Interactions of the 5-Hydroxytryptamine 3 Antagonist Class of Antiemetic Drugs with Human Cardiac Ion Channels

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ABSTRACT
Administration of the 5-hydroxytryptamine 3 receptor class of antiemetic agents has been associated with prolongation in the QRS, JT, and QT intervals of the ECG. To explore the mechanisms underlying these findings, we examined the effects of granisetron, ondansetron, dolasetron, and the active metabolite of dolasetron MDL 74,156 on the cloned human cardiac Na+ channel hH1 and the human cardiac K+ channel HERG and the slow delayed rectifier K+ channel KvLQT1/minK. Using patchclamp electrophysiology we found that all of the drugs blocked Na+ channels in a frequency-dependent manner. At a frequency of 3 Hz, the IC50 values for block of Na+ current measured 2.6, 88.5, 38.0, and 8.5 μM for granisetron, ondansetron, dolasetron, and MDL 74,156, respectively. Block was relieved by strong hyperpolarizing potentials, suggesting a possible interaction with an inactivated channel state. Recovery from inactivation was impaired at −80 mV compared with −100 mV, and the fractional recovery was impaired by drug in a concentration-dependent manner. IC50 values for block of the HERG cardiac K+ channel measured 3.73, 0.81, 5.95, and 12.1 μM for granisetron, ondansetron, dolasetron, and MDL 74,156, respectively. Ondansetron (5 μM) also slowed decay of HERG tail currents. In contrast, none of these drugs (10 μM) produced greater than 30% block of the slow delayed rectifier K+ channel KvLQT1/minK. We concluded that the antiemetic agents tested in this study block human cardiac Na+ channels probably by interacting with the inactivated state. This may lead to clinically relevant Na+ channel blockade, especially when high heart rates or depolarized/ischemic tissue is present. The submicromolar affinity of ondansetron for the HERG K+ channel likely underlies the prolongation of cardiac repolarization reported for this drug.

Voltage-dependent Na+ and K+ channels are important determinants of the human electrocardiogram (ECG). The human cardiac Na+ channel hH1 (Gellens et al., 1992) (SCN5A) is responsible for the upstroke of the cardiac action potential, propagation of the cardiac impulse, and contributes to the plateau of the cardiac action potential (Wilson et al., 1985; Fozzard and Hanck, 1996). Voltage-dependent K+ channels are important for the repolarizing current I Kr and the two most important channels in human heart are thought to be HERG (KCNH2) and KvLQT1 (KCNQ1)/minK (KCNE1). HERG produces the rapid repolarizing current I Kr (Sanguinetti et al., 1995) and KvLQT1/minK produces the slow repolarizing current I Kr (Barhanin et al., 1996; Sanguinetti et al., 1996). Thus, hH1 is a determinant of the QRS of the ECG, whereas HERG and KvLQT1/minK are determinants of the QT interval. Mutations in KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3), and KCNE1 (LQT5) cause hereditary long QT syndrome in which QT prolongation is associated with torsade de pointes and sudden cardiac death (for review, see Priori et al., 1999). Drugs that block K+ channels may produce QT prolongation, whereas drugs that block Na+ channels may produce widening of QRS and in both cases ventricular arrhythmias may result.

Antagonists of the 5-HT₃ serotonin receptor are widely used in the treatment of postoperative and chemotherapy-induced nausea and vomiting. Clinically available drugs are granisetron (Kytril), ondansetron (Zofran), and dolasetron (Anzemet). In addition to block of 5-HT₃ receptors, these drugs have been reported to widen the QRS complex and prolong JT, QT, and PR intervals (Benedict et al., 1996; Jantunen et al., 1996; Boike et al., 1997). For example, dolasetron (1.2–4.0 mg/kg i.v.) can prolong QRS by 5 to 20%, whereas ondansetron has been shown to increase QT and JT intervals by an average of 2 to 5% (Hunt et al., 1995; Benedict et al., 1996; Boike et al., 1997). To understand better the ECG changes associated with administration of granisetron, ondansetron, and dolasetron we examined their effects of on hH1, HERG, and KvLQT1/minK.

