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Panel Discussion

Chairman: *Professor Arthur Moss*

During the various discussion sessions, it became clear that there were several recurring themes, and the most pertinent of the various comments have been grouped together under titles appropriate to these themes. As stated in the prologue, some of the discussion has been incorporated into the manuscripts and is not repeated here.

1. Do Purkinje Fibres Provide the Best Preclinical Model for Predicting Arrhythmogenic Activity with a Noncardiovascular Compound?

Prof. A. Moss: The question one of the speakers raised during his presentation was 'What is the reason for studying the drugs in Purkinje fibres?' In the Committee for Proprietary Medicinal Products (CPMP) draft document *Points to Consider*, this was the only model proposed for initial screening, and, as such, its methodology was described in considerable detail. It has frequently been asked why this model is considered to be so special. In my opinion, the reasons are probably that (i) Purkinje fibres are easily accessible and that (ii) they have a very long action potential and are probably the closest representation of M cells. Their recommendation by the CPMP clearly relates to a particular individual from France who has done much of his work on Purkinje fibres. I think that this is simply one of many models.

Dr F. de Andrés: I feel this comment is directed at me, because the CPMP guidelines have been mentioned and I was lucky enough to attend some of the meetings of the CPMP *ad hoc* group of experts who drafted the document. The guidelines have now been released for individuals to comment on as they wish. I agree with Professor Moss that the Purkinje fibres preparation is one of many models to be chosen for testing the arrhythmogenic potential of drugs. However, other considerations are whether or not compounds are undergoing preclinical research or are already marketed. For the latter, what can be seen in the postmarketing databases is important. In the case of antihistamines, we know from databases that some have cardiac effects and others apparently do not. If we wish to make preclinical predictions for drugs not yet marketed, first we need to validate the models. Of course, one can invent a model for a particular drug and then state that the drug performs well in this model, but this is not fair. One should avoid generating hypotheses and confirming them in the same model.

Dr D.J. Roberts: It is equally unfair to invent a model to show that a competitor drug performs badly.

However, returning to the question of Purkinje fibres, where carebastine but not ebastine had a small effect, it has recently been shown that neither has any effect on the action potential duration (APD) of guinea-pig papillary muscle. Why should one model be considered valid and the other not?

Furthermore, the absence of the Kv1.5 channel in the rabbit Purkinje fibre means that blockade of this channel by drugs such as loratadine, as has been shown by Professor Tamargo and his team, would not be detected in this model.

Additionally, both fexofenadine (at high concentrations) and especially descarboethoxyloratadine have been shown to affect the action potential in the rabbit Purkinje fibre.

2. APD/QT Prolongation and Torsade de Pointes Arrhythmia

Dr de Andrés: My question is whether we

should be concerned about torsade de pointes whenever the APD is prolonged? Amiodarone, for example, has a large effect on the APD but is not associated with excessive torsade de pointes.

Prof. J. Tamargo: This is an interesting question, and I want to address your point about amiodarone. I think everybody agrees that the incidence of torsade de pointes with this drug is significantly lower than with all other class III compounds. However, amiodarone is not a pure class III antiarrhythmic, but rather a class I, II, III and IV drug, which also has vasodilator and anti-ischaemic effects. Which of all these effects is/are responsible for conversion to sinus rhythm? Maybe different ones in different patients, although it has been proposed that amiodarone could block early afterdepolarisation. Furthermore, as with prazosin, amiodarone does not have the reverse use-dependent prolonging effect on APD seen with other drugs. Amiodarone is a drug that prolongs the APD but protects against, instead of producing, rhythm disturbances.

Dr Roberts: One of the more classical explanations of the lack of rhythm disturbances with amiodarone use is that there is no dispersion of the APD/QT prolongation over the different areas of the myocardium, whereas it has been suggested that, with some of the other drugs, its dispersion is more important than the QT prolongation *per se*.

Prof. Tamargo: These data came from a group in France more than 15 years ago. They found that amiodarone lengthened the action potential in the fibres with the shortest APD, whereas prolongation was minimal in those with the longest APD.

