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A comparison of the receptor binding and HERG channel affinities for a series of antipsychotic drugs

Sathapana Kongsamut, Jiesheng Kang, Xiao-Liang Chen, Joachim Roehr, David Rampe *

Aventis Pharmaceuticals, Inc., Mail Code: EM-A1A, Route 202-206, P.O. Box 6800, Bridgewater, NJ 08807-0800, USA

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Abstract

Many antipsychotic drugs produce QT interval prolongation on the electrocardiogram (ECG). Blockade of the human cardiac K^+ channel known as *human ether-a-go-go*-related gene (HERG) often underlies such clinical findings. In fact, HERG channel inhibition is now commonly used as a screen to predict the ability of a drug to prolong QT interval. However, the exact relationship between HERG channel blockade, target receptor binding affinity and clinical QT prolongation is not known. Using patch-clamp electrophysiology, we examined a series of seven antipsychotic drugs for their ability to block HERG, and determined their IC_{50} values. We then compared these results to their binding affinities (K_i values) for the dopamine D_2 receptor, the 5-HT_{2A} receptor and, where available, to clinical QT prolongation data. We found that sertindole, pimozide and thioridazine displayed little (< 10-fold) or no selectivity for dopamine D_2 or 5-HT_{2A} receptors relative to their HERG channel affinities. This lack of selectivity likely underlies the significant QT interval prolongation observed with administration of these drugs. Of the other drugs tested (ziprasidone, quetiapine, risperidone and olanzapine), olanzapine displayed the greatest selectivity for dopamine D_2 and 5-HT_{2A} receptor binding (100–1000-fold) compared to its HERG channel IC_{50}. We also compared these HERG channel IC_{50} values to QT interval prolongation and plasma drug levels obtained in a recent clinical study. We found that the ratio of total plasma drug concentration to HERG IC_{50} value was indicative of the degree of QT prolongation observed. Target receptor affinity and expected clinical plasma levels are important parameters to consider for the interpretation of HERG channel data.

Keywords: HERG channel; Antipsychotic; Arrhythmia; QT prolongation; K^+ channel

1. Introduction

Voltage-dependent K^+ channels play an important role in the repolarization of the human myocardium and therefore are important determinants of the QT interval on the electrocardiogram (ECG). Advances in molecular biology and cellular electrophysiology have led to the cloning and characterization of several human cardiac K^+ channels. For example, KvLQT1 is known to complex with the minK subunit to form the K^+ channel that carries the slow component of the delayed rectifier, I_{Ks}, in the human heart (Barhanin et al., 1996; Sanguinetti et al., 1996). The *human ether-a-go-go*-related gene (HERG) carries the rapid component of the delayed rectifier, I_{Kr}, in the human heart (Sanguinetti et al., 1995). The HERG cardiac K^+ channel is now playing an increasingly important role in the drug development process. This is due to the fact that many medications have been shown to block this channel with high specificity, and to do so at therapeutically relevant concentrations (Brown and Rampe, 2000). These interactions can result in a prolongation of the QT interval on the electrocardiogram, a condition that may contribute to the generation of ventricular arrhythmias like torsades de pointes (Ben-David and Zipes, 1993). This drug-induced (or acquired) long QT syndrome has lead to the withdrawal of several marketed products for safety reasons. These include the antihistamines terfenadine and astemizole (Roy et al., 1996; Zhou et al., 1999) and the gastric prokinetic agent cisapride (Rampe et al., 1997; Mohammad et al., 1997).

Antipsychotic drugs represent a chemically diverse group of compounds. However, all of these drugs are believed to derive at least some of their therapeutic efficacy via blockade of dopamine D_2 receptors, 5-HT_{2A} receptors, or both

* Corresponding author. Tel.: +1-908-231-3078; fax: +1-908-231-2520.
E-mail address: david.rampe@aventis.com (D. Rampe).

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(Schotte et al., 1996; Arnt and Skarsfeld, 1998; Richelson, 1999). Unfortunately, many of these drugs also share a tendency to prolong QT interval. As with other medications, it is likely that the drug-induced QT prolongation observed with antipsychotics involves the inhibition of the HERG cardiac K^+ channel. Pimozide and sertindole, for example, have previously been shown to block HERG in the low nanomolar range (Rampe et al., 1998; Kang et al., 2000). The present study was undertaken to determine the HERG channel affinity of seven distinct antipsychotic drugs. These data were then compared to the affinity each drug displayed on the dopamine D_2 and 5-HT_{2A} receptors, respectively. Finally, for most of these drugs, we compared our HERG channel affinity data to the drug plasma levels and QT prolongation reported in a clinical trial, Study 054, recently presented to the Food and Drug Administration (FDA).

