EVALUATION OF THE CARDIAC SAFETY OF NEW ANTIDEPRESSANT DRUGS: PREDICTIVITY OF A COMBINED IN VITRO AND IN VIVO APPROACH.
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INTRODUCTION
Cardiac toxicity of Tricyclic Antidepressant drugs (TCAs) is in part related to the blockade of cardiac ionic channels such as sodium, calcium or potassium channels (1), leading to lengthening both depolarisation and repolarisation phases of the cardiac action potential. These electrophysiological effects result in changes in the ECG, such as prolongation of the PR, QRS or QT intervals, and contribute to life threatening ventricular arrhythmias (2)(3)(4)(5).

In contrast, on the basis of animal studies (6)(7) as well as human clinical data (8), new generation of Serotonin Reuptake Inhibitor antidepressant compounds (SRIs), are considered to have fewer and more benign sided cardiovascular effects than TCAs however, some arrhythmias associated with the use of these compounds have been reported (8). Moreover, toxicity in overdose remains an important issue (9).

The aim of this study was to develop a strategy in order to predict early the cardiotoxicity of the new antidepressant candidates using some selected preclinical models, ranging from the simplest cellular hERG or Na⁺,I₅ current assays to the more complex in vivo Purkinje assay and in vivo anaesthetised guinea pig model. Thus, cardiac profiles of some representative TCAs (imipramine, amitriptyline) as well as SRIs (paroxetine, fluoxetine, venlafaxine) antidepressant agents have been compared.

MATERIAL AND METHODS
Patch clamp hERG & Na⁺,I₅ in HEK-293 cells
Using the conventional patch-clamp technique in whole cell configuration, the effects of the compounds have been studied at room temperature (27 ± 2°C) on hERG (10) and Na⁺,I₅ (11) currents in HEK-293 cells. Cells were superfused at approximately 1 ml/min in the presence of extracellular solution (preequilibration), vehicle (distilled water 0.1% or DMSO 0.1%) during 10 minutes (baseline) and increasing cumulative concentrations of paroxetine, fluoxetine, imipramine, venlafaxine, amitriptyline (10⁻¹² to 10⁻⁶ M) for 10 minutes followed by a 5-minute recovery to baseline. Changes were calculated from individual variation of tail current amplitude for each cell to baseline.

Action potential parameters in isolated Rabbit Purkinje fibres
Groups of 3 or 4 fibres obtained from left ventricle of female rabbits anaesthetised with sodium pentobarbital were electrically stimulated at 1 Hz and superfused with Tyrode’s solution (preequilibration), vehicle (distilled water 0.1% or DMSO 0.1%) during 15 minutes. Following an equilibration period of at least 15 min, necessary to obtain stable haemodynamic conditions, action potentials were recorded. Action potentials were measured as maximal sodium conductance (GNa), evaluated from the difference between the sodium current and total current. Moreover, percentage changes from baseline were calculated.

RESULTS - CONCLUSION

Despite dose-dependent hERG inhibition, all the antidepressant drugs tested do not lengthen APD₉₀, consistent with their multi-channel blockade.

Most of the compounds tested exhibited a dose-dependent inhibition of Na⁺,I₅ and, consistently, lengthened PR interval in anaesthetised guinea pig, at relative high dosage.

Only TCAs reduced the Vₐ₉₅ in Purkinje fibres assay and, consistently, increased QRS interval width in vivo.

TCAs were more potent than SRIs in shortening the AP₉₀, related at least in part to the interaction with calcium channel (data not shown).

Finally, although TCAs appeared more potent in shortening AP₉₀, as compared to SRIs, they were more potent in lengthening QTc interval.

Among SRIs, venlafaxine exhibited the best cardiac safety profile.

These results confirm that, for some classes of drugs such as antidepressants, hERG assay oversimplifies drug effects on the complex repolarisation process and that neither assay alone adequately predicts pro-arrhythmic risk. However, PK/PD data should be considered to complete the interpretation of these data.

On the basis of these studies and clinical data, the combination of the Purkinje model data in parallel with ECG results in guinea pig appears as the most relevant assays in order to differentiate between two classes of antidepressants and could therefore constitute a useful predictive approach for the early selection of new antidepressant drugs with improved cardiac safety.

REFERENCES