Prof. Moss: I do not think we should spend much time with amiodarone. It is a complex and controversial drug with potential for serious adverse effects – possibly no better than placebo as an antiarrhythmic agent – and is diverting attention from what we should be focusing on. The whole concept of developing antiarrhythmic agents and prolonging APD seems a little strange. I think the field of antiarrhythmic agents is complex and, at present, the focus should be on drugs that are prescribed for other indications and that can affect ventricular repolarisation. At what point should serious questions be put regarding particular drugs? There may have been millions of prescriptions written for terfenadine, the agent that has caused all the concern, while to my knowledge there have been only 14 to 15 major adverse effects reported. So, it seems to me that if one can show that a drug is in the same general category as terfenadine (i.e. a nonsedating antihistamine), if it can be used once daily at similar (or lower) doses, if its therapeutic effect is equal (or superior) to that of terfenadine, and if in humans and in animal models the cardiac effects are an order of magnitude less in terms of either ADP/QT prolongation or channel dysfunction, then this is the best we can do.

Dr Roberts: Has it really been shown that there is a clear relationship *only* between an absolute prolongation of the QTc and the induction of torsade de pointes, or is something else required, such as the morphological changes that Professor Moss was discussing?

Prof. Moss: But we do know that torsade de pointes is related to the length of the QTc interval. There is a direct exponential relationship between the length of the QTc interval and the likelihood of torsade de pointes. Thus, it is a continuum.

Dr Roberts: I have read that anything <500 msec represents a low risk of torsade de pointes. Do you agree with that?

Prof. Moss: Yes, but it's not a zero risk, since I showed that, if the QTc interval is increased from 0.44 to 0.49 sec, this would represent a negligible increased risk of 1.1 (1.052^5). Thus, it would have some potential to induce torsade de pointes, although we generally don't see complex rhythms until the QTc exceeds 0.5 sec or, according to many people, not until say >0.52.

Dr Roberts: In all the studies we have conducted, even at high doses and in the presence of ketoconazole, we have never observed a QTc of ≥0.50 sec.

By contrast, I think all but one of the cases of torsade de pointes reported in the literature for terfenadine had QTc values, where measured, >0.50 sec.

Prof. Moss: We had the opportunity of reviewing 128 cases of Benadryl® (diphenhydramine) overdose, and found some modest QTc prolongations. These were genuine diphenhydramine overdoses, and no malignant arrhythmias were observed in any of the patients.

Dr I. Cavero: Have any overdoses of ebastine been reported in Spain.

Dr X. Luria: No, there are no reports.

3. What Model Is the Most Relevant for Evaluating the Proarrhythmic Effects of a Noncardiovascular Drug?

Prof. Moss: Let me ask a very focused question: with the information we have, what would be the most relevant model in which to evaluate the proarrhythmic potential of a drug such as ebastine?

Prof. Tamargo: I would select the rat, the guinea-pig and the rabbit, and start with *in vivo* experiments recording ECG. I choose 3 animal species because the currents responsible for repolarisation are different in each one *in vivo*. I would then move immediately into simple *in vitro* experiments, such as Purkinje fibres and isolated papillary muscles; finally, I would select a specific channel such as the human erg-related channel (HERG).

Prof. Moss: Would you still go through 2 or 3 different animal species?

Prof. Tamargo: These are very simple experiments, because with an ECG recording one can obtain the required information – that specific K^+ channels are involved – in less than a couple of weeks.

Dr Cavero: In my opinion, the question is 'Does an effect found in rabbits, or in any other animal species, have any clinical relevance?'

What we should consider first is the concentration at which the relevant electrophysiological effects are observed. If the concentration is 10 μmol/L, I would be quite confident of the cardiac safety of compounds such as ebastine and carebastine, since the free plasma concentrations of these compounds are much less than 0.1 μmol/L, and because the compound predominantly present in plasma does not accumulate substantially in cardiac tissue. Even if one wanted to commit suicide with these drugs, myocardial concentrations of 10 μmol/L would be extremely difficult to attain. The problem is in patients with additional cardiac risks. I do not know what the safety margin would be for such individuals, but I suppose that a 100-fold separation between the clinically achievable concentration in the heart and the one producing a significant change in one or more relevant potassium currents [such as I_{Kr} (HERG), I_{to}, I_{Ks}, I_{sus} and I_{K1}] would be sufficiently safe. No company should reject *a priori* an excellent drug with a 100-fold or even a 30-fold cardiac safety margin for clinical trials.