2. Material and methods

2.1. Molecular biology and cell culture

The cDNA encoding the HERG K^+ channel was isolated and transfected into Chinese hamster ovary cells (CHO cells, American Type Culture Collection, Manassas, VA) as described previously (Rampe et al., 1997; Kang et al., 2000). Cells were grown in Ham's F-12 media supplemented with 10% fetal bovine serum and G418 (Geneticin, 500 μg/ml) in an atmosphere of 95% air/5% CO_2. Cells used for electrophysiology experiments were seeded onto plastic coverslips 12–24 h before use.

Human 5-HT_{2A} and dopamine D_2 receptors were stably expressed into baby hamster kidney (BHK) and CHO cells, respectively (American Type Culture Collection) as described previously (Kongsamut et al., 1996). The dopamine D_2 receptor was isolated from a human striatal cDNA library and subcloned into the expression vector pRC/RSV (Invitrogen). The 5-HT_{2A} receptor was isolated from a human substantia nigra cDNA library. BHK cells were grown in Dulbecco's Modified Eagle's Medium containing 10% fetal bovine serum albumin, 1% penicillin–streptomycin, 1% Na-pyruvate, and G418 (400 μg/ml). CHO cells expressing the human dopamine D_2 receptor were maintained in Ham's F12 containing 10% fetal bovine serum, penicillin/streptomycin (100 U/ml and 100 μg/ml), and G418 (400 μg/ml). Cells were harvested by mechanical scraping, washed in phosphate-buffered saline, spun down, resuspended in dH_2O, aliquoted in dH_2O with 10% dimethyl sulfoxide (DMSO), and stored in a −80 °C freezer until used. Protein was determined using the method of Lowry (Biorad DC Assay Kit).

2.2. Electrophysiology

HERG channel currents were recorded using the whole-cell configuration of the patch-clamp technique (Hamill et al., 1981). Electrodes (3–6 MΩ resistance) were fashioned from TW150F glass capillary tubes (World Precision Instruments, Sarasota, FL). Electrodes were filled with the following solution: 120 mM potassium aspartate, 20 mM KCl, 4 mM Na_2ATP, 5 mM HEPES, 1 mM $MgCl_2$, pH 7.2 with KOH. The external solution contained 130 mM NaCl, 5 mM KCl, 2.8 mM sodium acetate, 1.0 mM $MgCl_2$, 10 mM HEPES, 10 mM glucose, 1.0 mM $CaCl_2$, pH 7.4 with NaOH. Currents were recorded at room temperature using an Axopatch 200 B amplifier (Axon Instruments, Foster City, CA) and were conditioned by a four-pole, low-pass filter with a cutoff frequency of one-half to one quarter of the sampling frequency. Currents were analyzed using the pCLAMP suite of software (Axon Instruments). IC_{50} values were obtained by nonlinear least-squares fit of the data (GraphPAD Software, San Diego, CA).

2.3. Radioligand binding

Radioligand binding assays followed previously published methods (Kongsamut et al., 1996). Briefly, membranes from cells expressing human 5-HT_{2A} or dopamine D_2 receptors were thawed, homogenized, and diluted to the appropriate protein concentration (~ 50 μg/well). Incubations were carried out in a buffer containing 50 mM Tris–HCl, 120 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$ pH 7.4 at 37 °C for 40 and 60 min for 5-HT_{2A} and dopamine D_2 receptors, respectively, and were terminated by vacuum filtration through GF/B unifilter plates (Packard) using a TomTec Harvester 96. [^{3}H]*N*-methylspiperone was used as the radioligand for both receptors. All K_i values are the mean of 3 to 6 determinations in duplicate. Specific binding was defined as the difference between total binding and binding in the presence of 30 μM methysergide (for 5-HT_{2A}) and 10 μM eticlopride (for dopamine D_2). %Specific binding was >90% for both receptors. IC_{50}'s were calculated using a one-site, non-linear curve analysis program (ActivityBase, IDBS), and K_i's were calculated according to the Cheng–Prusoff equation using the K_D values of 0.92 nM for 5-HT_{2A} and 0.09 nM for dopamine D_2 receptors, respectively (Cheng and Prusoff, 1973).

2.4. Chemicals

Drugs used in this study were obtained from Research Biochemicals International (Natick, MA) or synthesized at Aventis Pharmaceuticals. All other compounds were obtained from Sigma (St. Louis, MO).