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ABBREVIATIONS: HERG, human ether-a-go-go-related gene; KvLQT1/minK, slow delayed rectifier K+ channel; 5-HT, 5-hydroxytryptamine; G418, geneticin; AV, atrioventricular.
Materials and Methods

Materials. All chemicals used in bath and electrode solutions were purchased from Sigma (St. Louis, MO) unless otherwise noted and were at least of American Chemical Society reagent grade purity or higher. Dolasetron mesylate and MDL 74,156 were synthesized at Aventis Pharmaceuticals, Inc. (Bridgewater, NJ). Granisetron (1- mg/ml solution) and ondansetron (2-mg/ml solution) were purchased commercially from hospital pharmacy. Stock solutions of all drugs (1 mM) were made up in the external recording buffers used for the electrophysiological experiments.

Cell Culture. HEK-293 cells (CRL 1573; American Type Culture Collection, Rockville, MD) stably transfected with the SCNSA (the human cardiac Na-channel gene) cDNA were maintained in tissue culture incubators at 37°C in a humidified 95% O2, 5% CO2 atmosphere. Stable transfectants were selected by coexpression of the sodium channel cDNA and neomycin resistance gene incorporated into the expression plasmid. Selection pressure was maintained by including the antibiotic geneticin (G418) in the culture media. Cells were cultured in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal calf serum and 50 µl/ml G418. The cDNA encoding the HERG K-channel was stably transfected into HEK-293 cells as described previously (Rampe et al., 1997) and cells were grown as described above. HERG channel currents were not detected in untransfected cells. KvLQT1 was cloned into the NheI (5’ end) and BamHI (3’ end) sites of pcDNA3.1 (Invitrogen, Carlsbad, CA), which also contained the G418 resistance gene. The gene encoding minK was cloned into the same restriction sites of pcDNA3.1 containing the zeocin resistance gene. Chinese hamster ovary cells (ATCC no. CRL611) were transfected using lipofectamine (Life Technologies, Grand Island, NY) and stable transfectants were selected by growing the cells in the presence of 400 µg/ml G418 and 50 µg/ml zeocin.

Electrophysiology. Cells used for electrophysiology were plated on glass coverslips. For whole-cell Na+ currents recording coverslips were transferred to the recording chamber and superfused with a modified Tyrode’s solution (40 mM NaCl, 97 mM N-methyl-D-glucamine-aspartate, 5.4 mM KCl, 1.8 mM CaCl2, 1 mM MgCl2, 5 mM HEPES, 10 mM glucose, pH adjusted to 7.4 with N-methyl-D-glucamine). Pipette solution was composed of the following: 130 mM cesium-aspartate, 5 mM MgCl2, 5 mM EGTA, 2 mM disodium-ATP, 0.1 mM GTP, 10 mM HEPES, pH adjusted to 7.2 with CsOH. Patch pipettes were fabricated from 7052 glass capillaries on a P-97 horizontal puller (Sutter Instruments, Novato, CA) to generate pipettes with 1 to 3 MΩ resistance after fire polishing. Axon Instruments’ patch clamp amplifiers were used for cell patch-clamp recordings and all currents were recorded at room temperature. Current records were analog filtered at 0.2 of the sampling frequency of 50 kHz for digital conversion. Consistent with previous studies (Rampe et al., 1997), whole-cell K+ current recordings used electrodes (2–4 MΩ) 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, 4.0 mM disodium-ATP, 5.0 mM HEPES, 1.0 mM MgCl2, pH 7.2 with KOH. When recording KvLQT1/minK currents this solution was supplemented with 14 mM sodium phosphocreatine, 0.3 mM sodium GTP, and 50 units/ml creatine phosphokinase. The external solution for K+ current recordings contained 130 mM NaCl, 5.0 mM KCl, 2.8 mM sodium acetate, 1.0 mM MgCl2, 10 mM HEPES, 10 mM glucose, 1.0 mM CaCl2, pH 7.4 with NaOH. Currents were recorded at room temperature and were conditioned by a four-pole low-pass filter with a cutoff frequency of between one-quarter to half the sampling frequency.

Data Acquisition and Analysis. Data were stored on the hard disk of a PC compatible computer for off-line analysis. All data acquisitions and most analyses were done with the suite of pCLAMP programs (Axon Instruments). Statistical analysis of data used Student’s t test for paired observations. Where multiple comparisons were required, ANOVA was used.

