Clinical Relevance of Relative Receptor Binding Affinity: Quetiapine and Ziprasidone as Examples

SHELDON H. PRESKORN, MD

The last column in this series on antipsychotics focused on the early history of antipsychotics, from reserpine and chlorpromazine to haloperidol. This column returns to the issue of relative binding affinity, which was first discussed with reference to antidepressants in a column almost a decade ago. The focus of this column will be antipsychotics, using quetiapine and ziprasidone as examples to illustrate the clinical relevance of relative receptor binding affinity. This discussion will set the stage for subsequent columns that will discuss the concept of “atypical” antipsychotics.

The regular reader will recognize Equations 1 and 2 (see next page), which are hallmarks of this column. Equation 1 shows that the effect of any drug is a function of three variables: 1) its affinity for and intrinsic activity at one or more sites of actions (almost always a regulatory protein), 2) the concentration achieved at that (or those) site(s) of action, and 3) the specific biology of the patient being treated. Equation 2 specifies that the concentration achieved at that (or those) site(s) of action is in turn determined by the dosing rate going into the patient divided by the ability of that specific patient to clear the drug from his or her body.

Relative binding affinity

Relative binding affinity is the ratio of the concentration of the drug needed to bind to the site of action for which it has highest affinity in comparison to the concentration needed to bind to a site (or sites) of action for which it has lower affinity. The larger the ratio, the more likely that the drug is selective (i.e., has effects that are directly mediated by only one site of action). The smaller the ratio, the more likely that the same dose or concentration of the drug will have effects mediated by different sites of action. Between these two extremes are drugs whose effects change in nature as their dose, and hence their concentration, is increased, as will be illustrated in this column using the examples of quetiapine and ziprasidone.

Binding affinity (Kᵢ) is the concentration of a drug needed to bind to 50% of a site of action. Over the last several decades, the methodology of in vitro binding affinity studies has been refined. Briefly, these studies involve putting a receptor or other site of action in a test tube and “tagging” it with a high affinity radioactively labeled ligand (or drug). Next, the drug whose binding for that receptor is being quantified (i.e., the drug of interest) is added in increasing concentrations to a series of test tubes containing an identical amount of the tagged site of interest. As the concentration of the nonlabeled drug of interest increases, it occupies the site of action by displacing the radioactive labeled ligand. The percent occupancy of the site of action that is achieved by a given concentration of the “cold” drug of interest (i.e., the drug that is not radioactively labeled) can then be measured as the reduction in radioactivity bound to the site of interest after a standardized period of incubation. The different percentages of occupancy can then be plotted as a function of the different concentrations of the drug added to the test tubes, and the affinity of the drug of interest for the site of interest can thus be determined.

This type of experiment can be done for many different drugs that affect the same site of interest (i.e., to determine the relative binding affinities of different drugs for the same site of action) or for different sites of action for the same drug (i.e., to determine the relative binding affinities of the same drug for different sites of action). Both types of results can be used to determine the structure-activity relationship relevant to either high affinity and/or selectivity for a site of action. That information can in turn be used to “discover” or synthesize new compounds that either have higher affinity or...
greater selectivity for a given site of action. Further discussion of this topic is beyond the scope of this column, but it has been addressed in an earlier series of columns on the human genome project and drug discovery in psychiatry.4

Two different measures have been used to quantify binding affinity. These are the inhibition concentration at 50% maximum (IC$_{50}$) and the kinetic dissociation constant (K$_d$). The latter is now the preferred measure but readers may still encounter the previous term. Hence, a brief discussion of the relationship between these two terms is given here. Figure 1 shows the IC$_{50}$ plot. As the concentration of the drug increases, it binds to various sites of action. Figure 1 illustrates the in vitro binding affinity of ziprasidone for two different sites of action: the serotonin (5-hydroxytryptophan) 2A (abbreviated 5-HT$_{2A}$) receptor and the dopamine-2 (D$_2$) receptor. The 50% position on the curve (the IC$_{50}$) has traditionally been chosen as the reference point because it is on the steepest portion of the curve and hence is the most reproducible and sensitive. Equation 3 shows that the IC$_{50}$ is identical to the K$_d$ as long as the concentration of the radio-ligand used in the assay is kept very low relative to the binding affinity of the drug of interest for its target(s). The IC$_{50}$ concept is still useful because it may more intuitively explain for the clinician the concentration-dependent nature of the occupancy of the target. That in turn relates back to Equations 1 and 2 and explains why both dose and clearance are equally important when determining the clinical response of a patient to a given drug.

