Antipsychotic Dosing in Preclinical Models Is Often Unrepresentative of the Clinical Condition: A Suggested Solution Based on in Vivo Occupancy

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ABSTRACT
What is the appropriate dose of an antipsychotic in an animal model? The literature reveals no standard rationale across studies. This study was designed to use in vivo dopamine D2 receptor occupancy as a cross-species principle for deriving clinically comparable doses for animal models. The relationship between dose, plasma levels, and in vivo dopamine D2 receptor occupancy was established in rats for a range of doses administered as a single dose or multiple doses (daily injections or osmotic minipump infusions) for five of the most commonly used antipsychotics. As a single dose, haloperidol (0.04–0.08 mg/kg), clozapine (5–15 mg/kg), olanzapine (1–2 mg/kg), risperidone (0.5–1 mg/kg), and quetiapine (10–25 mg/kg) reached clinically comparable occupancies. However, when these “optimal” single doses were administered as multiple doses, either by injection or by a mini-pump, it led to no or inappropriately low trough (24-h) occupancies. This discrepancy arises because the half-life of antipsychotics in rodents is 4 to 6 times faster than in humans. Only when doses 5 times higher than the optimal single dose were administered by pump were clinically comparable occupancies obtained (e.g., haloperidol, 0.25 mg/kg/day; olanzapine, 7.5 mg/kg/day). This could not be achieved for clozapine or quetiapine due to solubility and administration constraints. The study provides a rationale as well as clinically comparable dosing regimens for animal studies and raises questions about the inferences drawn from previous studies that have used doses unrepresentative of the clinical situation.

A search of the Medline database for the terms “antipsychotic or neuroleptic” and “human” reveals 38,000 articles since the 1960s. When the term human is replaced with “animal,” the search returns an almost equal number of articles, 34,000 articles. Studies of antipsychotics in animal models are almost as important a scientific enterprise as their study in humans (Lipska and Weinberger, 2000). In humans, the antipsychotics are effective in treating psychosis in a very narrow therapeutic dose range, a dose range that can be determined only in careful clinical trials of psychosis. Since psychosis per se cannot be modeled or measured in animals, what is the representative dose of antipsychotics in animal models?

A sampling of published papers shows three different approaches to this question (Kapur et al., 2000a). Most commonly, the dose of an antipsychotic is listed in the methods section without any justification for the particular choice. Less commonly, authors refer to previous papers (which may have been as arbitrary in their choice) as their reason to choose a particular dose. Least commonly, one finds a reasoned discussion of the choice of dose or finds a complete dose-response experiment. Thus, despite the critical importance of dosing, most of the studies in the literature have neglected this issue, leading in some instances to confounding and misleading conclusions (Kapur et al., 2000a).

Determination of the correct antipsychotic dose in animals is complicated by several factors. First, the symptoms that these drugs treat in patients, delusions and hallucinations, cannot be modeled by themselves in animals (Lipska and Weinberger, 2000). What is used instead are a series of paradigms with predictive validity (e.g., amphetamine-induced hyperlocomotion, stereotypy, sensorimotor gating, etc.) (Arnt et al., 1997). However, just because an antipsychotic “works” in one of these predictive models, it does not mean that the dose at which it does so is representative of the clinical condition. Second, most of the currently popular atypical antipsychotics block multiple receptors with affinities...
varying by two orders of magnitude (Schotte et al., 1996). A classic example is clozapine, which blocks more than a dozen different receptors with affinities ranging from <1 nM to >100 nM. As a result of this nonspecificity, when used at different doses, the drug produces a very different pharmacodynamic profile. Finally, antipsychotics in the clinical situation are used under multiple-dosing conditions. Whereas the half-life of these antipsychotics in humans is usually 12 to 24 h, their half-life in rodents tends to be 2 to 4 h. Thus, if the human practice of once-a-day or twice-a-day dosing is emulated in rodents, the rat receives a dose only once every four to eight half-lives. As a result, whereas a steady state in humans leads to a substantial presence of the drug at the active site throughout the 24 h, in rats the drug is almost completely eliminated at trough.

