^{1}H-NMR based metabonomics as a potential tool to assess cardiotoxicity in drug development

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Introduction

Currently, the main cause of drug post-approval withdrawal from the market is cardiovascular toxicity. Indeed, safety cardiovascular issues account for 45% of the total post-approval withdrawal, compared to 32% for hepatic issues *(1)*. The severity and the high incidence of cardiovascular toxicity in the late-stage of clinical drug development can lead to several consequences : restrictions of medical use, special pre- and/or post-approval monitoring and drug withdrawal. However, cardiovascular toxicity accounts only for 9% of drug attrition during phase I of clinical development *(2)*. The data suggest that there is a need to develop more predictive methods to assess cardiotoxicity in preclinical studies and in early stages of clinical trials to avoid the progression of drug candidates with a high risk for the cardiovascular system. Therefore, a ^{1}H-NMR based metabonomics was used to reassess the cardiotoxicity of 2 nonsteroidal anti-inflammatory drugs (NSAIDs), Diclofenac and Rofecoxib, recently incriminated with an increased incidence of heart infarct *(3,4)*.

Methods

Two molecules were selected for our investigations : Diclofenac and Rofecoxib. The SHR and DAHL/SS rat strains were used as a hypertension model in view to potentiate the NSAIDs cardiotoxicity. One study was performed for the Diclofenac in SHR rats. For the Rofecoxib, one study in SHR rats and one study in DAHL/SS rats were carried out. The rats were exposed *per os* daily to the molecules during a 28 days treatment and were randomly divided into 3 groups : a control group, a low dose group and a high dose group. Urine and blood samples were collected at different times during the treatment. The rats were euthanazed at different times of the studies for cardiac histological investigations. For each study, a metabonomics analysis was carried out on the urine samples, using a 500,16 MHz Bruker Avance spectrometer with a 5 mm DUX 3H-1H probe. A multivariate data analysis was performed to highlight discriminant metabolites concentration changes. The data obtained were compared to data from histological and *serum* conventional protein biomarkers measurement.

Results and conclusions

Myocardial histological analysis did not show any difference between the exposed and control rats. Moreover, no significant change was found in the measurement of 3 conventional protein biomarkers (cardiac troponin I (cTnI), cardiac myosin light chain-1 (CMLC-1) and myoglobin). The metabonomics study identified metabolic changes in the rats exposed to the high dose of Diclonefac and Rofecoxib. These changes allowed us to highlight several biochimical pathways alterations, which could be linked to early myocardial necrosis events : Krebs cycle alteration, acidosis with creatinine synthesis increase, oxidative stress, osmotic stress, choline and purines metabolism disturbance and adaptative protection mechanisms such as cellular osmolytes concentration adaptation and glutathione synsthesis.

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