**Table 1. Binding affinity of selected antipsychotics for specific neuroreceptors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>D$_2$</th>
<th>5-HT$_{2A}$</th>
<th>$\alpha_1$</th>
<th>$H_1$</th>
<th>$M_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>0.34*</td>
<td>3.4*</td>
<td>57</td>
<td>61*</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>Clozapine</td>
<td>126</td>
<td>16</td>
<td>7</td>
<td>6</td>
<td>1.9</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.7</td>
<td>45</td>
<td>6</td>
<td>440</td>
<td>&gt;1,500</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>11</td>
<td>4</td>
<td>19</td>
<td>7</td>
<td>1.9</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>160</td>
<td>295</td>
<td>7</td>
<td>11</td>
<td>120</td>
</tr>
<tr>
<td>Risperidone</td>
<td>4</td>
<td>0.5</td>
<td>0.7</td>
<td>20</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>5</td>
<td>0.4</td>
<td>11</td>
<td>50</td>
<td>&gt;1,000</td>
</tr>
</tbody>
</table>

Data represented as K$_d$ (nM); *Data with cloned human receptors

**Equation 1**

\[
\text{Clinical response} = \text{Affinity for and intrinsic activity at the site of action (pharmacodynamics)} \times \text{Drug concentration at site of action (pharmacokinetics) (ADME)} \times \text{Underlying biology of patient (GADE)}
\]

- Absorption
- Distribution
- Metabolism
- Elimination
- Genetics
- Age
- Disease
- Environment

**Equation 2**

\[
\text{Concentration} = \text{dosing rate} / \text{clearance}
\]

**Equation 3**

\[
K_d = \frac{IC_{50}}{1 + [(\text{ligand}) / K_d]}
\]

If [ligand] <<<< K$_d$ then K$_d$ = IC$_{50}$

**Equation 4**

\[
\text{Relative binding affinity} = \frac{K_d \text{ for lower affinity sites}}{K_d \text{ for highest affinity site}}
\]

**Binding affinities of various antipsychotics**

Table 1 will be familiar to many, if not all, readers. It shows the binding affinities of a number of antipsychotics relative to a series of receptors of either established or presumed clinical relevance. The receptors with known clinical relevance include the D$_2$, histamine-1 ($H_1$), muscarinic-1 acetylcholine ($M_1$), and alpha-1 norepinephrine ($\alpha_1$) receptors. In contrast, the 5-HT$_{2A}$ receptor is thought to be of clinical relevance, but a recent survey of experts in this area found that there was no consensus as to precisely what clinical effects this receptor mediates.12 (For more discussion of this topic, readers are referred to a recently published supplement in the *Journal of Clinical Psychiatry*.)
To fully appreciate the clinical relevance of Table 1, one must consider the concept of relative binding affinity. Relative binding affinity again refers to a drug's relative affinity for a series of different binding sites, with the point of reference being the target for which it has the highest affinity (i.e., the smallest affinity value) (Equation 4).4

To illustrate how this concept works in clinical practice, Table 2 shows the relative binding affinities for quetiapine and ziprasidone calculated using the data in Table 1 and the formula in Equation 4. (Interested readers can calculate the relative binding affinities for the other drugs listed in Table 1 if they wish.) Relative binding affinities are useful when one wants to examine the properties of a single drug rather than comparing the effects of different drugs, because each value is relative to that drug's highest affinity target.

