INTRODUCTION

Myocardial accumulation of pharmaceutical compounds is an important matter encountered, particularly with neuropsychiatric or anticancer drugs. There are few models described in literature to evaluate this issue in vitro. Among them, the isolated perfused heart may constitute a rapid and low cost approach [1]. In this study, we have determined the optimal experimental conditions allowing concomitant evaluation of myocardial pharmacokinetic profile of cardiac accumulation, ECG, left ventricular pressure (LVP) and coronary flow of 2 compounds (bepridil and amitriptyline) well known to accumulate in the heart [2, 3, 4] and of a Servier compound (SX) with unknown accumulation data.

MATERIAL AND METHODS

- At first, an assay (n=1 to 3 per compound) with 3 increasing concentrations at 10 min-interval was performed for bepridil, amitriptyline and SX. Relevant ECG or LVP parameters were used to select the best concentration to be tested on the time-dependent study over 120 min.
- Then, interaction of each compound with perfusion buffer and tubing system was evaluated through solubility, stability and dummy-run adsorption studies, in order to validate the experimental conditions related to each compound.
- Finally, time-dependent effects of the 3 compounds (bepridil at 1 µM, amitriptyline at 1 µM and SX at 3 µM) were evaluated on cardiac functions at constant perfusion pressure (n=2 or 3 per compound). The hearts were perfused with Krebs’ solution (prevalue), distilled water 0.1%, DMSO 0.1% or DMSO 0.3% (baseline), followed by test compounds for 120 min. For each heart ECG, LVP and coronary flow signals were amplified and recorded at the sampling rate of 1 kHz. Among the measured parameters, dP/dt\text{max} (= maximal contraction velocity, mmHg/sec) and QT\text{c} interval (= QT interval corrected with Fridericia's formula, ms) are reported in the results.
- The pharmacokinetic profile of these compounds was evaluated through solution analysis at different stages of the time-dependent experiments (stock solution, pre-perfusion samples at the beginning, and post-perfusion samples taken at the heart outflow at 2, 4, 6, 8, 10, 15, 20, 30, 40, 60, 80, 100 and 120 min), using HPLC method previously validated. Time-dependent concentration curves were constructed to calculate the pharmacokinetic parameters of accumulation. Among them, $V_p$ (= apparent volume of distribution of the deep compartment, mL), $M_{ss}$ (= accumulated total amount in the myocardium at steady state, µg) and $P_{ss}$ (= amount in the deep compartm, µg) are reported in the results.

RESULTS - CONCLUSION

### Bepridil - 1 µM

<table>
<thead>
<tr>
<th>Concentration (n=1)</th>
<th>Nominal</th>
<th>Pre-perf</th>
<th>Mean</th>
<th>Post-perf</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.84</td>
<td>0.42</td>
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<td></td>
</tr>
</tbody>
</table>

- Loss of compound : adsorption and degradation in oxygenated buffer

### Amitriptyline - 1 µM

<table>
<thead>
<tr>
<th>Concentration (n=1)</th>
<th>Nominal</th>
<th>Pre-perf</th>
<th>Mean</th>
<th>Post-perf</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>1.03</td>
<td>0.90</td>
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</table>

- Slight loss of compound : adsorption minimized after modification of tubing system

### SX - 3 µM

<table>
<thead>
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<th>Concentration (n=1)</th>
<th>Nominal</th>
<th>Pre-perf</th>
<th>Mean</th>
<th>Post-perf</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3.12</td>
<td>2.99</td>
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</tbody>
</table>

- No loss of compound : neither adsorption, nor instability

**Effects on isolated heart: LVP and ECG parameters**

- Progressive time-dependent decrease of dP/dt\text{max} and increase of QT\text{c} interval, from 20 to 120 min

**Effects on isolated heart: Pharmacokinetic evaluation**

- Accumulation of bepridil in heart

- Accumulation of amitriptyline in heart

- No accumulation of SX in heart

**Time-dependent changes in LVP and ECG parameters correlated with the heart pharmacokinetic profile of each compound. Useful model for detection of drug-induced cardiac effects related to myocardial accumulation, but it requires preliminary determination of experimental conditions.**

REFERENCES