering effects of dopamine. The following equation derived from receptor theory describes this type of agonist and competitive antagonist interaction (Ariens and Simons, 1964):

\[
r_{in.prl} = r_{in.prl.max} \cdot \frac{1 - \frac{c_{da}}{EC_{50}}}{1 + \frac{1 + c_{cpx}}{K_t} + c_{da}}
\]  

(2)

where \( r_{in.prl.max} \) is the maximal prolactin secretion rate, \( c_{da} \) is the dopamine concentration (agonist), \( c_{cpx} \) is the chlorprothixene concentration (antagonist), \( EC_{50} \) is the dopamine concentration producing 50% of \( r_{in.prl.max} \) and \( K_t \) is the chlorprothixene dissociation constant at the dopamine D_2 receptor.

As far as dopamine concentrations were not known, the \( EC_{50} \) value could not be determined in the present study. Therefore, we used \( T \) instead of \( c_{da}/EC_{50} \) and designated \( T \) as the \( EC_{50} \)-normalized dopamine concentration:

\[
r_{in.prl} = r_{in.prl.max} \cdot \frac{1 - \frac{T}{1 + \frac{c_{cpx}}{K_t} + T}}
\]  

(3)

This equation included baseline, drug, and opposing effect. A tolerance model was incorporated to account for the opposing effect.

**Tolerance Model.** Tolerance was modeled as counterregulation of the prolactin secretion by the feedback increase of \( T \). The hormonal-neuronal feedback loop was modeled by an indirect response model:

\[
\frac{dT}{dt} = r_{in.T} - k_{tol} \cdot T
\]  

(4)

where \( r_{in.T} \) is the secretion rate of \( T \). The loss of \( T \) determined the rate of equilibration between prolactin and dopamine. Therefore, \( k_{tol} \) was used as rate parameter for the development of tolerance.

At baseline, without drug and opposing effect, prolactin and dopamine concentrations were considered to be constant. This corresponds to steady-state conditions (\( dT/dt = 0 \) and \( dm_{prl}/dt = 0 \)). The baseline concentrations of dopamine (\( T_{ss.0} \)) and prolactin (\( c_{ss.prl.0} \)) were:

\[
T_{ss.0} = \frac{r_{in.T.0}}{k_{tol}}
\]  

(5)

\[
c_{ss.prl.0} = \frac{r_{in.prl.0}}{k_{el.prl} \cdot V_{prl}}
\]  

(6)

where \( r_{in.T.0} \) is the secretion rate of \( T \) at baseline. The secretion rate of prolactin at baseline (\( r_{in.prl.0} \)) and secretion rate of prolactin without opposing effect (\( r_{in.prl.p} \)) (i.e., without compensatory increase of \( T \)) were calculated as follows:

\[
r_{in.prl.0} = r_{in.prl.max} \cdot \left( 1 - \frac{T_{ss.0}}{1 + T_{ss.0}} \right)
\]  

(7)

\[
r_{in.prl.p} = r_{in.prl.max} \cdot \left( 1 - \frac{T_{ss.0}}{1 + T_{ss.0} + \frac{c_{cpx}}{K_t}} \right)
\]  

(8)

The prolactin concentration that resulted from \( r_{in.prl.p} \) (\( c_{prl.p} \)) determined the homeostatic response. A proportional relationship was assumed for the stimulation of dopamine secretion by prolactin:

\[
r_{in.T} = P \cdot c_{prl.p}
\]  

(9)

where \( P \) is a proportionality factor. Based on this equation, \( r_{in.T.0} \) is:

\[
r_{in.T.0} = P \cdot c_{ss.prl.0}
\]  

(10)

The proportionality factor \( P \) determined the extent of compensatory increase of \( T \) that resulted in a loss of sensitivity. A parameter for the extent of tolerance development, which was based on the comparison of the sensitivity with and without compensatory increase of \( T \), was derived as follows: The dissociation constant \( K_t \) is the chlorprothixene concentration at half-maximal receptor occupancy and expresses the affinity to the dopamine D_2 receptor. \( IC_{50} \) is the chlorprothixene concentration required to inhibit the prolactin-lowering effects of dopamine by 50%. The relationship between \( IC_{50} \) and \( K_t \) was expressed by the following relationship (see Appendix):

\[
IC_{50} = K_t \cdot \frac{T_{ss.0} \cdot (T_{ss.0} + 2) - T_{ss.0}}{T_{ss.0}}
\]  