Based on the discussion above, it should be clear that binding affinity is a concentration-dependent term (i.e., variable 2 in equation 1). Concentration, in turn, is determined by the dosing rate divided by the patient's ability to clear the drug. The ratios of the drug's binding affinity for its most potent site of action to its affinity for other secondary sites of action explain how much the concentration of the drug has to be increased before those additional sites of action come into play in determining the overall clinical effect of the drug, as shown in Figure 1. The drug illustrated in Figure 1 is 10 times more potent in binding to the site for which it has the highest affinity than in binding to the site for which it has the next highest affinity. For such a drug to have an effect mediated by the site of action for which it has the next highest affinity, the dose has to be increased or the clearance reduced sufficiently to produce a concentration 10 times higher than is needed for the drug to produce effects mediated by the site of action for which it has the highest affinity. Quetiapine and ziprasidone are examples of such antipsychotics and are used here to illustrate the clinical relevance of relative binding affinity.

The relative binding affinity of quetiapine and ziprasidone for the sites of action listed in Tables 1 and 2 is illustrated graphically in Figure 2. This type of plot complements Figure 1 by visually illustrating how much the concentration of each drug has to be increased (via either a dose increase or a reduction in clearance) for the drugs to engage sites of action for which they have a lower affinity.

**Relative binding affinity as illustrated by quetiapine**

As shown in Figure 2 and Table 2, the site for which quetiapine has the highest affinity is the alpha-1 receptor followed closely by the H1 receptor. The concentration of quetiapine needed to block D2 receptors is approximately 15 times that needed to block H1 receptors. This relative binding affinity is consistent with the clinical dose-response relationships seen with quetiapine.

Quetiapine is frequently used at low doses (e.g., 50–100 mg) at night to help individuals sleep. At these doses, quetiapine is not an antipsychotic but rather an hypnotic. This is consistent with the fact that these doses exert an antihistaminic effect but not an antidopamine effect at the D2 receptor.
As a general rule, positron emission tomography (PET) studies have shown that at least 50% occupancy of D₂ receptors is needed to produce an antipsychotic effect. Therefore, to achieve an antipsychotic effect with quetiapine, either the dose has to be increased by approximately 10-fold (i.e., to 500 mg/day or higher) or the clearance of quetiapine has to be comparably reduced, consistent with the difference in the relative binding affinity of quetiapine for the D₂ versus the H₁ receptor. To date, all drugs that are effective antipsychotics have the ability to blockade D₂ receptors at antipsychotic doses or concentrations.

In essence, when quetiapine is given at a dose of 50–100 mg at night, it is an antihistaminic agent rather than an antipsychotic, despite its therapeutic classification—it does not become an antipsychotic until higher concentrations are achieved. Thus, low-dose (i.e., 50–100 mg/day) quetiapine added to an antipsychotic dose of a drug such as risperidone does not represent the concurrent use of two antipsychotics but rather the combination of an antihistaminic agent with an antipsychotic.

Interested readers are referred to an earlier column for a discussion of the four ways that drugs can be classified: a) structurally, b) pharmacodynamically, c) pharmacokinetically, and d) therapeutically. That column made the point that the therapeutic classification of psychiatric medications is less important clinically than their pharmacodynamic and pharmacokinetic classifications because those latter attributes determine the clinical effects of the drug when used alone or in combination with other drugs, as illustrated in Equation 1.

Parenthetically, from a pharmacokinetic standpoint, quetiapine is principally a substrate for cytochrome P450 (CYP) 3A, which determines its clearance. With that knowledge, the reader can accurately predict that the clearance of quetiapine will be reduced when it is co-administered with a CYP 3A inhibitor such as ketoconazole and will be increased when it is co-administered with a CYP 3A inducer such as carbamazepine. Based on a formal in vivo drug-drug interaction (DDI) study, co-administration of ketoconazole 200 mg/day for 4 days will increase plasma concentrations of quetiapine 3.35-fold and co-administration of carbamazepine 600 mg/day for 14 days will decrease plasma concentrations of quetiapine by 80%. The regular reader of this column will understand that the consequences of these changes are comparable to what would happen if the dose of quetiapine was increased 3.35-fold or reduced 80%, respectively. The consequences of such pharmacokinetic DDIs have been discussed in several earlier columns.