Given that a true anti-"psychotic" effect cannot be achieved in an animal, how does one choose representative doses for animal studies? Perhaps the most valid approach is to find doses that produce patient-equivalent effects on a critical target within the brains of experimental animals. This is now possible for most antipsychotics. With the advent of positron emission tomography and single photon emission computerized tomography imaging, it has been possible to measure the effects of most antipsychotics on dopamine D<sub>2</sub> receptors in vivo, in patients, at clinically relevant doses in the "therapeutic window" (Kapur and Remington, 2001). These findings are now well replicated across different laboratories, seem to correlate with clinical efficacy and side effects, and also help understand clinical differences between the available antipsychotics (Kapur et al., 1999; Nyberg and Farde, 2000; Bressan et al., 2001). We do not wish to suggest that action at D<sub>2</sub> receptors is the exclusive or central mechanism of action of these antipsychotics. However, it does provide an empirical and plausible marker that can be measured reliably and analogously in both species, and thus provides one basis for choosing clinically comparable doses of drugs for studies in animal models.

To obtain such clinically comparable doses for five of the most common antipsychotics (in use currently (haloperidol, risperidone, olanzapine, quetiapine, and clozapine), we chose to measure their dopamine D<sub>2</sub> receptor occupancy using a validated method of calculating in vivo receptor occupancy that is similar to that used in clinical studies. Once the clinically comparable single doses were identified, we carried out studies using multiple-dosing regimens, by daily injections or continuous-infusion pumps, to obtain the clinically comparable doses for multiple-dosing studies.

Materials and Methods

Animals. Male Sprague-Dawley rats (Charles River Canada, Montreal, PQ, Canada) with initial body weight of 250 to 275 g were used. All animals were housed two per cage with food and water available ad libitum.

Drugs. Haloperidol (Sabex Inc., Boucherville, QC, Canada) and risperidone (Sigma-Aldrich, St. Louis, MO) were dissolved in distilled water, whereas olanzapine (gift from Eli Lilly & Co., Indianapolis, IN), quetiapine (gift from AstraZeneca, Mississauga, ON, Canada), and clozapine (ANAWA Trading SA, Wangen, Zurich, Switzerland) were dissolved in 1 to 2% glacial acetic acid in distilled water. All drugs were administered subcutaneously. [3H]Raclopride (PerkinElmer Life Sciences, Boston, MA) was used as the radioligand for occupancy studies and given intravenously via the tail.

Single-Dose Conditions. Animals (n = 150) were allocated to one of five drug conditions, and then further subdivided to one of five or six doses per drug or corresponding vehicle: haloperidol (0.025–1 mg/kg), clozapine (2.5–60 mg/kg), olanzapine (0.1–2 mg/kg), risperidone (0.05–2 mg/kg), and quetiapine (5–100 mg/kg). Rats that received a subcutaneous injection of haloperidol, olanzapine, or risperidone were sacrificed 2 h after drug administration (Campbell et al., 1980; Schotte et al., 1996). Those rats that received clozapine or quetiapine were sacrificed 1 h after drug administration since these drugs have been shown to have peak effects in the brain earlier than the other antipsychotics (Burki, 1986; Saller and Salama, 1993). It should be pointed out that the "peak" times were chosen based on previous studies relating to pharmacokinetics and functional effects and therefore should be regarded as approximations as opposed to definitive periods of maximal occupancy.

Ten minutes before sacrifice, the animals were tested for catalepsy. Animals were placed on an inclined (60°) grid and observed by a rater blind to the treatment assignment status of the animals. To establish a reliable baseline, the first 30 s were excluded from the actual rating time. The time the rat remained in the same position was then measured for a maximum of 2.5 min. The catalepsy was scored from 0 to 5 according to the time (square root transformation) the animal remained immobile (minutes): 0 = 0 to 0.08, 1 = 0.09 to 0.35, 2 = 0.36 to 0.80, 3 = 0.81 to 1.42, 4 = 1.43 to 2.24, and 5 = ≥2.25 min. An animal was considered cataleptic with a score greater than or equal to 2.

