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Effects of H_1 Antihistamines on Animal Models of QTc Prolongation

Jordi Gras and *Jesús Llenas*

Department of Pharmacological Development, Research Centre, Almirall Prodesfarma, Barcelona, Spain

Abstract

Objective: The clinical use of some nonsedating H_1 antihistamines (histamine H_1 receptor antagonists) has been associated with a rare but life-threatening type of arrhythmia, torsade de pointes, especially when these drugs are coadministered with cytochrome P450 (CYP) 3A4 enzyme inhibitors. On the basis of the latter observation and the fact that most of these H_1 antihistamines undergo extensive first-pass metabolism to active metabolites apparently devoid of cardiovascular adverse effects, this arrhythmogenicity has been attributed to the parent drug. The objective of this study was to find an animal model with the ability to predict the proclivity of drugs to produce torsade de pointes.

Design: Two experimental approaches were used: (i) blockade of CYP3A4 metabolism by coadministration of ketoconazole to increase the plasma concentrations of the parent compound in the conscious guinea-pig, and (ii) administration of the compound directly into the coronary circulation of the anaesthetised dog in order to circumvent first-pass metabolism.

Results: The first approach demonstrated that terfenadine administered in the presence of ketoconazole prolongs the corrected QT (QTc) interval of the electrocardiogram, whereas ebastine does not. Similarly, when terfenadine was administered through the coronary circulation, a statistically significant increase in the QTc interval was also seen, whereas ebastine and carebastine were without effect. Thus, it is clear that ebastine was much better tolerated than terfenadine from a cardiovascular standpoint, since ebastine and its metabolite are devoid of effects on cardiac repolarisation, as measured by the QTc interval in these animal models.

Antihistamines are among the most frequently prescribed drugs in developed countries and, unlike their predecessors, the new generation of such drugs are essentially without sedative or anticholinergic adverse effects. Terfenadine, the first nonsedating H_1 antihistamine (histamine H_1 receptor antagonist) to be approved in the US by the FDA (Federal Drug Administration) for the treatment of allergic rhinitis,[1] is extensively metabolised by hepatic first-pass metabolism. After the usual therapeutic dosages, plasma concentrations are below the limit of detection.[2] A specific cytochrome P450 (CYP) enzyme, CYP3A4, converts terfenadine to an active acid metabolite[3] now known as fexofenadine (INN).

Reports of the arrhythmogenic effects (torsade de pointes) of terfenadine and astemizole in the early part of this decade[4,5] have been subsequently confirmed. There has been much concern that other H_1 antihistamines might produce the

same effects, either when administered alone or with CYP3A4 blockers such as ketoconazole and erythromycin,[6,7] which inhibit the metabolism of most new generation antihistamines.

Torsade de pointes is defined as a polymorphic ventricular tachycardia that is characteristically preceded by a prolongation of ventricular repolarisation, which is reflected on the electrocardiogram (ECG) as a prolongation of the corrected QT (QTc) interval,[8] and is associated with the blockade of certain K^+ channels.[9]

There is an obvious interest in the development of preclinical pharmacological models capable of predicting such adverse cardiac effects. However, many of the models proposed have been single patch-clamped K^+ channels,[9-12] which do not allow for the possibility that the effects of inhibiting one ion channel may be nullified by opposing effects on other channels. Additional models have been based on other *in vitro* electrophysiological measurements that fail to take into account the influence of important pharmacokinetic parameters such as absorption, distribution, metabolism and elimination.[13,14]

There are considerable obstacles to be overcome before *in vivo* models can be used to predict the proclivity of drugs to induce torsade de pointes in humans. These include the lack of homogeneity of cardiac ion currents among animal species, together with the extensive first-pass metabolism of most H_1 antihistamines to metabolites that do not exert cardiovascular effects. Thus, although several attempts to find predictive animal models have been described in the literature,[15] none have offered results that are sufficiently clear to permit conclusions regarding the prediction of arrhythmias in humans.