(11)

This equation demonstrates that \( IC_{50} \) depends on \( T \). With counter-regulation, higher concentrations of chlorprothixene were required to produce the same effect than without; therefore, the following ratio was used for the extent of tolerance development (\( E_T \)):

\[
E_T = \frac{IC_{50.n}}{IC_{50.p}}
\]  

(12)

where \( IC_{50.n} \) is the \( IC_{50} \) value with compensatory increase in \( T \) and \( IC_{50.p} \) without the compensatory increase in \( T \). The calculation for \( IC_{50.p} \) and \( IC_{50.n} \) was based on equation 11 (see Appendix):

\[
IC_{50.n} = K_t \cdot (T_{ss.0} + 1)
\]  

(13)

\[
IC_{50.p} = K_t \cdot (T_{ss.0} + 1) \cdot (T_{ss.0} + 1)
\]  

(14)
With insertion of equations 13 and 14 in equation 12, $E_T$ became:

$$E_T = T_{ss} + 1$$ (15)

Considering the proportional relationship in equation 10 and transformation of equation 15, the following relationship was obtained between $E_T$ and $P$:

$$E_T = \sqrt{T_{ss}} + \frac{r_{\text{in.prl.max}}}{k_{\text{tol}} \cdot k_{\text{el.prl}}} \cdot V_{\text{prl}} \cdot P + \frac{1}{2}$$ (16)

Data Analysis

The pharmacokinetic and pharmacodynamic/tolerance parameters were fitted sequentially on each individual. The disposition kinetics and drug absorption rate after oral administration were fitted to the serum chlorprothixene concentrations using least-squares nonlinear regression (Bagli et al., 1996a,b).

The pharmacodynamic and tolerance model was fitted simultaneously to the time course of prolactin concentration from both routes of drug administration of one individual, also with the use of least-squares nonlinear regression. The fits were performed with the use of WinNonlin (Scientific Consulting, Inc., Cary, NC); different weighting schemes were tested by visual inspection and residual analysis. The following parameters were obtained directly from the fit of the prolactin concentration-time profiles: $r_{\text{in.prl.max}}$, $K_I$, $k_{\text{el.prl}}$, and $k_{\text{tol}}$. Secondary parameters such as $E_T$ and $c_{\text{ss.prl.0}}$ were estimated from these parameters. The relationship between the pharmacodynamic parameters were assessed by the Spearman’s correlation coefficient.

Results

Concentration-Time Profile of Chlorprothixene. For a prototypical individual, the time course of the observed and predicted serum concentration after oral and intravenous administration of chlorprothixene showed a marked difference between these two routes of administration (Fig. 3, a and b). Due to an absolute oral bioavailability of 17%, the maximal serum concentration of chlorprothixene after oral administration was about 13-fold lower than after i.v. infusion. The parameters of the pharmacokinetic model of chlorprothixene disposition and absorption were presented previously (Bagli et al., 1996a,b).

Concentration-Time Profile of Prolactin. The prolactin concentration rapidly reached a maximum at 0.75 to 1 h after i.v. infusion and at 2 to 6 h after oral administration of chlorprothixene, and within 24 h, it returned gradually to baseline (Fig. 3, c and d). The effects on prolactin after i.v. infusion were greater than those after oral administration, but considering the significant differences in the time courses of chlorprothixene, the differences were smaller than expected. The pharmacodynamic model described above adequately predicts the data for both routes of drug administration; the weighting scheme of 1/concentration$^2$ gave the best results (Fig. 3, c and d). The solid line is the effect predicted by the model, and the dashed line is the EC$50$-normalized dopamine concentration that represents the opposing effect. The opposing effect becomes significant with increasing concentrations of prolactin.

Pharmacodynamic and Tolerance Parameters. Table 1 presents the pharmacodynamic ($r_{\text{in.prl.max}}$, $K_I$, and $k_{\text{el.prl}}$) and tolerance parameters ($P$ and $k_{\text{tol}}$) obtained from the fit to the data of eight subjects. This table also shows the secondary parameters ($E_T$ and $c_{\text{ss.prl.0}}$) that were calculated based on the pharmacodynamic and tolerance parameters. The $c_{\text{ss.prl.0}}$ showed a coefficient of variation of 34% for the interindividual variability, which was in accordance with that reported in the literature for male subjects; the coefficients of variation for the other pharmacodynamic parameter estimates were in the same range, whereas that for $K_I$ was much higher. This high variation was due to one subject, who
showed a 4-fold higher $K_I$ than the mean $K_I$ of the other subjects. There was no significant correlation between the pharmacodynamic/tolerance parameters.