Multiple-Dosing Conditions. Animals (n = 144) were allocated to one of five antipsychotic drug groups to receive daily doses of antipsychotic either by subcutaneous injection or by Alzet osmotic minipump at a rate of 5.0 µl/h (model 2M2, DURECT Corp., Cupertino, CA) for 7 days. Since the half-life of all antipsychotics is of the order of 2 to 4 h, 7 days is more than sufficient to obtain steady-state kinetics. All animals underwent surgery for implantation of a minipump or sham procedures. The rats were anesthetized with 1 to 2% isoflurane, and pumps were inserted into the subcutaneous space through a small incision on the back. All animals with drug-releasing minipumps received a daily injection of vehicle, whereas those that had undergone sham surgery received a daily injection of drug. The doses chosen for this multiple-dosing experiment were based on the dose that gave rise to clinically comparable D<sub>2</sub> occupancy under acute conditions and, where feasible, 5 times this dose. Although this was possible for haloperidol and olanzapine, we were not able to do it for risperidone due to nonavailability of sufficient quantities of the compound. With clozapine and quetiapine we ran into a dissolution/tolerability problem. To administer the 5-times single dose required concentrations in excess of 100 mg/ml drug in solution to be administered via the Alzet pump. Although such concentrations could be achieved by lowering the pH of the solvent into the range of 2 to 3, these low pH solutions led to tolerability problems when implanted subcutaneously for long periods of time. Thus, animals received pump delivery or daily injections of haloperidol (0.05 or 0.25 mg/kg), olanzapine (1.5 or 7.5 mg/kg), risperidone (1 mg/kg), quetiapine (10 or 25 mg/kg) or clozapine (7.5 or 15 mg/kg). Corresponding controls received sham surgery and daily vehicle injections. The experimental design is summarized in Fig. 1.

D<sub>2</sub> Occupancy Measurement. On the day of occupancy determination, the animals receiving daily injections of antipsychotic for 7 days were further split into two groups to examine the trough and peak occupancy levels. Animals that were assigned to the "trough" group were sacrificed at the time that they would have usually received their next injection (i.e., 24 h after last injection), while the animals in the "peak" group received a final injection on the seventh day and were sacrificed 1 h (clozapine and quetiapine groups) or 2 h (haloperidol, olanzapine, and risperidone groups) after drug administration.

Thirty minutes before sacrifice all animals received an i.v. injection of [3H]Raclopride (7.5 µCi/rat, in a volume of 0.4 ml of 0.9% NaCl solution) via the lateral tail vein. Animals were sacrificed by decap-
itation, and plasma was collected and stored at −80°C until drug levels could be assayed. The brains were immediately removed, and striata and cerebellum were rapidly dissected. The cerebellum was homogenized with a small spatula, and approximately one-third (50–100 mg) of this was sampled. The left and right striata were pooled into a single sample (60 mg). Tissue samples were collected in previously weighed 20-ml glass scintillation vials. The vials were then weighed with tissue, and 2 ml of Solvable (Canberra Packard Canada, Montreal, QC, Canada) was added. The vials were kept on an automated shaking tray and gently agitated for 24 h at room temperature. Thereafter, 5 ml of Aquasure (Canberra Packard Canada) scintillation fluid was added and allowed to mix for another 24 h. [3H]Raclopride radioactivity was determined by liquid scintillation spectrometry using a Beckman Coulter LS5000 CE liquid scintillation counting system (Beckman Coulter, Inc., Fullerton, CA). Striatal and cerebellar counts were obtained and expressed as dpm/mg.

The D₂ receptor binding potential (D₂BP) was obtained for each of the animals as (striatum dpm/mg − cerebellum dpm/mg)/(cerebellum dpm/mg). The receptor occupancy in each rat was then determined with reference to the D₂BP in the control group using the same formula as used in human studies (Farde et al., 1988; Kapur et al., 1999): % Occupancy = 100 × (D₂BPcontrol − D₂BPindiv/D₂BPcontrol). For further details on the protocol for receptor occupancy assessment and its validation versus [¹¹C]raclopride, see Wadenberg et al. (2000).