One obviously needs to conduct some studies in humans, to examine accumulation very carefully (both in rabbits and, if possible, in human cardiac tissue), make comparisons with a reference compound (in this case terfenadine or astemizole), and draw clear-cut pharmacological conclusions.

I don't think there is another approach, unless one studies 10 million patients.

In the case of ebastine, it is clear we should also study the metabolite.

Prof. Moss: Since we already have a drug that is widely marketed, any questions relating to preclinical models, i.e. before administration in humans, would therefore appear to be a little late. One could spend the next 10 years exploring every conceivable channel; I don't think this is particularly relevant in view of what is known about terfenadine, which is the drug that ebastine is being compared with.

Dr de Andrés: I feel it is always tricky, and not likely to be successful, to try to resolve postmarketing problems with screening methods, because such methods are meant to forecast potential postmarketing problems. In this instance, the postmarketing programme is already underway and, unless we have an absolute and unequivocal explanation for the problem with terfenadine, we are at a standstill. Thus, if we say that terfenadine is bad because it blocks a certain potassium channel, we could then test ebastine (or any other drug)

on a pure population of that channel, whether expressed in a particular cell, patch clamp, or whatever, and subsequently conclude that if ebastine doesn't block the channel there is no problem. However, if one cannot be certain of the channel implicated in the cardiotoxicity of terfenadine, there will always be an alternative channel, an alternative explanation, and there will always be some people who don't want to believe it and who say so in writing.

If the drug is already marketed, such suggestions do not make sense. If there are a large number of well controlled patients in whom the QT intervals etc. are measured and it can be seen how safe this drug is in this respect, then this is sufficient.

However, if there were results relating to the potassium channels that could clarify a point of view, then that is a different matter.

Dr J. Llenas: Let me add some as yet unreported information that refers to the cardiac accumulation of antihistamines. I agree with Dr Cavero that the effects of a compound at a concentration as high as 10 μmol/L on whatever relevant ion channel should not be taken into account, unless a similar concentration could be achieved in the target organ – in the present case the heart. This is the explanation that has been given for the lack of arrhythmogenicity with cetirizine, despite the fact that it does cause some prolongation of the APD in the already much discussed rabbit Purkinje fibre model recommended by the CPMP.

In order to see whether this also applied to carebastine, we investigated its accumulation in the left ventricle of the rabbit heart perfused according to Langendorff's technique, in comparison with astemizole, terfenadine, cetirizine and, although it does not affect the APD in rabbit Purkinje fibres, ebastine. After 1 hour of perfusion with a solution containing a concentration of 1 μmol/L (much more than 10 times the maximum free plasma concentration achievable when the drugs are given either at supra-therapeutic doses or when they are administered concomitantly with cytochrome P450 3A4 inhibitors), we found myocardial tissue content to perfusion medium content ratios of 238 ± 23, 180 ± 22, 35 ± 4, 16 ± 2 and 1 ± 0.1 for astemizole, terfenadine, ebastine, carebastine and cetirizine, respectively.

Dr Cavero: These results allow separation of the compounds into two different classes: those which markedly accumulate and those which do not; however, are you sure that 1 hour's exposure is sufficient to attain steady state?

Dr Llenas: To answer this question, we recently performed a new experiment with carebastine that prolonged the perfusion time for up to 3 hours. The myocardial tissue content to perfusion medium content ratios from this new experiment were 470 ± 34, 7 ± 1 and 0.5 ± 0.1 for astemizole, carebastine and cetirizine, respectively.

