Cyamemazine metabolites: effects on human cardiac ion channels in-vitro and on the QTc interval in guinea pigs

William Crumb, Amine Benyamina, Christophe Arbus, George P. Thomas, Ricardo P. Garay and Ahcène Hameg

Abstract

Monodesmethyl cyamemazine and cyamemazine sulfoxide, the two main metabolites of the antipsychotic and anxiolytic phenothiazine cyamemazine, were investigated for their effects on the human ether-a-go-go related gene (hERG) channel expressed in HEK 293 cells and on native INa, ICa, Ito, Isus or IK1 of human atrial myocytes. Additionally, cyamemazine metabolites were compared with terfenadine for their effects on the QT interval in anesthetized guinea pigs. Monodesmethyl cyamemazine and cyamemazine sulfoxide reduced hERG current amplitude, with IC50 values of 0.70 and 1.53 μM, respectively. By contrast, at a concentration of 1 μM, cyamemazine metabolites failed to significantly affect INa, ICa, Ito or IK1 current amplitudes. Cyamemazine sulfoxide had no effect on ICa at 1 μM, while at this concentration, monodesmethyl cyamemazine only slightly (17%), albeit significantly, inhibited ICa current. Finally, cyamemazine metabolites (5 mg kg\(^{-1}\) i.v.) were unable to significantly prolong QTc values in the guinea pig. Conversely, terfenadine (5 mg kg\(^{-1}\) i.v.) significantly increased QTc values. In conclusion, cyamemazine metabolite concentrations required to inhibit hERG current substantially exceed those necessary to achieve therapeutic activity of the parent compound in humans. Moreover, cyamemazine metabolites, in contrast to terfenadine, do not delay cardiac repolarization in the anesthetized guinea pig. These non-clinical findings explain the excellent cardiac safety records of cyamemazine during its 30 years of extensive therapeutic use.

Introduction

Antipsychotic phenothiazines have the potential to induce fatal polymorphic ventricular arrhythmias known as Torsades de Pointes (TdP) (Glassman & Bigger 2001; Haddad & Anderson 2002). However, cyamemazine (Tercian; see chemical structure in Figure 1) is the most widely used antipsychotic drug in France (more than 5.7 millions days of treatment), has been associated with only a single case of cardiac arrhythmia since 1974 when it was first introduced onto the French therapeutic market (Gury et al 2000).

Chlorpromazine, the prototype phenothiazine moiety of cyamemazine, reduces the K\(^+\) current carried by the cardiac hERG channel (Thomas et al 2003). This pharmacologic effect tends to delay the repolarization phase of the ventricular action potential, thus increasing the risk of TdP and sudden death (Cavero et al 2007). Indeed, chlorpromazine can prolong the QT interval and increase the risk of TdP, particularly in patients with confounding factors (Warner et al 1996; Hoehns et al 2001). By contrast, we previously reported that cyamemazine does not prolong the QT interval in anesthetized guinea pigs and that high cyamemazine concentrations are required to inhibit the hERG channel (Crumb et al 2006).

Pharmacokinetics and metabolic studies in human volunteers showed that cyamemazine is metabolized in the liver (half-life 11 h) into two main metabolites: monodesmethyl cyamemazine and cyamemazine sulfoxide (see chemical structures in Figure 1), which are both eliminated by urinary excretion over 72 h (Bourin 2004). It appeared to us that these two main cyamemazine metabolites should also be examined for their cardiac safety profile using the same tests previously used for cyamemazine (Crumb et al 2006). Therefore, we investigated the effects of cyamemazine metabolites on IK, determined in cloned hERG channels and on native ion currents generated by Na\(^+\), Ca\(^{2+}\) and K\(^+\) (INa, ICa and IK1) channels present in human atrial myocytes. In addition, the electrocardiographic effects of cyamemazine metabolites were determined in the anesthetized guinea pig and compared
with those of terfenadine, a drug withdrawn from the pharmaceutical market for its life-threatening effects consequent to prolongation of the QTc interval (Lindquist & Edwards 1997). The anesthetized guinea pig was selected for this investigation since it has the power to easily disclose QT interval prolongation induced by terfenadine (Testai 2004) and other drugs signalled to exert this effect in humans (Batey et al 1997; Chiang et al 2002; De Clerck et al 2002; Hamlin et al 2003; Testai et al 2004; Crumb et al 2006).

**Figure 1** Chemical structures of cyamemazine (2-cyano-10-[3-(dimethylamino)-2-methyl-propyl]-phenothiazine) and its main metabolites.