Drug Plasma Level Measurement. Plasma obtained from animals at the time of sacrifice for the occupancy studies detailed above was stored for analysis for drug levels. In general, drug levels were quantified using a liquid-liquid extraction to prepare the specimen for analysis. The samples obtained from liquid extraction were separated using liquid chromatography and then introduced into the mass spectrometer using electrospray ionization implemented using an HP 1100 LC-DAD-MSD system controlled by HP LC-MSD Chemstation software (Hewlett-Packard, Palo Alto, CA). As applied to haloperidol, the method has a lower limit of quantitation of 1 nM and a linearity limit of 212 nM with CV ranging from 3 to 10% across the dose range. Clozapine is detected with a lower limit of quantitation of 10 nM and a linearity limit of 6100 nM with CV ranging from 2 to 7% across the dose range. Risperidone is quantified with a lower limit of 1 nM and a linearity limit of 7200 nM with CV ranging from 2 to 7% across the dose range. Olanzapine was quantified with a lower limit of 5 nM and a linearity limit of 800 nM with CV ranging from 2 to 10% across the dose range. Quetiapine levels were quantified with a lower limit of 3 nM and a linearity limit of 2265 nM with quality control samples within ±10%.

Results

In single-dose models, the doses that were required to achieve 50% D₂ receptor occupancy (ED₅₀) are listed in Table 1. Based on these data, the estimated doses that would approximate the clinically comparable D₂ receptor occupancy are: haloperidol, 0.04 to 0.08 mg/kg s.c.; olanzapine, 1 to 2 mg/kg s.c.; risperidone, 0.5 to 1 mg/kg s.c.; quetiapine, 10 to 25 mg/kg s.c.; and clozapine, 5 to 15 mg/kg s.c. (Table 1 and Fig. 2).

The same doses administered repeatedly by injection achieved peak occupancy similar to human levels, but the trough occupancy at the end of the day was minimal and not at all comparable with what is seen in patients (Fig. 3). If the single therapeutic dose was administered daily via
minipump, the occupancies were stable through the day, but the average occupancies were much lower than clinically comparable therapeutic levels (see Fig. 3 for details). When administered by pump, a dose approximately 5 times higher than the single doses achieved stable therapeutic occupancies comparable with that seen in humans (Fig. 3 and Table 2): 0.25 mg/kg haloperidol, 7.5 mg/kg olanzapine. We were unable to examine the doses for quetiapine and clozapine that were 5 times higher than the representative single dose because it was not feasible to dissolve these concentrations without making the solutions too acidic for prolonged administration (for 100 mg/kg/day, the concentration required would be approximately 292 mg/ml).

Drug plasma levels reflected the same overall pattern as the occupancy data (Table 2). With the injection approach, the peak levels were very high, often multiple times higher than that seen in clinical conditions. However, this was accompanied by nearly undetectable trough levels, multiply lower than that seen in patients. When the “optimal” single dose was administered as a continuous infusion, the levels were often undetectable or unrepresentatively low (see Table 2 for details). Only when the drug was administered with a pump, at levels 5 times the representative single dose, were the levels close to that seen in clinical conditions at steady state.

**Discussion**

There are few studies that have systematically addressed the issue of antipsychotic dosing in animal models previously. Al-

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**TABLE 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>% D₂ Occupancy in Patients</th>
<th>Dose for 50% D₂ Occupancy In Rats</th>
<th>Dose for Clinically Comparable D₂ Occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>65–80</td>
<td>0.02 (0.016–0.024)</td>
<td>0.04–0.08</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>65–80</td>
<td>0.57 (0.42–0.72)</td>
<td>1–2</td>
</tr>
<tr>
<td>Risperidone</td>
<td>65–80</td>
<td>0.32 (0.16–0.48)</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>30–60</td>
<td>11.81 (8.59–15.03)</td>
<td>10–20</td>
</tr>
<tr>
<td>Clozapine</td>
<td>45–65</td>
<td>7.26 (2.24–12.27)</td>
<td>5–15</td>
</tr>
</tbody>
</table>

**Fig. 2.** Relationship between drug dose and D₂ receptor occupancy after single-dose subcutaneous administration. Shaded box depicts the occupancy range that corresponds to clinically comparable conditions. A, haloperidol; B, olanzapine; C, risperidone; D, quetiapine; E, clozapine.