**Discussion**

We present an integrated pharmacokinetic and physiological indirect pharmacodynamic/tolerance model that is applicable to neuroendocrine challenge tests in biological psychiatry. This model adequately characterizes the pharmacodynamic response after i.v. and oral drug administration on account of different pharmacokinetic input profiles. The tolerance development is considered a counterregulatory process.

The application of conventional pharmacodynamic models, which assumes that the model parameters stay constant over time, does not hold here. Time-variant models presume that pharmacodynamic parameters undergo time-dependent changes. Various mechanisms may be responsible for functional tolerance and require specific models. In our model, the drug-induced effect triggers a regulatory mechanism that influences dopamine, which maintains the baseline effect, and provokes an effect opposite that of the drug. We succeed in incorporating this model to predict the time course of prolactin concentrations after i.v. as well as after oral administration with one set of pharmacodynamic parameters for each subject.

The pharmacodynamic and tolerance model is presented in Fig. 4. An increase in $T$ causes a reduction in the prolactin secretion, whereas an increase in chlorprothixene provokes a shift of this concentration-effect curve (Fig. 4, left). The magnitude of the shift is inversely correlated to $K_I$. Figure 4, right, represents the drug effect without and with compensatory increases in $T$. For graphical consideration, the time aspect of tolerance is left out. The shift between these curves represents the extent of tolerance ($E_T$). The compensatory increase in $T$ results in a loss of potency [i.e., with the compensatory increase in $T$, higher concentrations of chlorprothixene ($IC_{50,n}$) are required to produce the same effect than without ($IC_{50,p}$)].

Our model differs from the previously reported models for a reduced response to antipsychotic drugs after repetitive or continuous drug administration. Movin-Osswald and Hammarlund-Udenaes (1995) used the availability of prolactin in the pool to describe time-dependent differences in the prolactin response after two consecutive administrations of the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pharmacodynamic</th>
<th>Tolerance</th>
<th>Secondary$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r_{in.prl,max}$</td>
<td>$K_I$</td>
<td>$k_{tol}$</td>
</tr>
<tr>
<td></td>
<td>nmol/h</td>
<td>nmol/liter</td>
<td>1/h</td>
</tr>
<tr>
<td>1</td>
<td>3.4</td>
<td>137.5</td>
<td>1.19</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>33.2</td>
<td>0.77</td>
</tr>
<tr>
<td>3</td>
<td>2.4</td>
<td>32.2</td>
<td>1.10</td>
</tr>
<tr>
<td>4</td>
<td>1.1</td>
<td>18.4</td>
<td>1.62</td>
</tr>
<tr>
<td>5</td>
<td>2.6</td>
<td>49.3</td>
<td>1.74</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>57.6</td>
<td>1.91</td>
</tr>
<tr>
<td>7</td>
<td>2.2</td>
<td>18.5</td>
<td>1.39</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>7.3</td>
<td>0.82</td>
</tr>
<tr>
<td>Mean</td>
<td>2.2</td>
<td>44.3</td>
<td>1.32</td>
</tr>
<tr>
<td>c.v. (%)</td>
<td>31.6</td>
<td>93.0</td>
<td>31.9</td>
</tr>
</tbody>
</table>

$^a$ The secondary parameters were calculated based on the following equations:

$$E_T = \frac{1}{4} \left( \frac{r_{in.prl,max}}{k_{tol}} \right) \frac{k_{dil.prl}}{V_{prl}} \frac{P}{1} \left[ \frac{r_{in.prl.max}}{k_{dil.prl}} \right]$$