3. Results

Fig. 1 shows the effects of various antipsychotic agents on HERG K^+ channel currents. In these experiments, cells were held at −80 mV and depolarized to +20 mV for 2 s. This was followed by repolarization of the cell to −40 mV

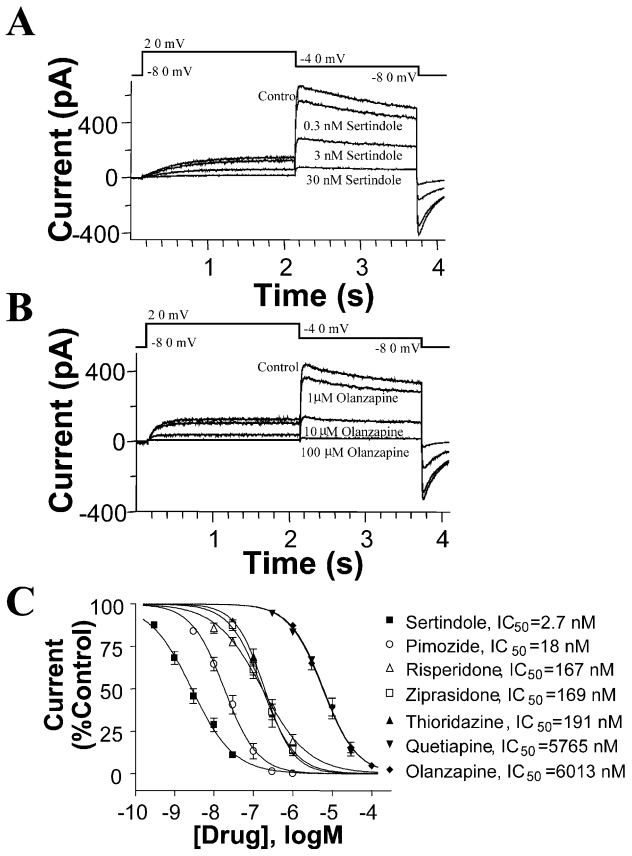

Fig. 1. Effects of antipsychotic drugs on HERG. Whole-cell HERG currents were elicited by 2-s depolarizing pulses to +20 mV from a holding potential of −80 mV. The membrane potential was then returned to −40 mV to generate large outward tail currents. The effects of sertindole and olanzapine are shown in A and B, respectively. In C, the dose–response relationships for all the antipsychotic drugs tested are shown. Inhibition of peak outward tail currents at −40 mV was used to generate the dose–response curves. Data for pimozide were taken from Kang et al. (2000). Error bars denote S.E.M. (n=4–6).

to produce large, slowly inactivating tail currents typical of HERG (Sanguinetti et al., 1995). The effects of sertindole, which displayed the highest affinity for HERG of all the drugs tested, are shown in Fig. 1A. The effects of olanzapine, the drug with the lowest affinity for HERG, are shown in Fig. 1B. All of the antipsychotic drugs tested reduced peak tail current amplitude measured at −40 mV in a dose-dependent manner, but with very different potencies. Dose–response relationships (Fig. 1C) generated from this protocol yielded IC_{50} values (95% confidence limits) as follows: sertindole, 2.7 nM (2.1–3.5 nM); pimozide, 18 nM (14–22 nM); risperidone, 167 nM (128–215 nM); ziprasidone, 169 nM (133–212 nM); thioridazine, 191 nM (162–224 nM); quetiapine, 5765 nM (4688–7079 nM) and olanzapine 6013 nM (5140–7030 nM).

Table 1 compares the affinities (K_i values) of these antipsychotic drugs for the human dopamine D_2 and human 5-HT_{2A} receptors, to their HERG channel IC_{50}'s. The K_i values reported here are similar to those reported previously for binding to these two receptors (Schotte et al., 1996; Richelson, 1999). One exception was quetiapine, which, in our hands, was 5–10-fold less potent on the 5-HT_{2A} receptor than previously reported. The rank order of potency of these drugs on the dopamine D_2 receptor was not the same as that seen for HERG. Several drugs, most notably sertindole, pimozide and thioridazine displayed little selectivity for dopamine D_2 receptors versus HERG (<10-fold) while olanzapine displayed the most selectivity of all the drugs tested (ca. 200-fold). Selectivity for quetiapine was not calculated due to its lack of affinity for the dopamine D_2 receptor (Richelson, 1999). Similarly, the rank order of potency of these antipsychotic drugs for the 5-HT_{2A} receptor was not the same as that derived for HERG. Once again it was seen that sertindole, pimozide and thioridazine displayed little, if any, selectivity for the 5-HT_{2A} receptor versus HERG, while olanzapine displayed the most selectivity.