**Fig. 3.** D₂ occupancy levels produced by daily injections (at trough or peak) or osmotic minipump. Intermittent daily injection does not result in sustained clinically relevant D₂ occupancy. D₂ occupancy comparable to the clinical condition is achieved with the minipump at approximately 5 times the clinically comparable single dose. Shaded box depicts the occupancy range that corresponds to clinically comparable conditions. A, haloperidol; B, olanzapine; C, risperidone; D, quetiapine; E, clozapine.
D2 occupancy in our study is 0.06 mg/kg, whereas it was 0.36 mg/kg in Zhang and Bymaster (1999). Both of these studies find the same relative dissociation of antipsychotic in the incubation bath (Kapur et al., 1999, 2000b,c; Nyberg and Farde, 2000; Bressan et al., 2001). Zhang and Bymaster (1999) injected the radiotracer subcutaneously, a route that does not establish equilibrium conditions in the short period of time (30 min) and is likely to underestimate occupancy (Olsson and Farde, 2001).

A simple approach using just the same milligram per kilogram dose in animals and humans would not work well (Tables 1 and 3). For example, in patients at steady state, a dose of 0.2 mg/kg/day olanzapine provides plasma levels in the range of 50 nM and a receptor occupancy of about 70%. Such a dose in the rats would provide neither adequate plasma levels nor significant occupancy. Conversely, in rats, 7.5 mg/kg/day, which leads to 430 nM in the plasma, is what leads to 70% occupancy. Such a dose in animals and humans would not work well (Tables 1 and 3). In contrast, Schotte et al. (1996) used an ex vivo autoradiography approach, an approach shown to be less sensitive due to the dissociation of antipsychotic in the incubation bath (Kapur et al., 2001). Though none have examined the issue of multiple-dosing, two studies have systematically determined dopamine D2 occupancy with single doses (Schotte et al., 1996; Zhang and Bymaster, 1999). Both of these studies find the same relative pattern of D2 occupancy as we did: the potency for D2 occupancy is haloperidol > risperidone/olanzapine ≫ clozapine ≫ quetiapine. However, the dose of haloperidol required to produce 75% D2 occupancy in our study is 0.06 mg/kg, whereas it was 0.36 mg/kg in Zhang and Bymaster (1999) and 0.6 mg/kg in Schotte et al. (1996), a difference of an order of magnitude. We believe that our estimates are more representative of the human condition because the method used (raclopride i.v. injection and in vivo competition) is identical to those used in humans (Kapur et al., 1999, 2000c; Nyberg and Farde, 2000; Bressan et al., 2001). However, none of these studies have systematically determined dopamine D2 occupancy with single doses (Schotte et al., 1996; Zhang and Bymaster, 1999). Both of these studies find the same relative pattern of D2 occupancy as we did: the potency for D2 occupancy is haloperidol > risperidone/olanzapine ≫ clozapine ≫ quetiapine. However, the dose of haloperidol required to produce 75% D2 occupancy in our study is 0.06 mg/kg, whereas it was 0.36 mg/kg in Zhang and Bymaster (1999) and 0.6 mg/kg in Schotte et al. (1996), a difference of an order of magnitude. We believe that our estimates are more representative of the human condition because the method used (raclopride i.v. injection and in vivo competition) is identical to those used in humans (Kapur et al., 1999, 2000c; Nyberg and Farde, 2000; Bressan et al., 2001). In contrast, Schotte et al. (1996) used an ex vivo autoradiography approach, an approach shown to be less sensitive due to the dissociation of antipsychotic in the incubation bath (Kapur et al., 2001). Zhang and Bymaster (1999) injected the radiotracer subcutaneously, a route that does not establish equilibrium conditions in the short period of time (30 min) and is likely to underestimate occupancy (Olsson and Farde, 2001).

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effective means to obtain valid and representative antipsychotic doses in animals.

Most importantly, even if one uses the dose that provides comparable single-dose effects, it does not lead to clinically comparable occupancies with multiple dosing. The half-life of the drugs is, on average, 4 to 6 times faster in rodents than in humans: haloperidol, rodent 1.5 h versus human 12 to 36 h (Cheng and Paalzow, 1992; Bezchlibnyk-Butler and Jefries, 1999); risperidone, rodent 1 h versus human 20 to 24 h (van Beijsterveldt et al., 1994; Bezchlibnyk-Butler and Jefries, 1999); olanzapine, rodent 2.5 h versus human 21 to 54 h (Aravagiri et al., 1997; Bezchlibnyk-Butler and Jefries, 1999);quetiapine, rodent 0.5 h versus human 6 to 7 h (Saller and Salama, 1993; Bezchlibnyk-Butler and Jefries, 1999); and clozapine, rodent 1.5 h versus human 5 to 16 h (Baldessarini et al., 1993; Bezchlibnyk-Butler and Jefries, 1999). For a certain peak concentration (occupancy), the trough is inversely proportional to the exponent of the half-life of the drug (Rowland and Tozer, 1995). Since animals have a 4 to 6 times shorter half-life, it is only to be expected that for similar peak levels/occupancies, the animals would show significantly lower trough levels/occupancies than those seen in humans.