4. Effects of H_1 Antihistamines on Animal QTc Interval Measurement

Prof. Moss: Dr Gras has mentioned different animal models in which the QTc interval (or the ability to produce arrhythmias is measured), and it seems that in almost all of them terfenadine (and perhaps astemizole) shows a significant effect. However, this does not appear to be the case for the other antihistamines studied, such as fexofenadine, ebastine, carebastine, loratadine, and descarboethoxyloratadine, which appear to be active in only one or two tests. How can this fact be explained?

Dr J. Gras: In my opinion (and available data would seem to be in agreement with this), terfenadine blocks most ion channels, which have a major role in the ventricular repolarisation process, whereas the other antihistamines do not. Ebastine, for example, blocks the HERG only at a concentration >30 times higher than the corresponding terfenadine concentration, when their therapeutic doses are taken into account. Another example is loratadine and descarboethoxyloratadine, which seem to block the human cardiac K^+ channel (hKv1.5) only. The fexofenadine- and cetirizine-induced arrhythmias seen only in some specific models should also be related to their blocking effects on at least one, but not necessarily the same one, of the many such ion channels present in cardiac cells.

Incidentally, we have recently shown that high intravenous doses of descarboethoxyloratadine also prolong the QTc interval and induce arrhythmias in the anaesthetised guinea-pig.

Dr J.M. Palacios: I would also like to emphasise the fact that the pharmacological models are comparing potencies at the same dose levels, whereas in clinical practice the dose of ebastine (10 to 20mg daily) is much lower than that of terfenadine (60mg twice daily or 120mg daily).

Dr Roberts: It is also important to remember that the *in vivo* models are measuring, in most instances, QT intervals or related phenomena in the anatomically and physiologically complete animal, where individual effects on a single system may be compensated for by appropriate homeostatic mechanisms.

This is also true, but less so, for whole cell *in vitro* preparations where the effect on one channel could be compensated for by another effect on a different channel.

This option is obviously not available for studies conducted using single channel preparations. This means that, although such models are useful for providing possible pharmacological mechanistic explanations of phenomena found *in vivo*, they are not necessarily predictive of what might happen in the complete organism.

5. What is the Evidence for Cardiac Arrhythmias in Man?

Dr Roberts: There are clearly now numerous reports of the arrhythmogenic effects of astemizole and terfenadine. The only other antihistamine whose clinical use has been associated with published arrhythmias is loratadine. The literature reports are predominantly of supraventricular arrhythmias, a finding perhaps not surprising considering the relatively potent effects of loratadine on the hKv1.5 channel, as described by Professor Tamargo.

Data from the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, confirm this situation: although only 29 of the 45 countries reporting to the WHO have authorised the general availability of their data, as of December 1996 some 913 reports of arrhythmias had been received for terfenadine, 287 for astemizole and 348 for loratadine.

Of the reports that actually mentioned whether the arrhythmia was supraventricular (atrial) or ventricular, for astemizole 92 (94%) were ventricular (4 torsade de pointes) and the corresponding figures for terfenadine and loratadine were 195 (91%) with 13 torsade de pointes, and 48 (51%) with 5 torsade de pointes, respectively. Cases of prolonged QTc were listed, in the same order, as 27, 58 and 12, respectively.

It is of course important to note that these data do not take into account differences in exposure levels due to differences in sales, that the information is not homogeneous at least with respect to origin or the likelihood that the pharmacological product caused the adverse reaction and, of course, that the information does not represent the opinion of the WHO.

Also important to note is that the vast majority of reports came from the USA and that the only other antihistamine with more than 100 reports was promethazine (113) with 8 ventricular arrhythmias, of which one was torsade de pointes. There were 26 reports for cetirizine, 3 ventricular arrhythmias and no torsade de pointes, whereas there were no reports for ebastine, reflecting in both cases the limited exposure in the countries allowing public access to their data kept at the WHO Collaborating Centre for International Drug Monitoring.

Dr Palacios: In view of these results, is there evidence that the arrhythmogenicity of the antihistamines might be a class effect?

Dr Roberts: There are now several published reports of cohort population-based studies that have failed to find significant differences between the H_1 antihistamines in the risk of life-threatening ventricular arrhythmias and related events.