For analysis of frequency-dependent block, data were expressed as the mean of the last five pulse amplitudes normalized by the amplitude of the first pulse. Drug inhibition at a particular frequency was calculated with the following equations: percentage of inhibition is expressed as (1−Y)×100 and Y = [average(drug[n], drug[n−1]) . . . drug[n−4]/drug[0]]/[average(control[n], control[n−1]) . . . control[n−4]/control[0]].

The indexed variables drug[n] and control[n] are the peak current amplitudes for the last pulses in drug and control (index = n), second to last (index = n−1) up to the fifth pulse from the end of the pulse train with index = n−4. IC50 values for HERG channel inhibition were determined by nonlinear least-squares fit of the data (GraphPad Software, San Diego, CA).

Results

In the whole-cell configuration, untransfected HEK-293 cells displayed no Na+ currents, whereas cells stably transfected with the human cardiac Na+ channel produced rapidly inactivating sodium currents with peak amplitudes of 0.5 to 5.0 nA (Fig. 1Aa). The voltage-dependent currents are typical of cardiac Na+ channel currents and give rise to the characteristic peak current-voltage relationship shown in Fig. 1Ab. Inactivation was voltage dependent and had a half-maximal value of about −85 mV (Fig. 1Ac).

At 0.05-Hz stimulation, a conditioning prepulse to −140 mV, and a test pulse of −20 mV, there was no reduction in peak current. Bath application of either dolasetron, granisetron, ondansetron, or MDL 74,156 at concentrations of 1 to 100 µM for as long as 10 min had no effect on either peak amplitude or current waveforms. In the absence of a prepulse and the presence of higher stimulation frequencies application of these drugs produced suppression of Na+ currents elicited by the test pulses. In the experiment shown in Fig. 1B, the holding potential was −90 mV and the initial frequency of stimulation was 0.05 Hz. Addition of 10 µM MDL 74,156 to the bath had no effect at this frequency but an increase of frequency to 3 Hz produced clear suppression of peak test current. In the drug-free solution stimulation at 3 Hz for 150 s produced a steady-state peak current that was reduced on average by 11 ± 6% (n = 6). In the presence of 100 µM MDL 74,156 the peak test current at steady state was reduced by 82 ± 7% (n = 4), which was statistically significant (P < 0.05; Fig. 1C). At 1 Hz the reduction was less, 57 ± 7% (n = 3), but still significant (P < 0.05; Fig. 1C). Frequency- and time-dependent reductions in current amplitude were also obtained with dolasetron, ondansetron, and granisetron. In all cases the current waveforms were unchanged.

At 3-Hz stimulation in the presence of 1 µM drug the steady-state reduction of peak currents were as follows: ondansetron, 17 ± 5% (n = 4; P < .493); dolasetron, 21 ± 4% (n = 5; P < .23); MDL 74,156, 28 ± 5% (n = 6; P < .043); and granisetron, 59 ± 4% (n = 6; P < .001). In the presence of 100 µM drug the reductions were 58 ± 7% (n = 4; P < .01), 65 ± 8% (n = 4; P < .01), 82 ± 7% (n = 4; P < .01), and 96 ± 2% (n = 5; P < .01) for ondansetron, dolasetron, MDL 74,156, and granisetron, respectively. The effects were concentration dependent and were plotted as dose-response curves (Fig. 2). IC50 values were 88.5, 38.0, 8.5, and 2.6 µM for ondansetron, dolasetron, MDL 74,156, and granisetron, respectively, so that the order of Na+ channel blocking potency was granisetron > MDL74,156 > dolasetron > ondansetron.
In addition to frequency and concentration dependence the block was voltage dependent and was quickly relieved at strongly hyperpolarized potentials. In the experiment illustrated on Fig. 3A, the cell was stimulated at 3 Hz with a 200-ms prepulse of −140 mV in the presence of 100 μM granisetron. When the prepulse hyperpolarizing step was