One such animal model involves administering the α_1-agonist methoxamine to anaesthetised rabbits in order to evaluate the induction of torsade de pointes.[16] However, since a well known inducer of torsade de pointes in humans such as sotalol was unable to produce arrhythmia in this model,[15] it cannot be considered to be predictive. Another model, based on induction of hypokalaemia by high doses of furosemide (frusemide) in dogs with surgically induced complete atrioventricular block, has also been reported.[17] Quinidine and sotalol elicited torsade de pointes under these conditions, but the crucial limitation of this model is that the incidence of torsade de pointes is much higher than in the clinical setting and therefore it cannot be used to estimate quantitatively the proarrhythmic potency of new compounds in humans.[15]

Straightforward measurements of QTc intervals from ECGs would seem to be a much simpler, and the most logical, approach. However, with oral administration, interactions with inhibitors of metabolism need to be considered, and intravenous administration has obvious limitations concerning the relevance of the dose administered to the clinical situation. Furthermore, explicit comparisons of the effects of different antihistamines in the guinea-pig have been confounded and biased by the use of different scales with regard to the dose and change in QTc axes, and the administration of toxic doses of ketoconazole, which themselves rapidly induce prolonged increases in the QTc interval.[18,19]

We have therefore been interested in finding *in vivo* animal models that could more accurately predict the arrhythmogenic potential of new compounds by measuring effects on the QTc interval. Two different approaches were used: (i) inhibition of the metabolism of the compound by coadministering subtoxic doses of ketoconazole, and (ii) circumvention of first-pass gastrointestinal and hepatic metabolism by administering the compounds directly into the coronary circulation.

Comparative Effects of Terfenadine and Ebastine in Conscious Restrained Guinea-Pigs

The guinea-pigs were restrained minimally to permit implantation of ECG leads. ECG records were taken every 15 minutes until the QTc interval stabilised.

The effects of different doses of orally administered ketoconazole on the ECG of the conscious

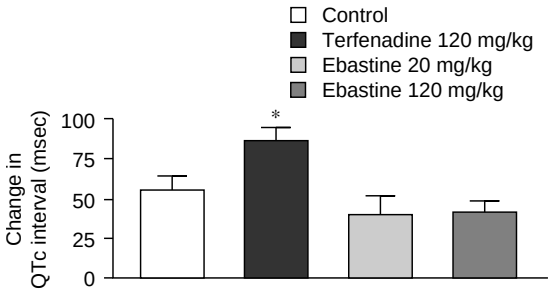

Fig. 1. Comparative effects of orally administered terfenadine and ebastine on the corrected QT (QTc) interval of ketoconazole-pretreated (50 mg/kg) conscious guinea-pigs. * represents a $p < 0.05$ difference *vs* control, according to Dunnet's multiple comparison test.

restrained guinea-pigs were then evaluated. Two hours after administration of 25, 35, 50 and 400 mg/kg, the QTc interval showed increases of 18 ± 10, 28 ± 10, 41 ± 9, and 64 ± 7 msec, respectively; 50 mg/kg was chosen as the most suitable dose for ensuring a submaximal prolongation of the QTc interval, thereby allowing scope for additional antihistamine-induced effects.

A subsequent experiment examined the effects of terfenadine and ebastine in animals pretreated with ketoconazole 2 hours previously. Under these conditions, administration of terfenadine (120 mg/kg), but not ebastine (20 and 120 mg/kg), produced an increase in the QTc interval (fig. 1), a finding confirming that previously reported effects of ebastine in this model were attributable to the direct effects of ketoconazole.[20]

Comparative Effects of Terfenadine and Ebastine and their Metabolites in the Anaesthetised Dog Model

The rationale behind this model is to avoid hepatic metabolism by directly administering the drugs into the coronary circulation, and to mimic the gradual and progressive bioavailability associated with oral administration.