Relative binding affinity as illustrated by ziprasidone

The binding site for which ziprasidone has the highest potency is the 5-HT₂A receptor, while its binding affinity...
for the D₂ receptor is 10 times less (Figure 2).¹¹ Although the reader may wonder whether this in vitro difference in binding affinity holds up in clinical reality, this question has been addressed with regard to ziprasidone using PET. In essence, the same approach used in the in vitro binding studies described above can be used in vivo using PET to assess the ability of a given drug to occupy different receptors at different concentrations. In these studies, a ligand is labeled with a positron emitting radioisotope that is given intravenously to the subject. The ligand then binds to the site of interest (e.g., a specific receptor) and the number of receptors so labeled can be measured using PET. Then, the non-labeled (i.e., “cold”) drug of interest is given and its concentration-response curve for occupying the site of interest can be measured by the displacement of the radioisotope ligand and analogous to what is done in the in vitro binding assay, except the measurement is being made in a living individual under clinically relevant dosing conditions.

Figure 3 illustrates the results of just such an experiment with ziprasidone. In this study, one radio-labeled ligand was used to mark the 5-HT₂A receptors and another to mark the D₂ receptors. The results are expressed as the occupancy of these two different receptors as a function of the concentration of ziprasidone. The curves illustrate that the in vitro difference in relative binding affinity of ziprasidone for the 5-HT₂A and D₂ receptors holds up in vivo. At low doses and hence low concentrations, ziprasidone substantially occupies 5-HT₂A but not D₂ receptors in the human brain. However, as the dose and hence concentration of ziprasidone are increased, it begins to occupy D₂ receptors.

This differential occupancy is relevant to the clinical effects of ziprasidone. At low oral doses (20–40 mg), ziprasidone has little or no antipsychotic effect.²⁰,²¹ As the dose of ziprasidone is increased, the occupancy of D₂ receptors increases and the antipsychotic efficacy of ziprasidone becomes manifest. As noted above, PET studies with a variety of antipsychotics have shown that at least 50% occupancy of D₂ receptors is needed to produce an antipsychotic effect. The average concentration of ziprasidone needed to produce 50% occupancy of D₂ receptors is 120 mg/day.²²

At a dose of 160 mg/day taken within 2 hours of a meal consisting of at least 500 calories irrespective of fat content, the concentration of ziprasidone does not drop below the concentration needed to produce 50% occupancy.²³ This result is consistent with efficacy trials of ziprasidone that have shown antipsychotic efficacy at a dose of 160 mg/day.²⁰,²¹ In fact, meta-analyses of the ziprasidone clinical trials show that the antipsychotic efficacy of ziprasidone at doses of 120–160 mg/day is superior to its efficacy at doses of 40–80 mg/day.²¹

Some clinicians have reported that low doses of ziprasidone can activate patients with chronic psychiatric illnesses such as schizophrenia without reducing their psychosis. This “activation” could be consistent with unopposed 5-HT₂A receptor blockade. In such a case, the relative binding affinity of ziprasidone would suggest a strategy—increasing the dose of the activating drug—that might seem paradoxical, since one might anticipate getting even more activation at a higher dose. However, based on the findings described here, it is clear that increasing the dose of ziprasidone will lead to meaningful D₂ receptor blockade, which in turn will produce antipsychotic effects and moderate the activation, so that the strategy is not paradoxical at all. Moreover, this strategy is supported by the clinical trial results reviewed above.²⁰,²¹

Conclusion
Relative binding affinity is an important pharmacological principle for clinicians to understand regardless of the therapeutic class of drug being used. Armed with this knowledge, clinicians can better understand dose-response relationships and better tailor their treatment to the specific patient. They will have fewer failed pharmacologic trials and be better able to interpret what their patients’ responses to medication really mean. This pharmacological principle is also relevant to the clinical utility of measuring plasma concentrations of drugs and adjusting the dose accordingly as well as understanding why CYP enzyme-mediated DDIs can cause patients to appear to be “sensitive” (i.e., due to reduced clearance and hence higher than expected con-
centrations) or “resistant” (i.e., due to increased clearance and hence lower than expected concentrations) to a given dose of a given drug.

References