**Fig. 1.** $\text{Na}^+$ currents in HEK293 cells stably transfected with the human cardiac sodium channel cDNA and frequency-dependent block by MDL 74,156. Whole-cell currents (Aa) and current-voltage relationships (Ab) obtained from a representative cell (40 mM Na$^+$ in external solution). Ac, steady-state inactivation curve of $I_{\text{Na}}$ ($V_{0.5} = -84.5 \pm 0.2$ mV and $k = 6.9 \pm 0.2$ mV; n = 13). B and C, MDL 74,156 produces use- and frequency-dependent block of Na$^+$ channels. Currents were elicited at 0.05-hz (squares; n = 4), 1-hz (circles; n = 3), and 3-Hz (triangles; n = 4) frequency. Currents were measured, averaged, and every fifth point (for 1 and 3 Hz) was plotted. Dotted line indicates an averaged reduction of steady-state level of the peak current at 3 Hz stimulation in control bath solution. At 1-Hz stimulation the reduction was negligible.
omitted the steady-state block reached about 95% but when the prepulse was restored block was relieved within a few seconds. Similar voltage-dependent effects were observed with MDL 74,156 (Fig. 3B), dolasetron, and ondansetron. In a further set of experiments we increased test pulse duration from 20 to 50 ms but observed no enhancement of block.

The relief of block by a hyperpolarizing prepulse pointed toward block of an inactivated state of the Na$^+$ channel. To test this idea further we compared recovery from inactivation in the absence or presence of the most potent drug, granisetron. At a recovery potential of −100 mV granisetron had no significant effect on kinetics or fractional recovery. The $\tau$ values were 16.7 ± 2.2, 18.5 ± 3.2, and 18.6 ± 2.0 ms ($P < .81$; ANOVA) and fractions of recovery (after 150 ms) were 92.3 ± 1.4, 91.0 ± 1.7, and 88.6 ± 2.0% ($P < .32$; ANOVA) for 0 (n = 6), 10 (n = 6), and 100 (n = 5) $\mu$M granisetron, respectively (Fig. 4A). At a recovery potential of −80 mV recovery kinetics in control was slowed but granisetron had no apparent further effect. Values of $\tau$ were 45.6 ± 6.6, 41.2 ± 4.0, and 46.8 ± 3.2 ($P < .66$; ANOVA) for 0 (n = 5), 10 (n = 5), and 100 (n = 7) $\mu$M granisetron, respectively.

**Fig. 2.** Effect of varying concentrations of granisetron (●), MDL 74,156 (■), dolasetron (□), and ondansetron (●) on the steady-state peak Na$^+$ current at a stimulation frequency of 3 Hz (n = 4–6, for each point). Data were normalized to the control steady-state values at 3 Hz. Data were fit with the Hill equation, fractional block = \( \left[ 1 + \left( \text{Drug}/IC_{50} \right) \right]^{-n} \).

**Fig. 3.** Reversibility of granisetron (A) and MDL 74,156 (B) effects at hyperpolarized membrane potentials. The cell was held at −90 mV and tested at −10 mV at 3 Hz. Currents were normalized to the first pulse and plotted as function of time. Prepulses (−140 mV; 200 ms) were applied as shown.

**Fig. 4.** Granisetron reduced fractional recovery of Na$^+$ channels from inactivation in a voltage-dependent manner. Cells were held at −90 mV, prepulsed to −140 mV for 1 s, test pulsed to −10 mV for 20 ms, repolarized to −100 mV (A) or −80 mV (B) for times ranging from 10 to 150 ms (interpulse duration), and depolarized again to −10 mV for 20 ms. The peak current during the second depolarizing pulse was normalized to the peak current during the first depolarizing pulse and plotted as function of interpulse duration. The data were obtained in control solution (□) and with addition of 10 $\mu$M (○) or 100 $\mu$M (△) granisetron.
fractional recovery was impaired significantly and amplitudes relative to control were 44.2 ± 1.3, 28.6 ± 5.4, and 23.0 ± 3.3% (P < .003; ANOVA) at 0, 10, and 100 µM granisetron, respectively (Fig. 4B).

Figure 5 shows the effects of the antiemetic agents on HERG cardiac K⁺ channel currents. In these experiments, a 2-s depolarizing pulse to +20 mV from a holding potential of −80 mV was followed by repolarization of the cell to −40 mV to produce large, slowly deactivating tail currents characteristic of HERG (Sanguinetti et al., 1995). The effect of these agents is typified by dolasetron (Fig. 5A), which reduced peak tail current amplitude in a dose-dependent manner. Dose-response relationships generated from inhibition of peak tail currents at −40 mV yielded IC₅₀ values of 808 nM, 3.73 µM, 5.95 µM, and 12.1 µM for ondansetron, granisetron, dolasetron, and MDL 74,156, respectively.