The pharmacodynamic and tolerance parameters of prolactin secretion obtained directly from the fit of the prolactin concentration-time after i.v. and oral administration of 100 mg chlorprothixene to eight subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pharmacodynamic</th>
<th>Tolerance</th>
<th>Secondary$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r_{in.prl,max}$</td>
<td>$K_I$</td>
<td>$k_{tol}$</td>
</tr>
<tr>
<td></td>
<td>nmol/h</td>
<td>nmol/liter</td>
<td>1/h</td>
</tr>
<tr>
<td>1</td>
<td>3.4</td>
<td>137.5</td>
<td>1.19</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>33.2</td>
<td>0.77</td>
</tr>
<tr>
<td>3</td>
<td>2.4</td>
<td>32.2</td>
<td>1.10</td>
</tr>
<tr>
<td>4</td>
<td>1.1</td>
<td>18.4</td>
<td>1.62</td>
</tr>
<tr>
<td>5</td>
<td>2.6</td>
<td>49.3</td>
<td>1.74</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>57.6</td>
<td>1.91</td>
</tr>
<tr>
<td>7</td>
<td>2.2</td>
<td>18.5</td>
<td>1.39</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>7.3</td>
<td>0.82</td>
</tr>
<tr>
<td>Mean</td>
<td>2.2</td>
<td>44.3</td>
<td>1.32</td>
</tr>
<tr>
<td>c.v. (%)</td>
<td>31.6</td>
<td>93.0</td>
<td>31.9</td>
</tr>
</tbody>
</table>

$^a$ The secondary parameters were calculated based on the following equations:

$$E_T = \frac{1}{4} \left( \frac{r_{in.prl,max}}{k_{tol}} \right) \frac{k_{dil.prl}}{V_{prl}} \frac{P}{1} \left[ \frac{r_{in.prl.max}}{k_{dil.prl}} \right]$$

The pharmacodynamic and tolerance models for the effects of chlorprothixene on the prolactin secretion. The curves were constructed according to the parameters derived from the data of subject 3. Left, concentration-effect curves between the prolactin secretion rate and the EC$_{50}$ normalized dopamine concentration (T) at different chlorprothixene concentrations ($c_{cpp}$). The intersection of these curves with the vertical line at $T_{ss.0}$ (baseline concentration of T) corresponds to the prolactin secretion rate at different concentrations of chlorprothixene without tolerance. The prolactin secretion rate is $r_{in.prl,max}/2$ when $c_{cpp} = 0$ and $T = 1$. Right, concentration-effect curves between prolactin secretion rate and $c_{cpp}$ without ($r_{in.prl,p}$ solid line) and with ($r_{in.prl,p}$ dashed line) tolerance. Tolerance was modeled as compensatory increase of $T$, the rate aspect of tolerance was left out for graphic consideration. The difference between $r_{in.prl,50}$ and $r_{in.prl,p}$ for $c_{cpp} = IC_{50,p}$ (A) is equal to the difference between the $r_{in.prl}$ observed for $c_{cpp} = IC_{50,n}$ and $r_{in.prl,50}$ (B).
same doses of remoxipride in healthy male volunteers. The rate constant for the prolactin elimination obtained by Movin-Osswald and Hammarlunds-Udenaes (1995) exactly matches our $k_{in.prl}$ value; both parameters are in accord with that of the experimentally determined prolactin half-life of 30 min (Cooper et al., 1979).

Movin-Osswald and Hammarlunds-Udenaes (1995) observed that the prolactin concentration returns to baseline levels even though remoxipride was still present. They conclude that the capacity of remoxipride to stimulate prolactin release is much larger than the ability of prolactin to respond. In our model, the maximal prolactin secretion rate is considered the limiting factor for the response. After i.v. infusion, we obtain maximal chlorprothixene concentrations that yield an average of 80% of the maximal prolactin secretion rate. The fact that prolactin returns to baseline despite the presence of chlorprothixene is considered to be due to the compensatory increase of $T$.

The persistence of the opposing effect while the drug wears off is called rebound phenomena; the prolactin secretion induced by the opposing effect drops below the baseline. This is not observed for chlorprothixene (Fig. 3). Whether rebound phenomena actually occur depends on the kinetic properties of the drug and those of the opposing system. Movin-Osswald and Hammarlunds-Udenaes (1995) provide simulations to demonstrate that rebound phenomena occur for drugs with short drug elimination half-lives (less than 1.2 h), but they assume in their simulation that the decrease in the prolactin levels below baseline is due to depletion of the prolactin pool and not due to persistence of the opposing effect.

Cheng and Paalzow (1990) present a hypothetical compartment model for tolerance to describe the time-dependent adaptation of dopaminergic activity during constant infusion of haloperidol to rats. Tolerance development (adaptation) was estimated by two parameters: 1) the potency of tolerance development, defined as steady-state concentration at which the naive effect is decreased to 50%, and 2) the rate of tolerance development, defined as the rate of the loss of drug from the tolerance compartment. The definition of the rate of tolerance development by Cheng and Paalzow (1990) is comparable to the definition of our $k_{tol}$. There was a significant difference between both parameters. One explanation for this is that $k_{tol}$ after the single dose (0.080 l/h) in our study represents the more rapid process of feedback adjustment (acute tolerance), whereas the rate of tolerance development after constant infusion (0.018 l/h) obtained by Cheng and Paalzow (1990) represents that of receptor alterations.