Briefly, beagle dogs of either sex were anaesthetised with sodium pentobarbital (30 mg/kg + 6 mg/kg/h intravenously) and artificially ventilated with room air. A left thoracotomy through the fourth intercostal space was performed and the heart was suspended in a pericardial cradle. The left circumflex coronary artery was dissected minimally 2 to 4cm distal to its origin and a polyethylene cannula inserted into the lumen of the artery. Another polyethylene catheter was inserted into the right common carotid artery for blood pressure and heart rate measurements.

An electrocardiograph (Hewlett Packard, model M1700A) was used to record 4-lead surface ECGs. Compounds were infused at doses of 10 and 30 μg/min over a 60-minute period to 5 separate groups of 3 dogs each. A period of 60 minutes was allowed between each intracoronary infusion.

The effects of terfenadine, terfenadine carboxylate (fexofenadine), ebastine and its active metabolite, carebastine, were evaluated after infusion (10 and 30 μg/min) into the coronary circulation of the anaesthetised dogs. No significant changes were observed in the measured parameters after drug administration at a dose of 10 μg/min, although terfenadine showed a tendency to increase (28

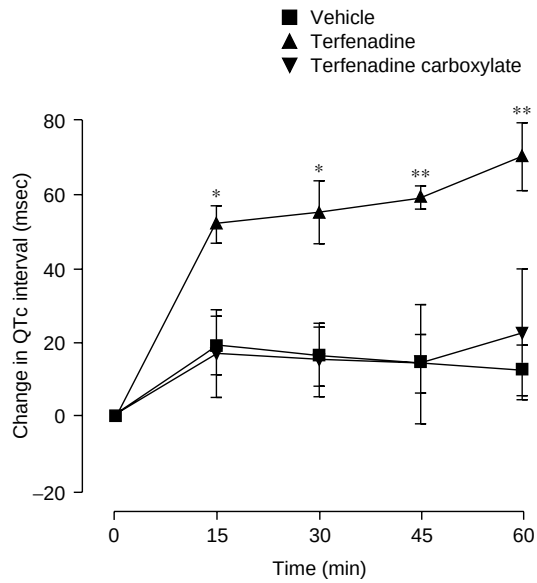

Fig. 2. Comparative effects of terfenadine and terfenadine carboxylate administered by intracoronary infusion (30 μg/min) on the corrected QT (QTc) interval in anaesthetised beagle dogs. * $p < 0.05$, ** $p < 0.01$ *vs* vehicle.

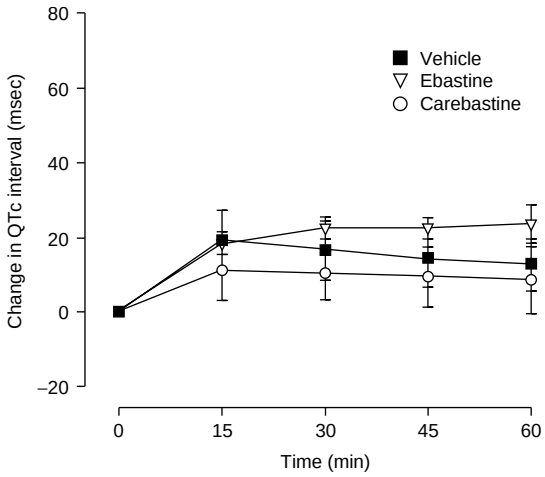

Fig. 3. Comparative effects of ebastine and carebastine administered by intracoronary infusion (30 μg/min) on the corrected QT (QTc) interval in anaesthetised beagle dogs.

msec), and carebastine tended to decrease (–7 msec), the QTc interval compared with the vehicle (10 msec). At a dose of 30 μg/min (figs 2 and 3), terfenadine caused significantly more prolongation (55 msec; $p < 0.05$) of the QTc interval than the vehicle (12 msec) after 30 minutes' infusion, with an even greater effect (70 msec; $p < 0.01$) after 60 minutes' infusion. No statistically significant effects were observed with either ebastine (23 msec), terfenadine carboxylate (22 msec) or carebastine (9 msec), even after 60 minutes' infusion. These results were previously communicated in part to the XXVth Annual Meeting of the European Academy of Allergology and Clinical Immunology (EAACI).[21]

Discussion

The main objective of the studies described was to establish appropriate *in vivo* animal models for detecting antihistamine-induced changes in the QTc interval of the ECG, in order to predict the proclivity to produce life-threatening arrhythmias such as torsade de pointes in humans.