Because ondansetron displayed the highest affinity for HERG relative to the other agents tested, we examined its effects in greater detail. Figure 6 shows the time course for ondansetron inhibition of HERG. Blockade of HERG currents by 3 µM ondansetron came to equilibrium in approximately 2 min (Fig. 6B). This inhibition was mainly reversible by washing the cell for the same period of time (Fig. 6, A and B). Furthermore, ondansetron appeared to enhance HERG current decay during depolarizing pulses to +20 mV (Fig. 6A).

In separate experiments, cells were depolarized for 2 s to

Fig. 5. Effects of antiemetic agents on HERG. A, whole-cell HERG currents were elicited by a 2-s depolarizing pulse to +20 mV from a holding potential of −80 mV. The cell was then returned to −40 mV to generate large outward tail currents. The effect of 1 and 10 µM dolasetron on these currents is shown. B, dose-response relationships for ondansetron (○), granisetron (■), dolasetron (□), and MDL 74,156 (○) are shown. Inhibition of peak outward tail currents at −40 mV was used to generate the dose-response relationships. Error bars indicate S.E.M. (n = 4–7).

Fig. 6. Time course of ondansetron block of HERG. A, HERG currents were elicited as described in Fig. 5. Control current, current in the presence of 3 µM ondansetron, and after washout of drug are shown. B, diary of peak tail current amplitude. Depolarizing pulses were delivered at 40-s intervals. The addition of drug and subsequent washout are indicated. Data points represent the average of four cells. Current is expressed relative to the first pulse in the series. Error bars indicate S.E.M.

Fig. 7. Effects of ondansetron on KvLQT1/minK⁺ channel currents. Whole-cell currents were elicited by 4-s depolarizing pulses to +20 mV from a holding potential of −80 mV. The effects of 10 µM ondansetron are shown.
cantly increased \((P < .05; \text{paired } t \text{ test})\) to 107 ± 12 ms \((n = 5)\).

Figure 7 shows the effects of ondansetron on KvLQT1/minK \(K^+\) channel currents. KvLQT1/minK currents were generated by 4-s depolarizations to +20 mV from a holding potential of −80 mV. None of the compounds tested displayed high-affinity block of this channel as typified by the response to ondansetron that is shown. At 10 \(\mu M\) concentration ondansetron, granisetron, dolasetron, and MDL 74,156 inhibited KvLQT1/minK currents by 11 ± 5\% \((P = .31; \text{paired } t \text{ test})\), 15 ± 5\% \((P = .03)\), 18 ± 7\% \((P = .10)\), and 30 ± 9\% \((P = .04)\), respectively, when measured at the end of the 4-s depolarizing pulse \((n = 4 – 5)\).

**Discussion**

The results show that the antiemetic 5-HT\(_3\) receptor antagonists blocked the human cardiac sodium channel stably expressed in HEK-293 cells in a concentration- and frequency-dependent manner. The frequency dependence was probably due to an excessive accumulation of drug-bound inactivated channels with the result that block was enhanced at depolarized potentials and relieved at hyperpolarized potentials. At potentials below −90 mV relief of block was too fast to show changes in the steady-state inactivation-voltage relationship. For this reason, the concentration dependence of drug effects on steady-state inactivation using standard protocols could not be determined. Rather, we measured concentration dependence using steady-state inhibition by drug at frequencies of 3.0 Hz, \(V_m = −90\) mV, and \(V_p = −10\) mV, 20 ms duration. Under these conditions this time constant of recovery from inactivation (Fig. 4B) was not concentration dependent probably because a second component of inactivation was too slow to be detected. The results are consistent with drug action on the slowest of two inactivated states that have been reported for cardiac \(Na^+\) currents (Dumaine et al., 1996A). An earlier description of low-affinity (millimolar) block by dolasetron was reported for human cardiac sodium channels transiently expressed in *Xenopus* oocytes (Dumaine et al., 1996B). However, drug block of ion channels in this preparation is known to be less potent than block observed in mammalian cells transfected stably or transiently with ion channel cDNAs. For this reason we used HEK-293 cells stably transfected with *SCN5A*. The \(Na^+\) channels expressed in these cells display pharmacological sensitivity similar to native tissues (An et al., 1996).