**Material and Methods**

**Human cardiac channel assays**

***hERG channel currents***

Studies were conducted to determine the human IKr (hERG) ion channel blocking effects of cyamemazine metabolites in stably transfected HEK 293 cells expressing the hERG mRNA by using a previously published method (Crumb et al 2006). A cloned equivalent of the human IKr (hERG) was used for this study, since it has the power to easily disclose QT interval prolongation induced by cyamemazine (Testai 2004) and other drugs signalled to exert this effect in humans (Batey et al 1997; Chiang et al 2002; De Clerck et al 2002; Hamlin et al 2003; Testai et al 2004; Crumb et al 2006).

**ECG study in guinea pigs**

Male Hartley guinea pigs, aged 4–7 weeks, were obtained from Elm Hill Breeding Laboratories (Chelmsford, MA, USA). After their delivery to the laboratory, they were checked for general health conditions and individually housed according to USDA guidelines. The experimental protocol was approved by the local ethical committee. A minimum 5-day period to acclimatize to laboratory conditions was allowed before an animal was subjected to the experimental protocol. The animal room environment was controlled by setting the room temperature at 15–24.4°C, the relative humidity at 17–59% and the light–dark cycle at 12/12 h. All animals had free access to certified guinea pig diet (Teklad; Harlan, Indianapolis, IN, USA) and water, unless otherwise specified.

**Allocation to treatment groups**

The animals (n = 5 per group) subjected to the experimental procedure were selected based on similar bodyweight and good health conditions. They were assigned to vehicle (0.2, 0.5 and...
2 mL kg⁻¹ of a water solution of DMSO 10% and polyethylene glycol 200 (90%). monodesmethyl cyamemazine (0.5 and 5 mg kg⁻¹), cyamemazine sulfoxide (0.5 and 5 mg kg⁻¹) and terfenadine (0.5, 1 and 5 mg kg⁻¹) groups and randomized in a way such that at least one animal from each group was tested each day of dose administration. Each treatment was administered as a slow (30–60 s) bolus intravenous injection.

Measurement of QTc interval
Guinea pigs were anesthetized by an intraperitoneal injection of 0.9 mL kg⁻¹ of a distilled water solution containing dialur-ethane (ethyl urea, 400 mg mL⁻¹), allobarbital (100 mg mL⁻¹) and urethane (400 mg mL⁻¹). Then, a 3–4-cm midline incision was made on the ventral side of the neck to insert a catheter in the jugular vein for intravenous administrations and into the trachea for artificial ventilation (Harvard model 683 rodent ventilator: Harvard Apparatus, South Natick, MA, USA), which was delivered throughout the entire experimental period at 50 strokes of 4–6 mL min⁻¹. The ventilation parameters were selected to respect the blood acid–base equilibrium. Dorsal, axial and inferior lead ECGs were recorded at a speed of 50 mm s⁻¹ on a writer (Hewlett Packard Page Writer II, model 4755A; Hewlett Packard, Palo Alto, CA, USA) from clip electrodes attached to the animal skin.

At the end of the experimental procedure, the animal was injected with an overdose of urethane (2–3 g kg⁻¹ i.p.) and the ECG monitored until cardiac arrest occurred.

Statistical analysis
Ion channels
Results are reported as means ± s.e.m. Experimental data were transformed in percent reduction of current amplitude. This was measured as current reduction after a steady-state effect had been reached in the presence of the test item relative to current amplitude measured before initiating test item superfusion (control). Each cell served as its own control. Log-linear plots representing the concentrations studied expressed in log values versus the corresponding percentages of blockade were drawn. A non-linear curve-fitting routine was used to obtain the best fit of the results to a three-parameter Hill equation. The mean IC50 was calculated by using MicroCal Origin software (version 6.0; OriginLab, Northampton, MA, USA). The equation used for the fitting was of the form y = Emax/[1 + (x/IC50)^n], where Emax a n d n w e r e kept as unconstrained variables. The significance (P < 0.05) of the effects was determined with a paired Student’s t-test using NCSS software (NCSS, Kaysville, UT, USA).

Criteria for QT interval evaluation
The PR, QRS, RR and QT intervals were measured manually from the ECG tracings and heart rate was derived from the RR intervals. These values were taken from single cardiac cycles and its accuracy verified from other nearby cycles in the chart. The ECG readings were done by a consultant veterinary cardiologist (D. K. Detweiler, VMD, Waverly Heights, Suite A 212, 1400 Waverly Road, Gladwyne, PA 19035, USA).