In our approach, the opposing and baseline effects are integral parts of the pharmacodynamic model. The primary and net drug effects are defined as $r_{in.prl.p} - r_{in.prl.0}$ and $r_{in.prl} - r_{in.prl.0}$ respectively. Accordingly, the opposing effect is defined as $r_{in.T} - r_{in.T.0}$. Consideration of changes in the baseline from within-day variations (circadian rhythm) does not demonstrate a significantly better performance (Franche- teau et al., 1991); therefore, baseline concentrations are taken to be constant. The prolactin baseline concentrations derived from the model are in accordance with those reported previously from 17 male healthy subjects during placebo conditions (Rao et al., 1994).

Compared with IC$_{50}$, $K_1$ represents solely the affinity of the drug to the tuberoinfundibular dopamine D$_2$ receptor. The in vivo $K_1$ value of 44 nM is higher than the $K_1$ value determined in vitro by means of radioligand-binding techniques. The differences could be due to methodology. Richelson and Nelson (1984) used dopamine receptor preparations of caudate nucleus of brain tissue from humans (8 nM); Rao (1986) used dopamine receptor preparations of brain tissue from pigs (14 nM).

The high interindividual variation of $K_1$ is in accord with the interindividual differences in response to antipsychotic therapy; one subject shows a 4-fold higher $K_1$ value than the average $K_1$ of the other individuals. Individuals with increased $K_1$ values require higher drug doses to attain the same effects. This provides the opportunity to spot patients with a lower receptor affinity (high $K_1$), which may indicate a poor therapeutic response to antipsychotic drugs.

It is hoped that neuroendocrine challenge paradigms could predict the therapeutic effect. However, the attempts to correlate antipsychotic-induced changes in prolactin concentrations with improvement in psychopathology have so far been inconclusive. The reasons may be that this requires the determination of the sensitivity of the subjects to drugs and the time course of adaptation with even more reliable parameters by means of the improved data analysis as that presented here because this allows a complete quantitative description of tolerance ($E_A$ and $k_{tol}$) and is able to define the efficacy ($r_{in.prl.max}$) and sensitivity ($K_1$). Further studies with schizophrenic patients will show whether low pituitary dopamine D$_2$ receptor sensitivity correlates with poor therapeutic response to antipsychotic drugs.

**Appendix**

**Relationship among IC$_{50}$, IC$_{50,p}$, IC$_{50,ss}$, and $K_1$.** The prolactin secretion rate obtained after 50% inhibition of the prolactin-lowering effects of dopamine ($r_{in.prl.50}$) is:

\[ r_{in.prl.50} = \frac{r_{in.prl.max} + r_{in.prl.0}}{2} \]  

(17)

\[ r_{in.prl.50} = r_{in.prl.max} \cdot \left(1 - \frac{T}{1 + T + \frac{IC_{50}}{K_1}}\right) \]  

(18)

The relationship between IC$_{50}$ and $K_1$ was derived by combining equations 17 and 18 and substituting equation 7 for $r_{in.prl.0}$:

\[ r_{in.prl.max} \cdot \left(1 - \frac{T}{1 + T + \frac{IC_{50}}{K_1}}\right) = \frac{r_{in.prl.max} + r_{in.prl.0}}{2} \]  

(19)

\[ \frac{K_1 + IC_{50}}{K_1 + K_1 \cdot T + IC_{50}} = \frac{T_{ss.0} + 2}{2 \cdot (T_{ss.0} + 1)} \]  

(20)

\[ K_1 + IC_{50} = \frac{(T_{ss.0} + 2) \cdot K_1 + (T_{ss.0} + 2) \cdot K_1 \cdot T}{2 \cdot (T_{ss.0} + 1)} + \frac{IC_{50} \cdot (T_{ss.0} + 2)}{2 \cdot (T_{ss.0} + 1)} \]  

(21)

\[ IC_{50} \cdot \left(1 - \frac{T_{ss.0} + 2}{2 \cdot (T_{ss.0} + 1)}\right) \]  

