Drug Safety 1999; 21 Suppl. 1: 89-92
0114-5916/99/0001-0089/$02.00/0

Epilogue

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Two years have passed since the presentation of the original cardiac tolerability data in the roundtable conference. It is therefore both desirable and obligatory to comment on new data generated since that event, and how such data and related considerations may have impacted on the ideas discussed and conclusions drawn at that time.

Ebastine is now on the market in some 33 countries including 16 in Europe, 9 in South America and 5 in Asia, and has received marketing authorisation in 16 more. As of December 1998, sales have reached 388.5 million DDDs (defined daily doses of 10mg), and no reports of torsade de pointes have been received.

On the negative side, presumably because of the absence of relevant published clinical data on the cardiac tolerability of ebastine, authors of antihistamine review articles have consistently used the disputed[1,2] guinea-pig data[3,4] to conclude that ebastine has 'arrhythmogenic potential'.[5-7] One of these reviews[7] went so far in its extrapolation from animal data to human risk that it was necessary to publish a rebuttal.[8] Others have more reasonably acknowledged that the doses of ebastine used in guinea-pigs were 'large', that 'there is no evidence that this effect is of any clinical relevance', and that it has been shown to be 'safe in patients', in whom 'no clinically relevant cardiac events have been observed with ebastine to date'.[9,10]

In any event, the demonstration that the main metabolite of loratadine, descarboethoxyloratadine, can also prolong the corrected QT (QTc) interval in anaesthetised guinea-pigs following intravenous administration of high doses[11] should presumably serve to convince the originators of the model[3] that it does not predict the proclivity of a drug to produce arrhythmias in humans, at least when used under these conditions.

By contrast, oral administration of antihistamines to conscious guinea-pigs pretreated with a dose of ketoconazole, which itself induces only a submaximal prolongation of the QTc interval, has shown that although terfenadine does indeed produce a further increase in the QTc interval, ebastine does not.[12]

Curiously, the various publications refuting the validity of the guinea-pig studies[1,2,13] have never been quoted in any of these review articles[5-7,9,10], perhaps indicating a problem of relying on database searches when the words 'ebastine' or even 'antihistamines' do not appear in article titles.

This is clearly not the case in a publication dedicated almost exclusively to the effects of ebastine on mammalian K^+ channels,[14] which was also identified by some reviewers, and which has been included in the review of antihistamine effects on K^+ and other channels appearing in this supplement to *Drug Safety*.[15]

In this paper,[14] the quoted effective dissociation constant (K_D) values for inhibition of the various K^+ channels are of course values for 50% of the different maximum inhibitions obtainable with the different antihistamines, and not 50% of complete inhibition of the channels. This leads to potential misinterpretations of potency when the former is considerably less than 100% as, for example, when the K_D value of ebastine in blocking the human erg-related (HERG) channel is quoted as 300 nmol/L compared with 400 nmol/L for terfenadine.[14] In reality, even 30 000 nmol/L of ebastine failed to produce 50% inhibition, and 300 nmol/L

represents 23% inhibition, or 50% of the 46% maximum inhibition.

By contrast, 3000 nmol/L of terfenadine produced 70% inhibition of the current, while 400 nmol/L represents 40% inhibition, or 50% of the 80% maximum inhibition.

In addition, the effects of ebastine on HERG currents have been recently investigated in comparison with other antihistamines, in experiments using Chinese hamster ovary cells transfected with this channel.[16]

Ebastine was found to have an IC_{50} value (concentration producing 50% inhibition) of 1 μmol/L and exerted a maximum inhibition (80%) of the current at 10 μmol/L. Terfenadine inhibited the current by 50% at a concentration of 130 nmol/L and exerted a maximum inhibition (90%) at 0.3 μmol/L. The IC_{50} value for carebastine was greater than 10 μmol/L (38% inhibition) and at the same concentration only minor effects were noted with loratadine (19%), descarboethoxyloratadine (19%) and fexofenadine (20%).

Clearly, despite the fact that the actual HERG channel is always the same clone, the results obtained with the different antihistamines are very dependent on the tissue used for transfection, as well as on the conditions applied (including ion concentrations, temperature of the external bathing liquid, and the strength and rate of the stimulations applied).