Since the vehicle, test and reference articles reduced heart rate, the QT interval was corrected to the reference heart rate of 60 beats min⁻¹ by using Bazett (QT/RR^(0.5)), Fridericia (QT/RR^(0.33)) and Van de Water (QT – [0.087 × (60/heart rate – 1)]) algorithms. QTc and heart rate data were analysed by analysis of variance followed by Tukey’s HSD multiple comparison test. A percent change >15% over baseline values attaining significance (P < 0.05) was considered physiologically relevant.

Results
hERG channels expressed in HEK-293 cells
Figure 2 shows the effects of monodesmethyl cyamemazine, cyamemazine sulfoxide and E-4031 on the current carried by the hERG channel stably expressed in a HEK-293 cell line (n = 5 per compound). All compounds reduced hERG current amplitude in a concentration-dependent manner. Monodesmethyl cyamemazine, but not cyamemazine sulfoxide, fully inhibited hERG current amplitude (Figure 2). A non-linear fitting of the experimental values using Hill’s equation allowed the calculation of the concentration of monodesmethyl cyamemazine reducing by 50% the hERG current (IC50), which was 0.70 μM, and Hill’s n = 0.87. Assuming full blockade for cyamemazine sulfoxide concentrations higher than 30 μM, the same analysis gave IC50 = 1.53 μM, and Hill’s n = 0.41 for this compound. Original hERG current traces in the presence and absence of cyamemazine can be found in a previous publication (Crumb et al 2006). Under the same experimental conditions, E-4031 (Herzberg et al 1998), a selective and potent hERG channel blocker, inhibited, as expected, the hERG current, with an IC50 of 18.1 ± 3.2 nm (n = 6–11 cells for each of the four concentrations studied). Haloperidol or olanzapine, studied at
30 and 300 nm reduced hERG current amplitude by 44.2 ± 3.9% and a 49.7 ± 4.2%, respectively.

In two unexposed cells, no current “rundown” (a phenomenon describing the time-dependent experimental decline in ion current occurring in patch experiments) over the course of a typical experiment lasting from 5 to 10 min was measured. This indicates that the current reduction observed in the presence of the test articles is unlikely to result from a current “rundown” event.

INa, Ito, Isus, and IK1 in isolated human atrial myocytes

Figure 3 shows the effect of monodesmethyl cyamemazine and cyamemazine sulfoxide on INa, Ito, Isus, IK1 and ICa channel currents. At a concentration of 1 μM, neither of these compounds significantly reduced INa, Ito, Isus or IK1 current amplitudes. At this concentration, cyamemazine sulfoxide had no effect on ICa, whereas monodesmethyl cyamemazine slightly, but significantly, reduced ICa current. Original INa, Ito, Isus, IK1 and ICa current traces in the presence and absence of cyamemazine can be found in a previous publication (Crumb et al 2006).

QTc in anesthetized guinea pigs

QT values measured before the administration of treatments (baseline data) were virtually the same for the vehicle (162 ± 7 ms), monodesmethyl cyamemazine (161 ± 7 ms), cyamemazine sulfoxide (155 ± 9 ms) and terfenadine (166 ± 9 ms) groups. Baseline heart rate values were also similar for the vehicle (236 ± 10 beats min⁻¹), monodesmethyl cyamemazine (247 ± 10 beats min⁻¹), cyamemazine sulfoxide (247 ± 10 beats min⁻¹) and terfenadine (234 ± 12 beats min⁻¹) groups. Finally, baseline values of PR, RR, QRS, QTcB, QTcF and QTcV were not significantly different between groups (data not shown). This allowed inter-group comparisons of absolute changes or percent changes without possible confounding influences due to differences in initial values.

Intravenous administration of the vehicle at intravenous doses of 0.2 and 0.5 mL kg⁻¹ did not modify heart rate or QTc interval. Monodesmethyl cyamemazine and cyamemazine sulfoxide did not significantly modify heart rate at the lowest dose investigated, but they significantly reduced this parameter at the higher intravenous dose of 5 mg kg⁻¹ (from the baseline value of 247 ± 10 to 192 ± 12 beats min⁻¹ and from 247 ± 10 to 192 ± 12 beats min⁻¹, for cyamemazine sulfoxide and monodesmethyl cyamemazine, respectively; P < 0.05) (Figure 4). Finally, terfenadine significantly reduced heart rate at the higher intravenous dose of 5 mg kg⁻¹ (from a baseline level of 236 ± 15 to 106 ± 6 beats min⁻¹; P < 0.05).

