LEADING ARTICLE

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Prologue

David J. Roberts

Scientific and Regulatory Affairs, Almirall Prodesfarma, Barcelona, Spain

The recognition by Dale[1] of an active role for histamine in the mediation of allergic and anaphylactic reactions was eventually followed by the introduction, now some 50 years ago, of drugs that had been shown to protect guinea-pigs from histamine-induced anaphylactic shock. These quickly became established in the treatment of rhinitis, conjunctivitis, urticaria and other manifestations of allergic disorders.[2]

However, the complete acceptance and utility of these 'antihistamines' was limited by the fact that, to a greater or lesser extent, they induced troublesome adverse effects consisting principally of sedation and atropine-like effects on secretions and visual accommodation.

Despite extensive research efforts to find compounds without these adverse effects, the situation remained essentially unchanged until the serendipitous discovery of terfenadine as the first of a new generation of nonsedating antihistamines,[3] to which astemizole was soon added.[4]

Several years of trouble-free extensive usage were followed, from 1986 onwards, by published reports associating overdoses of these two antihistamines with the appearance of ventricular arrhythmias in the form of torsade de pointes.[5] Soon after this, the same phenomenon was encountered in patients in whom the metabolism of the drugs was compromised, either by liver disease or concomitant treatment with specific cytochrome P450 CYP3A4 inhibitors such as azole antifungals and macrolide antibiotics, and/or who were at risk of torsade de pointes because of congenital prolongation of the QT interval, congestive heart failure, ischaemic heart disease or hypokalaemia.[6]

It was subsequently demonstrated in nonclinical models that terfenadine, but not its metabolite, could block cardiac potassium channels, delay the repolarisation phase of the action potential of cardiac myocytes or Purkinje fibres, and prolong the QT interval of the electrocardiogram. This provided a readily acceptable explanation of the mechanism of the arrhythmias found in the clinic and related them to high serum concentrations of unmetabolised drug.[5]

The reported incidence of torsade de pointes with terfenadine and astemizole was extremely low (1 in several million patients) – much too low for it to be even remotely identifiable as an adverse effect in the usual 4000 or so patients treated during the normal clinical development of a drug. Thus, there was an obvious and immediate interest in using nonclinical models as surrogate indicators of this potential arrhythmogenic hazard in humans with regard to other drugs under development.

Many such models were developed and 'validated' by the demonstration of positive results with terfenadine (or astemizole) and negative results with one or other of the apparently nonarrhythmogenic antihistamines.[6-9]

Meanwhile, the American Food and Drug Administration (FDA) progressively strengthened the labelling of terfenadine and astemizole to include 'black box' warnings in 1992,[10] and eventually insisted on the withdrawal of the former from the US market. They also facilitated the rapid replacement of terfenadine by its apparently noncardiotoxic metabolite, fexofenadine, produced and marketed by the same company.[11]

In Europe, there appeared to be much less of a problem; indeed, in several countries terfenadine, including the 'forte' 120mg presentation, was still

being sold as an over-the-counter product in 1997. Nevertheless, in February 1997, France presented to the European Agency for the Evaluation of Medicinal Products (EMEA) a referral under Article 12 of Council Directive 75/319/EEC, as amended by Directive 93/39/EEC, asking the Committee for Proprietary Medicinal Products (CPMP) 'to give an opinion on whether there [was] an unfavourable benefit/risk ratio for terfenadine in relation to its arrhythmogenic potential...in comparison with existing alternative nonsedative anti-histamine drugs available for the same indications in the European Union'. The CPMP opinion (not unanimous) finalised one year later was that there was no need for terfenadine to be withdrawn from the European market, but that its labelling should be extensively modified to include more warnings.[12]

The CPMP also issued a *Points to Consider* document for 'The assessment of the potential for QT interval prolongation by noncardiovascular medicinal products' (draft March 1997, final version December 1997). This goes into quite considerable detail in terms of 'recommendations' for both preclinical and clinical testing of compounds to identify QT prolongations, and the data requirements to provide reassurance concerning the safe clinical use of such products.[13]

In the midst of all this activity, ebastine, a new antihistamine marketed in Spain since 1990,[14] was being reviewed for international regulatory approval at the recommended doses of 10 or 20mg once daily.

Despite accumulated evidence of clinical safety, certain European regulatory authorities, who had obviously had members involved in the production of the *Points to Consider* document cited above, insisted on further nonclinical *in vitro* electrophysiological studies. The FDA also requested specific cardiac safety studies using ebastine alone, at high doses, and in the presence of ketoconazole and erythromycin, in humans.

Carebastine, the active metabolite of ebastine, but not the parent compound, was shown to have weak activity in prolonging the action potential of the CPMP-recommended *in vitro* rabbit Purkinje fibre preparation.[15] Small, statistically significant but not clinically meaningful, increases in the QTc interval were seen in humans following repeated administration of ebastine alone, at high doses,[16] and in the presence of ketoconazole and erythromycin.[17,18]

In vivo studies in the dog showed that oral (conscious) or intracoronary (anaesthetised) administration of ebastine or carebastine was without effect on the QTc interval.[19]

The use of what were later to be called 'flawed' protocols in guinea-pig QTc models for 'predicting' human arrhythmogenic potential served to complicate the situation, and it was claimed, also on the basis of a superficial similarity in the chemical structures of terfenadine and ebastine, that the latter should have 'similar arrhythmogenic proclivity' to the former.[20,21]

Evidence was soon provided to show that, in the oral administration interaction guinea-pig model, the apparent QTc interval prolonging effects of ebastine were in fact attributable to ketoconazole, which itself produced a maximal increase, of rapid onset and long duration, in the QTc interval.[22,23]

Likewise, in the intravenous guinea-pig model, the apparent similarity between the effects of terfenadine and ebastine was clearly a function of the use of different scales on the axes for both dose and change in QTc.[24] It was nevertheless true that, whereas high intravenous doses (10 to 50 mg/kg) of ebastine did cause some prolongation of the QTc interval, the same doses of carebastine did not.

This was completely contrary to what had been seen in the *in vitro* rabbit Purkinje fibre studies.

Since the high dose and interaction studies with ebastine in humans were producing evidence for only small, not clinically relevant, changes in the QTc interval, it was decided that steps should be taken to try and resolve the apparent anomalies seen in animals. To this end, a Round Table Conference was organised so that appropriate experts, under the chairmanship of Prof. Arthur Moss, could discuss 'the value of preclinical models in the prediction of antihistamine-induced torsade de pointes in man'.

This supplement to *Drug Safety* comprises the presentations made at the Round Table Conference held in Barcelona on April 25, 1997.

Publication has been delayed because of the need to repeat certain comparative studies, e.g. the Dupuis rabbit Purkinje fibre model, in order to generate data on compounds developed by other companies, which were not covered by confidentiality agreements. There were also some real or perceived initial doubts concerning copyright issues for the future publication *in extenso* of some of the important clinical data.

This delay has meant that several of the manuscripts have been updated. Nevertheless, this has in no way detracted from what is unquestionably a valuable attempt to put into perspective the importance or otherwise of pharmacological effects on cardiac repolarisation in nonclinical models, in terms of their relationship to QTc prolongation, torsade de pointes and other arrhythmias in humans.

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Correspondence and reprints: Dr *D. J. Roberts*, Scientific and Regulatory Affairs, Almirall Prodesfarma S.A., General Mitre, 151, 08022 Barcelona, Spain.