The most recent demonstration of this is the revelation[17] that, when the HERG channel transfected into human embryonic kidney cells was used and studied at 35°C, with an external physiological K^+ concentration of 4 nmol/L and a pacing rate of 0.1Hz, HERG was markedly blocked by 100 nmol/L loratadine ($49.6 \pm 53\%$, $n = 6$), to the same extent as by 100 nmol/L terfenadine ($41.1 \pm 5.1\%$, $n = 6$).

Previous studies with HERG expressed in *Xenopus oocytes*, studied at room temperature with an elevated external K^+ concentration of 10 nmol/L, had shown that concentrations of 30 μmol/L loratadine were required to show some blockade of HERG under these conditions.[6]

Observations such as these add weight to the point made in the Panel Discussion[18] about 'inventing a model' that makes any particular drug perform well (or badly). Overall, the new data made available since the round-table conference have confirmed the main conclusions reached at that time – that none of the models were valid *per se* for predicting the proclivity of drugs for inducing torsade de pointes and other ventricular arrhythmias in humans.

Whether the use of the HERG channel transfected into human cells and run under human physiological conditions will eventually change this conclusion remains to be seen. Certainly, studies are now underway with a variety of antihistamines and their metabolites (William Crumb, personal communication), and time alone will tell whether the results obtained correlate with clinical experience.

In the meantime, such esoteric considerations have not affected the operating procedures of many contract research organisations (CROs) who have taken the Committee for Proprietary Medicinal Products (CPMP) *Points to Consider* document[19] as a guideline, and who will offer to perform the specific preclinical tests and the precise clinical electrocardiography described in the document.

Because the preamble to the document[19] promises that 'since scientific knowledge in this field is developing rapidly, this document will need to be revised accordingly to keep pace with this ongoing development', it is presumed that the CROs will also have to modify their expertise accordingly, especially in the more controversial preclinical area. Furthermore, the CPMP document in its final version now allows for a certain amount of choice between the tissues (Purkinje fibres or papillary muscle) and species (rabbit, guinea-pig, dog or pig) to be used preclinically, and some drugs can affect repolarisation in some, but not all, of the multiple possible permutations of conditions. This again raises the question of the deliberate choice of models to make any particular drug perform well or badly.[18]

Since the publication of the CPMP document, measurement of drug effects on cardiac repolarisation and their significance in terms of drug-induced ventricular arrhythmias have also become an area of interest for the organisers of symposia. Sensing the regulatory concern and the consequent pressure exerted on the industry, they have stimulated debate between the different players involved in an attempt to obtain a consensus on how to predict arrhythmogenic potential in noncardiovascular drugs.[20-23]

The number of such extremely well attended meetings organised during the last 2 years – at least one of these was repeated 4 times in less than 12 months – is clear evidence of the concerns of the industry in deciding how to deal most appropriately with the new regulatory pressure. It also demonstrates the doubts that exist, in the minds of both the regulated and the regulators, about the validity of many of the proposals and interpretations that are being made.

Unfortunately, a consensus does not exist regarding the preclinical models that should be routinely used during drug development or the value of the various models in predicting arrhythmogenic effects in man.

Similarly, there are important differences of opinion concerning exactly how many msec of QTc prolongation seen in clinical studies should be considered relevant, a situation complicated by the difficulty of making accurate measurements from the ECG and the wide intra-individual diurnal variation in the QTc interval seen in the absence of drug treatment.[24,25]

Another unresolved question is how best to correct the measured QT interval for changes in heart rate, and this issue has special relevance in the case of ebastine, which induces small but dose-related increases in heart rate and correspondingly actually shortens the uncorrected QT interval. It is well known that the much used Bazett's (square-root) formula undercorrects the QT interval at heart rates slower than 60 beats/min and overcorrects at faster heart rates,[26-31] and it has been suggested that the uncorrected QT interval may be more valuable for the prediction of torsade de pointes.[26,27] Fridericia's (cube-root) formula, although still far from perfect, appears to provide more physiological correction and, when this formula was used, ebastine, even at 5 to 10 times the recommended dose, had no effect on the QTc interval in humans.[32]

Under these circumstances, any further considerations of the validity or otherwise of *in vitro* or *in vivo* animal models for predicting the proclivity of ebastine for inducing QT-related cardiac arrhythmias in man would not be helpful.

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