Table 1 shows the effects of cyamemazine sulfoxide and monodesmethyl cyamemazine on QT interval corrected to heart rate by using the Fridericia formula (QTcF), Van de Water formula (QTcV) and Bazett formula (QTcB). Neither cyamemazine sulfoxide nor monodesmethyl cyamemazine were able to significantly modify these parameters at any dose tested in relation to baseline values. Conversely, terfenadine significantly increased QTcF, QTcV and QTcB at the higher intravenous dose of 5 mg kg⁻¹.

Discussion

In this investigation, cyamemazine metabolites were found to concentration-dependently block hERG current, with IC50 values of 1.53 μM for cyamemazine sulfoxide and 0.70 μM for monodesmethyl cyamemazine. By contrast, at
a concentration of 1 μM, cyamemazine metabolites did not significantly reduce \( I_{\text{Na}} \), \( I_{\text{Ca}} \), \( I_{\text{K}} \) or \( I_{\text{k}} \) current amplitudes. Cyamemazine sulfoxide had no effect on \( I_{\text{Ca}} \) at 1 μM, while at this concentration monodesmethyl cyamemazine inhibited only slightly (17%), albeit significantly, \( I_{\text{Ca}} \) current. Finally, at this concentration monodesmethyl cyamemazine inhibited \( I_{\text{Na},I_{\text{sus}}} \) or \( I_{\text{K}} \) current amplitudes.

The blockade of the hERG channel current by cyamemazine metabolites should be evaluated by taking into consideration target receptor sites for therapeutic efficacy of the mother compound and concentrations required for achieving therapeutic activity. hERG IC50 values for cyamemazine metabolites are higher than those previously reported for cyamemazine (0.47 μM) (Crumb et al 2006). On the other hand, in patients treated for 15 days with 150 mg per day of cyamemazine, the total plasma concentration of cyamemazine metabolites reached a steady state value of 150 nM for monodesmethyl cyamemazine and 225 nM for cyamemazine sulfoxide (Arbus et al 2007). The free plasma concentrations of cyamemazine metabolites are not known, but given their chemical structures, it can be assumed that they are, as for thioridazine or chlorpromazine, strongly bound to protein (99%; see Kongsamut et al 2002), thus yielding free values of approximately 1.5 nM for mono-

desmethyl cyamemazine and 2.25 nM for cyamemazine sulfoxide. On the basis of this reasonable assumption and of the hERG IC50 value, safety ratios of approximately 680 and 467 (hERG IC50 divided by free plasma concentration value) are obtained for cyamemazine sulfoxide and monodesmethyl cyamemazine, respectively. This gives a total safety ratio (for cyamemazine and cyamemazine metabolites) of approximately 147; calculated by adding weighted (reciprocal; 1/x) values of all three safety ratios. Data published by Kongsamut et al (2002) allow us to compare this safety ratio with those of other therapeutically used antipsychotic drugs. The cardiac safety ratio ranged from approximately 10 for thioridazine (a phenothiazine with multiple reported cases of ventricular arrhythmia and cardiac sudden death), 12 for risperidone, 41 for ziprasidone and 501 for olanzapine (a compound with recognized cardiac safety) (Kongsamut et al 2002). Therefore, cyamemazine and cyamemazine metabolites are characterized by a cardiac safety factor closer to that of olanzapine. This finding is supported by the large clinical experience with cyamemazine, the most frequently prescribed antipsychotic agent in France, which since its introduction onto the therapeutic market in 1974 has not been characterized by any worrying cardiac safety issues (Gury et al 2000).

Kongsamut et al (2002) failed to uncover a significant correlation between the potential to prolong QT interval and the free plasma concentration required for therapeutic benefit for the antipsychotic agents thioridazine, risperidone, ziprasidone and olanzapine. By contrast, these authors advanced the hypothesis that a more reliable indicator of QT interval liability was the ratio hERG/IC50 over their affinity (\( K_c \)) for target dopamine D2 receptors and serotonin 5-HT2A receptors mediating the therapeutic activity of these compounds. Interestingly, this calculation provided evidence that QTc prolongation is likely to be produced by antipsychotic drugs characterized by a ratio value equal to or less than 10. In a previous study (Crumb et al 2006), we used \( K_c \) values for cyamemazine towards dopamine D2 receptors and serotonin 5-HT2A receptors (5.8 nM and 1.5, respectively; Hameg et al 2003), to obtain cardiac safety ratios for cyamemazine of 81 and 313, respectively. The same analysis for cyamemazine metabolites gives values of 87 and 340 for cyamemazine sulfoxide and 60 and 233 for monodesmethyl cyamemazine, confirming the good safety ratio discussed above.