Prof. Moss: That's true and I'm not sure how to interpret these data from the general reporting on loratadine. It's a widely used medication now. The point has already been made that millions of doses

of the drug need to be given before anything can be determined about rare adverse reactions.

6. Conclusions

Dr Roberts: As you know, I have been collating all the data presented and discussed into a table showing the activity of the various antihistamines and their metabolites in the various models that have been proposed for measuring the proclivity of a drug for inducing cardiac arrhythmias in man, in order to compare these data with what has actually been reported from experience in clinical practice. The final results are shown in table I.

The immediate visual impression is that astemizole and terfenadine, both associated with pharmacokinetic and pharmacodynamic interactions with ketoconazole and reported cases of torsade de pointes, also have a number of crosses in all of the preclinical models.

By contrast, the rest of the table shows very few crosses haphazardly distributed among the other antihistamines and metabolites as well as among the different models.

If we accept that the WHO data do indicate that ventricular arrhythmias, as opposed to the published cases of supraventricular arrhythmias, have been seen with loratadine, then an apparently logical (from the table) conclusion is that the hKv1.5 model is identifying such a potential. Nevertheless, the scientific logic is not so clear, since this is essentially an atrial channel and not a ventricular one, although of course it is possible that supraventricular arrhythmias could be transmitted to the ventricles.

Apart from this anomalous case, from the rest of the table it seems that 'you pays your money and you takes your choice' in terms of which of the models best predicts the proclivity for ventricular arrhythmogenicity in man.

Perhaps none of them do, perhaps one needs to block everything, or perhaps terfenadine- and astemizole-induced torsade de pointes is related to some other as yet undiscovered mechanism.

Dr de Andrés: In any event it is a very rare, almost idiosyncratic, phenomenon, as we have discussed before.

TABLE I

Table I. Summary of the results presented in 'Assessing the cardiac safety of ebastine'

	K^+ channels		Purkinje fibres (rabbit)	Papillary muscle (guinea-pig) IV	Accum. in heart (rabbit)	Histamine release (guinea-pig myocytes)	QTc (guinea-pig) IV	QTc (dog) IC	QTc (man) PO	PK interact. ketoconazole	PD interact. ketoconazole	Torsade de pointes (man)
	hKV1.5	HERG oocyte										
Astemizole	++	+++	+++	+++	+++	+++	++	+++	+++	+++	+++	++
Terfenadine	++	++	+++	+++	++	+++	+++	++	+++	+++	+++	+++
Fexofenadine	0	0	±	0	?	0	0	0	0	+	?	?
Ebastine	±	+	0	0	+	+	+	0	+	+++	+	0
Carebastine	0	0	+	0	±	0	0	0	?	+	?	0
Loratadine	++	0	0	0	?	0	0	0	0	++	+	+
DC-loratadine	+	0	+	0	?	++	+	0	0	?	?	?
Cetirizine	?	0	+	0	0	0	0	0	+	0	+	0

DC-loratadine = descarboethoxyloratadine; **HERG** = human erg-related channel; **hKv1.5** = human cardiac K^+ channel; **IC** = intracoronary; **IV** = intravenous; **PD** = pharmacodynamic; **PK** = pharmacokinetic; **PO** = orally; **QTc** = corrected QT interval; +, ++, +++ = significant effect, with each + representing approximately a 5- to 10-fold difference in potency; ± **=** threshold effect; **? =** unknown.

Prof. Moss: I would like to extrapolate the safety of ebastine in a different way. Terfenadine has had enormous clinical exposure, and the number of actual events are very few. Yet the effects observed in any of a variety of studies on the QT interval and APD, or on altered channel function, are found at relatively low doses/concentrations and are easily measured. With ebastine and carebastine, even in the very few models where one or other of them shows some activity, the effects are essentially an order of magnitude less. Thus, whatever the effect has been during the clinical marketing of terfenadine, anything predicted for ebastine is going to be at least an order of magnitude less.

All one can say in conclusion is that ebastine has a safety profile that looks promising, and I think that this is what any regulatory agency would want to look at. I personally think you have a useful and appropriate, safe and effective compound, and I wish you well.