Table 2 compares HERG affinity to pharmacokinetic (C_{max}) and pharmacodynamic (QT_c prolongation) parameters obtained in a recent clinical study (Study 054) of several antipsychotic drugs (Anonymous, 2000). The clinical data presented in Table 2 were obtained (through Freedom of Information) from a briefing document presented to the FDA Psychopharmacological Drugs Advisory Committee. In this study, changes in the corrected QT interval were measured at the time of peak plasma levels of the drugs. Corrected QT values were used since all the drugs listed here increased heart rate with the greatest increase associated with quetiapine (11 beats per minute increase). We used QT_c data corrected by Fridericia's formula as it was in close association with five other correction methods tested including Hodges, Framingham and baseline correction methods

Table 1
Comparison of HERG channel, dopamine D_2 and 5-HT_{2A} affinities for antipsychotic drugs

Drug	HERG IC_{50}, nM	D_2 K_i mean ± S.E., nM (N)	HERG IC_{50}/D_2 K_i	5-HT_{2A} K_i mean ± S.E., nM (N)	HERG IC_{50}/5-$HT_{2A}K_i$
Sertindole	3	6.55 ± 1.06 (5)	0.46	0.60 ± 0.08 (3)	4.97
Pimozide	18	11.70 ± 2.50 (6)	1.54	77.70 ± 6.32 (6)	0.23
Risperidone	167	2.70 ± 0.40[a]	61.85	1.10 ± 0.20[a]	151.82
Ziprasidone	169	8.50 ± 0.78 (6)	19.88	0.50 ± 0.11 (3)	338.00
Thioridazine	191	26.70 ± 4.29 (3)	7.15	42.30 ± 3.11 (5)	4.52
Quetiapine	5765	>1000 (2)	–	427.0 ± 44.7 (7)	13.50
Olanzapine	6013	31.80 ± 5.30 (4)	189.09	2.65 ± 0.25 (3)	2269.06

[a] From Kongsamut et al. (1996).

Table 2
Comparison of QT_c changes, HERG IC_{50} and plasma concentrations for various antipsychotic drugs[a]

Drug	ΔQT_c (ms)[b]	HERG IC_{50} (nM)	[Total plasma] (nM)	[Free plasma][c] (nM)	[Total plasma]/ HERG IC_{50}	[Free plasma]/ HERG IC_{50}
Thioridazine	29.6	191	2064	20.6	10.8	0.11
Ziprasidone	15.5	169	414	4.1	2.4	0.02
Quetiapine	4.8	5765	3329	566	0.6	0.10
Risperidone	3.0	167	143	14.3	0.9	0.09
Olanzapine	1.1	6013	176	12.3	0.03	0.002

[a] Clinical data from FDA Psych-pharmacological Advisory Committee Meeting, July 19th, 2000. Briefing document for Zeldox capsules.
[b] QT correction by Fridericia Formula.
[c] Percent plasma protein binding from manufactures' product information: Thioridazine, 99%; Ziprasidone, ca. 99%; Quetiapine, 83%; Risperidone, 90%; Olanzapine, 93%.

(but not Bazett's). As Table 2 indicates, when the ratio of total plasma drug concentration to HERG IC_{50} is calculated, a good correlation between this value and prolongation of QT_c is observed. Conversely, when this same comparison is applied using free drug levels (i.e. drug not bound to plasma proteins), no such correlation was observed.

4. Discussion

Due to its association with potentially fatal ventricular arrhythmia, drug-induced long QT syndrome is now a major safety concern for the pharmaceutical industry. It is becoming increasingly apparent that most drugs that prolong cardiac repolarization do so by blocking the HERG cardiac K^+ channel (Brown and Rampe, 2000). This has led to the use of HERG channel testing as an important, and now common, safety screen in the drug development process. However, a number of questions regarding the interpretation of data obtained from this screen remain. For instance, what degree of selectivity between the target receptor and HERG should be considered acceptable? How does HERG affinity measured in vitro relate to QT prolongation in clinical studies? The present report makes some of these comparisons using seven clinically available antipsychotic drugs.