There are other possible confounding factors to take into consideration when a cardiac safety ratio is calculated using the free plasma concentration required for therapeutic activity. In particular, a possible myocardial accumulation could reduce such a ratio (Cavero et al 2000). However, although there are no available studies on the myocardial concentrations of cyamemazine and metabolites, if such an accumulation occurs, this does not necessarily mean that the accumulated drug is freely available to the hERG channel population.

The effects of cyamemazine were also determined by using an in-vivo ECG assay. The experimental animal model selected for this study was the anesthetized guinea pig, since it has been shown to have the power to detect a prolongation in cardiac repolarization for terfenadine (Testai et al 2004) and other drugs with documented potential to prolong the QT interval in humans (Batey et al 1997; Chiang et al 2002; De Clerck et al 2002; Hamlin et al 2003; Crumb et al 2006). The latter contention is further supported by the results of this investigation, which confirmed that terfenadine, a drug withdrawn from the therapeutic market because of its serious

### Table 1 QTcB, QTcF and QTcV intervals measured 20 min after the administration of cyamemazine metabolites or terfenadine

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg kg(^{-1}))</th>
<th>QTcB (ms)</th>
<th>QTcF (ms)</th>
<th>QTcV (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyamemazine sulfoxide</td>
<td>Baseline</td>
<td>221±8</td>
<td>248±10</td>
<td>313±11</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>237±11</td>
<td>268±14</td>
<td>333±14</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>258±13</td>
<td>291±1</td>
<td>352±15</td>
</tr>
<tr>
<td>Monodesmethyl cyamemazine</td>
<td>Baseline</td>
<td>227±6</td>
<td>258±7</td>
<td>326±7</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>250±10</td>
<td>285±12</td>
<td>351±12</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>265±12</td>
<td>297±15</td>
<td>355±16</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Baseline</td>
<td>230±8</td>
<td>260±10</td>
<td>325±11</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>259±8</td>
<td>296±9</td>
<td>363±10</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>327±25*</td>
<td>354±26*</td>
<td>395±24*</td>
</tr>
</tbody>
</table>

*P < 0.05, statistically significant (analysis of variance) with respect to baseline values.
cardiac effects (Lindquist & Edwards 1997), prolonged the QT interval significantly in anesthetized guinea pigs (Testai et al 2004).

In the guinea pig, cyamemazine metabolites were unable to significantly increase QTc as derived by the three correction algorithms widely used in animal research (Bazett, Fridericia and Van de Waters). It is likely that, due to protein binding, metabolite concentrations are very low and consistent with the lack of effect of low concentrations on hERG.

In the present investigation, the plasma concentrations of cyamemazine metabolites were not measured, but it can be assumed with confidence to have attained levels much higher than those required in humans for therapeutic activity of the mother compound (150 nm for monodesmethyl cyamemazine and 225 nm for cyamemazine sulfoxide; Arbus et al 2007) since the compounds were injected intravenously at high doses (5 mg kg, i.v.). Indeed, by the intravenous route, the high doses of cyamemazine metabolites investigated are expected to be fully bioavailable and theoretically yield concentrations well above 75 μM. Thus, it is reasonable to presume that, in this study at least, the total plasma concentration after the high intravenous doses of cyamemazine metabolites investigated attained levels well above the concentration producing blockade of the hERG channel. However, as discussed previously, the protein binding of cyamemazine metabolites should be very high and, thus, the free plasma concentration, which is that seen by cardiac myocytes, may not attain a sufficiently high level to significantly impair the guinea pig IKr current. An alternative reason may be that cyamemazine is a weaker blocker of the guinea pig IKr channel than the hERG channel. However, relatively potent blockers of hERG and, including terfenadine, have been reported to significantly prolong the QT interval in the anesthetized guinea pig (Batay et al 1997; Chiang et al 2002; De Clerck et al 2002; Hamlin et al 2003; Testai et al 2004; Crumb et al 2006).