Thus if one wishes to capture the same pattern of diurnal occupancies as in patients, a single daily injection cannot suffice. Since the human dosing intervals are of the order of one half-life, to obtain peak/trough effects similar to those in humans, the drugs would have to be administered to animals in six to eight equally spaced injections through the day. Since this is not a practical approach, we examined whether administering the drug through the pump may more closely approximate the human occupancies. However, if just the optimal single dose was administered only via the pump through the day, the occupancy level was much lower (and in several cases undetectable) than those associated with routine clinical treatment (Table 2). The ratio of the maintenance daily dose versus the single loading dose to obtain a certain plasma level is inversely proportional to the plasma half-life (Rowland and Tozer, 1995); this may explain why the average maintenance dose required is about 5 to 6 times the single dose.

Based on the foregoing considerations, we propose that the doses presented in Table 1 form a reasonably valid approximation of the clinical situation in single-dose rat models. Insofar as multiple dosing is concerned, we propose that only administration by pump (or administration more than four times a day) can provide clinical-like occupancies for haloperidol, olanzapine, and risperidone. Due to shear administration limitations, it is hard to achieve clinically comparable effects for quetiapine and clozapine, and indeed, none of the previous preclinical studies may have achieved them. We are only aware of one study that expressly addressed this issue through the use of repeated dosing via the addition of clozapine to drinking water (Schmitt et al., 1999). In this study, 40 mg/kg/day were delivered via drinking water, yet the serum concentrations for clozapine were only 22 ng/ml (whereas clinically comparable concentrations are in the range of 350 ng/ml, 12 h after last dose), thus pointing to the limitation of this method of delivery, even though the nominal dose may seem reasonably high. Therefore, multiple-dosing studies of quetiapine and clozapine should be interpreted with caution, especially where they claim to be a representative model for the clinical condition.

Limitations of our data as well as its implications are outlined next. First, we observed that animals treated with 10 mg/kg/day quetiapine multiple dosing using the daily injection approach showed no detectable D₂ occupancy, even at peak (Table 2). This is a surprising finding given that when a single injection of the same dose is administered, it leads to 50% occupancy at peak. Furthermore, this dose showed a plasma level consistent with expectation (469 nM), and the next higher dose (25 mg/kg/day) showed occupancy (78%) and plasma levels (913 nM) also consistent with expectation. Although it is conceivable that multiple dosing may lead to changes in disposition that may account for this, a more likely explanation is that this result represents experimental error.

In a strict sense, the doses proposed here (Table 1) are only valid for the species studied (young Sprague-Dawley male rats) and the route of administration (subcutaneous). One would have to be cautious in extrapolating across species and strains, since pharmacokinetic differences are noted between them. Furthermore, one would have to be cautious in extrapolating across routes (s.c. versus oral or i.p.) because different first-pass and other metabolic considerations could change these optimal doses. Nonetheless, the general approach outlined here could be used for deriving the right estimates for these different strains and routes of administration. A limitation to this method of deriving optimal preclinical dosing of antipsychotics is that it is (and will be) relevant only for the current generation of atypical and typical antipsychotics, which have a significant level of D₂ occupancy in patients. As new drugs are developed, which totally avoid the D₂ receptors, obviously such an approach would not work. However, one could hope that once such new targets are developed, similar equivalent occupancy studies could be done across humans and animals to confirm the valid doses. Finally, we do not see the restricted optimal ranges we provide in Table 1 as a substitute for doing complete dose-response relationship studies. The ideal way to understand the findings in animal models still remains the complete dose-response relationship study; however, the ranges presented here will be important in interpreting the dose-response relationships into a clinical context.

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References


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