MDL 74,156 was severalfold more potent as a blocker of the human cardiac \(Na^+\) channel than the parent compound dolasetron. After i.v. administration, dolasetron is rapidly \((\tau_{1/2} < 10\) min\) converted to MDL 74,156 (Lerman et al., 1996). After a 200-mg i.v. dose of dolasetron peak free plasma levels of MDL 74,165 approximate 1 \(\mu M\) (Dimmitt et al., 1998), a concentration that significantly inhibits \(Na^+\) channel current by 28 ± 5\% in our experiments. QRS widening of 5 to 20\% is observed from 15 min to 2 h after administration of dolasetron (1.2–4.0 mg/kg i.v.) (Hunt et al., 1995; Benedict et al., 1996). During this time period, MDL 74,156 is by far the dominant species in the plasma (Lerman et al., 1996). Due to these pharmacokinetic considerations and the higher potency on the \(Na^+\) channel, it is most likely that the QRS interval prolongation observed with the administration of dolasetron results from block of the human cardiac \(Na^+\) channel by its active metabolite. This block is expected to be enhanced under conditions such as high heart rates or in the presence of depolarized tissue. Granisetron was the most potent antagonist of \(Na^+\) channel currents. Granisetron administration has been associated with prolongation in the PR interval and atioventricular (AV) block, but little or no change in the QRS duration (Watanabe et al., 1995; Jan- tunen et al., 1996). It is possible that the effects on PR interval and AV conduction reflect block of L-type \(Ca^{2+}\) channels and or inhibition of HERG in AV nodal tissue. Although granisetron was the most potent drug tested for blocking \(Na^+\) channels, its plasma levels approximate only 75 nM after 40-\(\mu g/kg\) i.v. administration (Kytril Prescribing Information, 1997). These levels may not be sufficient to produce significant \(Na^+\) channel block and QRS prolongation. Alternatively, clinically obvious block of cardiac \(Na^+\) channels may only be observed at high heart rates or in depolarized/ischemic tissue. Further clinical studies will be necessary to examine these possibilities. Prolongation of cardiac depolarization has typically not been observed for ondansetron (Benedict et al., 1996; Boike et al., 1997) consistent with the weak interaction on \(Na^+\) channel currents observed here.

KvLQT1/minK was not a target for block by dolasetron, MDL 74156, ondansetron, or granisetron because concentrations as great as 10 \(\mu M\) were required to produce observable block. On the other hand, HERG was blocked more potently with a rank order of ondansetron > granisetron > dolasetron > MDL 74,156. HEK-293 cells expressing HERG have proved to be a predictive model for drugs that prolong cardiac repolarization clinically, including cisapride and astemizole, and display pharmacological sensitivity similar to native \(I_{Kr}\) (Mohammad et al., 1997; Drolet et al., 1998; Zhou et al., 1999). Block of HERG by ondansetron was submicromolar and appeared to involve an activated state of the channel as shown by the relaxation of the steady-state current and slowing of the deactivation tails. These results are similar to those obtained for \(I_{Kr}\) with feline ventricular myocytes (de Lorenzi et al., 1994). After administration of ondansetron (32 mg i.v.), peak free concentrations in plasma are about 300 nM (Zofran Product Information, 1997), a concentration that produces 29 ± 5\% block of HERG in our experiments. This dose produces an approximately 5\% increase in JT interval 15 min after administration (Benedict et al., 1996). We therefore attribute prolongation of cardiac repolarization observed for ondansetron (Benedict et al., 1996; Boike et al., 1997) to block of HERG by this drug. High heart rates or other situations that favor activated states of the channel may enhance ondansetron's inhibition of HERG. Changes in QT interval have not been described for granisetron (Jantunen et al., 1996; Boike et al., 1997), whereas the QT prolongation described for dolasetron has been attributed to widening of the QRS (i.e., \(Na^+\) channel block) (Benedict et al., 1996). These results are consistent with the lower potencies of granisetron, dolasetron, and MDL 74,156 for HERG described presently.

In summary, we have examined the effects of several clinically available antiemetic agents on human cardiac \(Na^+\) and \(K^+\) channels. The rank order of potency for block of the \(Na^+\) channel was granisetron > MDL 74,165 > dolasetron > ondansetron and all drugs appeared to bind preferentially to the inactivated state of the channel. For blockade of the HERG \(K^+\) channel, the order of potency was ondansetron >
granisetron > dolasetron > MDL 74,156. The results help define the molecular mechanisms that underlie some of the ECG changes (especially JT, QT, and QRS prolongation) observed with administration of these drugs.

References


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