A number of theoretical limitations inherent to the model used in this investigation as well as to the pharmacokinetic properties of cyamemazine should be mentioned. In particular, there is not always a direct relationship between hERG channel blockade and the potential to induce TdP (Redfern et al 2003). Thus, some potent hERG blockers such as verapamil do not cause TdP in humans (Redfern et al 2003). The safety of verapamil is explained by a potent blockade of the L-type Ca channels, which tends to compensate for the repolarization disturbances induced by hERG channel blockade (Redfern et al 2003). A similar explanation was recently advanced for tolterodine, which potently blocks hERG and possesses excellent cardiac safety in humans (Kang et al 2004). So, a deviation of the hERG/TdP correlation can reflect an additional electrophysiological property of the compound. It is also possible that a drug with poor hERG activity is pro-arrhythmic in humans. The most obvious example is an active metabolite with hERG blocking activity or a compound interfering with other repolarization channels. However, in favour of the safety of cyamemazine is the vast clinical experience that mitigates any possible theoretical mechanism of TdP (cardiotoxic metabolite generated at clinically relevant concentrations, pharmacokinetic interactions with other drugs used concomitantly with cyamemazine, reduced repolarization reserve resulting from genetic or acquired factors, possible concurrent unfavourable cardiac electrophysiological properties), which could transform a weak hERG blocker, such as cyamemazine, into a dangerous proarrhythmic agent.

In conclusion, concentrations of cyamemazine metabolites required to inhibit hERG current had no relevant actions on \( I_{\text{IKr}}, I_{\text{INa}}, I_{\text{ISus}}, I_{\text{IK1}}, \) or \( I_{\text{ICa}} \) current amplitudes. Redfern et al (2003) suggest that drugs with a cardiac safety ratio greater than 30, appear to be clinically safe. Thus, comparison of the IC50 of cyamemazine metabolites against the hERG channel with therapeutic plasma concentrations or the affinities of the parent compound, strongly support the view that cyamemazine has a very high cardiac clinical safety profile. Cyamemazine metabolites in an in-vivo QT assay using anesthetized guinea pigs do not prolong the QT interval, appropriately corrected for the changes in heart rate. In contrast, the reference test article, terfenadine, delayed cardiac repolarization significantly, confirming the human QT interval liability of this drug, now withdrawn from the therapeutic market. Finally, the lack of adverse effects of cyamemazine metabolites on cardiac repolarization observed in this study is in accord with the excellent clinical cardiac tolerance records of this drug: over 30 years of clinical history has produced only a single case or cardiac arrhythmia (Gury et al 2000).

References


valle QT et le risque d’arythmies ventriculaires. Encephale 26: 62–72
prolongation, torsade de pointes and sudden death. Drugs 62:
1649–1671
Hameg, A., Bayle, F., Nuss, P., Dupuis, P., Garay, R. P., Dib, M.
(2003) Affinity of cyamemazine, an anxiolytic antipsychotic
drug, for human recombinant dopamine vs. serotonin receptor
Hamlin, R. L., Kijtawornrat, A., Keene, B. W., Hamlin, D. M.
(2003) QT and RR intervals in conscious and anesthetized guinea
pigs with highly varying RR intervals and given QTc-lengthening
test articles. Toxicol. Sci. 76: 437–442
Herzberg, I. M., Trudeau, M. C., Robertson, G. A. (1998) Transfer of
rapid inactivation and sensitivity to the class III antiarrhythmic
drug E-4031 from HERG to M-eag channels. J. Physiol. 511:
3–14
Hoehns, J. D., Stanford, R. H., Geraets, D. R., Skelly, K. S., Lee, H. C.,
Gaul, B. L. (2001) Torsades de pointes associated with chlorpro-
mazine: case report and review of associated ventricular arrhyth-
Kang, J., Chen, X. L., Wang, H., Ji, J., Reynolds, W., Lim, S.,
Hendrix, J., Rampe, D. (2004) Cardiac ion channel effects of
A comparison of the receptor binding and HERG channel
450: 37–41
antihistamines. Lancet 349: 1322
Palethorpe, S., Siegl, P. K. S., Strang, I., Sullivan, A. T., Wallis, R.,
preclinical cardiac electrophysiology, clinical QT interval prolonga-
tion and torsade de pointes for a broad range of drugs: evidence for
58: 32–45
Testai, L., Calderone, V., Salvatori, A., Breschi, M. C., Nieri, P.,
Martinotti, E. (2004) QT prolongation in anaesthetized guinea-
pigs: an experimental approach for preliminary screening of
torsadogenicity of drugs and drug candidates. J. Appl. Toxicol.
24: 217–222
Thomas, D., Wu, K., Katofer, S., Katus, H. A., Schoels, W., Kiehn, J.,
graphic changes in patients receiving neuroleptic medication.
Acta Psychiatr. Scand. 93: 311–313