Because it appears to be the parent drugs (i.e. terfenadine or astemizole), and not their main metabolites, that cause arrhythmias in clinical use, we have tried to ensure the presence of the drugs in the heart in sufficient concentrations, either by using ketoconazole to inhibit first-pass gastrointestinal and hepatic metabolism after oral administration, or by infusing the drugs directly into the heart through a coronary artery.

We found firstly that ketoconazole increased the QTc interval in conscious restrained guinea-pigs in a dose-dependent manner. The LD_{50} (dose that would be lethal to 50% of animals) of ketoconazole in male guinea-pigs is 178 mg/kg,[22] and a dose of 400 mg/kg produces a maximal prolongation of the QTc interval, thereby precluding detection of any additional prolongation caused by the subsequent administration of other compounds.[19] Thus, we tested ketoconazole at lower doses in order to identify submaximal effects, and chose the 50 mg/kg dose as the most appropriate. When this dose was used, a significant additional prolongation of the QTc interval was obtained with terfenadine but not with ebastine. This finding is clearly at variance with that recently described by Hey et al.,[23] who reported that ketoconazole did not affect the QTc interval, a misleading result presumably arising from the use of flawed protocols. The probable explanation for the discrepancy is that, in the non-telemetric studies of Hey et al.,[23] the period of time that had elapsed from the ketoconazole dosage to the first ECG measurement was sufficient for ketoconazole to have already exerted most of its effect on the QTc interval. Our results are consistent with those of Williams et al.,[24] who demonstrated that ketoconazole does in fact increase the QTc interval in telemetered guinea-pigs, and with the report of significant QTc prolongation at therapeutic doses of ketoconazole under clinical conditions.[25]

The second approach we tested (i.e. administering the compound directly into the heart through a coronary artery) allowed us to observe the effect of drugs on the ECG without inducing marked haemodynamic changes, an important consideration in view of the known effects of some antihistamines, including terfenadine, on calcium entry and consequently on blood pressure. In our study, terfenadine increased the QTc interval in a very

significant manner, although no arrhythmias occurred. No significant effects were observed after administration of ebastine, carebastine or fexofenadine at the same doses as terfenadine. Prolongation of the QTc interval was also noted in 25 cases of terfenadine-associated arrhythmias reported to the FDA in April 1992.[26]

The results obtained with the models described in this study agree with the conclusions reported by Woosley et al.,[26] Rampe et al.,[27] Crumb & Brown[28] and Valenzuela et al.,[29] who used cat ventricular myocytes, human atrial myocytes, a human cell line (HEK-293) transfected with a human rapidly activating delayed rectifier K^+ channel (FHK), and a human Kv1.5 channel expressed in Ltk^- cells, respectively. In these models, terfenadine, but not fexofenadine, blocked K^+ currents, which is consistent with its reported proarrhythmic tendencies in clinical settings.

Conclusions

In conclusion, the models described in this study can be useful for determining whether other H_1 antihistamines with important first-pass metabolism could have arrhythmogenic effects. The results obtained with ebastine and carebastine in both models suggest that ebastine is a much safer antihistamine than terfenadine in terms of potential cardiac adverse effects. This is consistent with findings from clinical settings, where ebastine has never been associated with serious adverse cardiovascular effects,[30] since both parent compound and metabolite are devoid of effects on cardiac repolarisation as measured by the QTc interval in these models.

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Correspondence and reprints: Dr *Jordi Gras,* Department of Pharmacological Development, Research Centre, Almirall Prodesfarma S.A., Cardener, 68-74, 08024 Barcelona, Spain.