The human dopamine D_2 and 5-HT_{2A} receptors were used as the in vitro counter-screens to HERG since it is generally believed that the antipsychotic compounds used in this study derive their therapeutic efficacy from binding to one, or more often both, of these receptors (Schotte et al., 1996; Kongsamut et al., 1996; Richelson, 1999). One finding that clearly stands out from these in vitro data is that pimozide, thioridazine and sertindole display little (<10-fold) or no selectivity for these receptors compared with their affinity for HERG. It is not surprising then that each of these drugs is associated with a clinical long QT liability. Thus, pimozide prolongs QT interval at therapeutic doses and may be associated with the development of torsades de pointes arrhythmia (Fulop et al., 1987; Krahenbuhl et al., 1995). Likewise, thioridazine and sertindole are also associated with significant QT prolongation in clinical use (Campbell et al., 1999; Buckley and Sanders, 2000; Glassman and Bigger, 2001). This has led to a "black box" warning from the FDA for thioridazine and withdrawal from marketing for sertindole, both due to these cardiovascular safety concerns. We therefore believe that drugs which display little selectivity (defined here as <10-fold) between their target receptor(s) affinity and their HERG channel IC_{50} value will be unlikely to divorce therapeutic efficacy from significant QT prolongation in the clinic.

The other drugs tested in this study displayed varying degrees of selectivity for dopamine D_2 and 5-HT_{2A} receptors compared to HERG. Thus, although quetiapine is a rather weak inhibitor of HERG (IC_{50} about 6 μM), its correspondingly weak activity at the 5-HT_{2A} receptor results in a selectivity ratio of about 14. A similarly low selectivity is noted for ziprasidone at the dopamine D_2 receptor. On the other hand, risperidone, and especially olanzapine, display the greatest degree of selectivity when the affinities for both dopamine D_2 and 5-HT_{2A} receptors are compared to that of HERG. Based upon in vitro criteria alone, it would be expected that olanzapine would have the least potential to produce QT prolongation in clinical settings.

In addition to HERG channel/receptor affinities, pharmacokinetic considerations will also determine the potential for a drug to prolong QT interval. Study 054, presented to the U.S. Food and Drug Administration (Anonymous, 2000), has examined the relationship between plasma levels and QT prolongation for five of the compounds used in this report. To these data we have added our HERG channel IC_{50}'s in order to find a relationship between this in vitro data and these clinical results (Table 2). For this limited series of drugs, the ratio of total plasma concentration to HERG IC_{50} appeared to correspond well with the observed changes in QT_c. This ratio ranged from approximately 11 for thioridazine (which displayed an almost 30 ms prolongation in QT_c) down to 0.03 for olanzapine (1 ms prolongation in QT_c). Interestingly, when we tried to apply this same analysis using free drug plasma levels (based on protein binding information reported by the manufacturers), no correlation with QT_c was observed. This result is in contrast to a similar comparison we recently made for a series of fluoroquinolone antibiotics (Kang et al., 2001). The reason(s) for this discrepancy is unclear. However, in contrast to the fluoroquinolones, the antipsychotic drugs used in this study are reported to have very high (ca. 99% in some cases)

plasma protein binding. Thus, even small errors in this determination could lead to large changes in free drug levels which in turn could alter the relationships reported in Table 2. Additionally, relative affinity for the plasma protein binding site versus HERG affinity might also be considered. While plasma protein binding affinities are considered to be relatively low (in the mM or μM range), and data for plasma protein binding affinities are not readily available for most drugs, such data are becoming increasingly important (see for example Procyshyn et al., 2001). For example, in the case of quetiapine, where the affinity for HERG is relatively low, it may be that a similar affinity of the drug for plasma proteins plays a role in keeping the drug away from the site of action on the HERG channel. Finally, most drugs that block HERG are believed to do so at the intracellular side of the channel (Mitcheson et al., 2000) and determination of free drug levels at the active site on HERG will likely be difficult.

In summary, the present study has compared the HERG IC_{50} values for a series of antipsychotic drugs to their receptor binding potencies in vitro and, where possible, to their ability to prolong the QT interval of the electrocardiogram in the clinic. The in vitro data suggest that when HERG IC_{50} data and receptor binding potencies are separated by less than a log unit, significant QT prolongation may be expected. Alternatively, when these ratios are well in excess of 100 (e.g. olanzapine), little effect on QT interval may be predicted. An examination of total plasma drug levels relative to HERG channel affinities also seems useful for predicting the potential of a drug to increase QT interval duration, at least for the highly protein bound antipsychotic drugs examined here. The results underscore the importance of interpreting HERG channel data in the context of other pharmacodynamic (target receptor affinity) and pharmacokinetic parameters whenever they are available.

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