(22)
\[
= K_1 \cdot \left( \frac{(T_{ss,0} + 2) \cdot T + (T_{ss,0} + 2)}{2 \cdot (T_{ss,0} + 1)} - 1 \right)
\]
\[\text{IC}_{50} \cdot \frac{T_{ss,0}}{2 \cdot (T_{ss,0} + 1)} = K_1 \cdot \frac{(T_{ss,0} + 2) \cdot T - T_{ss,0}}{2 \cdot (T_{ss,0} + 1)}
\] (23)

Equation 11
\[\text{IC}_{50} = K_1 \cdot \frac{T_{ss,0} \cdot (T_{ss,0} + 2) - T_{ss,0}}{T_{ss,0}}
\] (11)

demonstrates that \(\text{IC}_{50}\) depends on \(T\). For the sake of simplicity, the rate aspect was left out as far as the extent of tolerance was concerned; therefore, we considered \(dT/dt\) to be 0. Substituting \(T_{ss,0}\) for \(T\) in equation 11, we obtain \(\text{IC}_{50,p}\):
\[\text{IC}_{50,p} = K_1 \cdot (T_{ss,0} + 1)
\] (13)

The equation for \(\text{IC}_{50,n}\) was derived as follows. The difference between \(r_{in,prl,50}\) and \(r_{in,prl,p}\) observed for \(c_{\text{cpx}} = \text{IC}_{50,p}\) (denoted in Fig. 4 as A) is equal to the difference between the \(r_{in,prl}\) for \(c_{\text{cpx}} = \text{IC}_{50,n}\) and \(r_{in,prl,50}\) (denoted in Fig. 4 as B):
\[r_{in,prl,max} \cdot \left( 1 - \frac{T_{ss,0}}{1 + T_{ss,0} + \frac{\text{IC}_{50,p}}{K_1}} \right)
- r_{in,prl,max} \cdot \left( 1 - \frac{T_{ss,IC50p}}{1 + T_{ss,IC50p} + \frac{\text{IC}_{50,n}}{K_1}} \right) = r_{in,prl,max}
\] (24)

where \(T_{ss,IC50p}\) is the steady-state concentration of \(T\) at \(c_{\text{cpx}} = \text{IC}_{50,p}\) and \(T_{ss,IC50n}\) that at \(c_{\text{cpx}} = \text{IC}_{50,n}\):
\[T_{ss,IC50p} = T_{ss,0} \cdot \frac{P}{k_{tol} \cdot k_{el,prl} \cdot V_{prl}} \cdot \left( 1 - \frac{T_{ss,0}}{1 + T_{ss,0} + \frac{\text{IC}_{50,p}}{K_1}} \right)
\] (25)
\[T_{ss,IC50n} = T_{ss,0} \cdot \frac{P}{k_{tol} \cdot k_{el,prl} \cdot V_{prl}} \cdot \left( 1 - \frac{T_{ss,0}}{1 + T_{ss,0} + \frac{\text{IC}_{50,n}}{K_1}} \right)
\] (26)

Considering equation 13, solving equation 10 for \(P\) and substituting \(P\) in equations, these equations become:
\[T_{ss,IC50p} = \frac{T_{ss,0} \cdot (T_{ss,0} + 2)}{2}
\] (27)
\[T_{ss,IC50n} = (T_{ss,0} + 1) \cdot T_{ss,0} \cdot \left( 1 - \frac{T_{ss,0}}{1 + T_{ss,0} + \frac{\text{IC}_{50,n}}{K_1}} \right)
\] (28)

Equation 34 was yielded after transformation of equation 24 and substitution of equation 13 for \(\text{IC}_{50,p}\) and equation 27 for \(T_{ss,IC50p}\):
IC\textsubscript{50,n} was then derived after substitution of $T_{ss.IC50,n}$ for $T$ in equation 11:

\begin{equation}
IC_{50,n} = K_1 \cdot \left( \frac{T_{ss,0} \cdot T_{ss,0} + 2 \cdot T_{ss,0} + 2}{T_{ss,0} + 2} - T_{ss,0} \right)
\end{equation}

\begin{equation}
IC_{50,n} = K_1 \cdot \left( T_{ss,0} \cdot T_{ss,0} + 2 \cdot T_{ss,0} + 1 \right)
\end{equation}

References


Send reprint requests to: Dr. Metin Bagli, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Rheinische Friedrich-Wilhelms-Universität, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany. E-mail: bagli@uni-bonn.de