THE HIDDEN ELECTROPHYSIOLOGICAL CARDIOTOXIC EFFECTS OF ROFECOXIB ON RABBIT VENTRICULAR PREPARATIONS

Zoltán Husti[1], Gábor Brenner[2], Péter Bencsik[1,3], Zoltán Giricz[2,3], Anikó Görbe[2,3], András Varró[1], Péter Ferdinandy[2,3], István Baczkó[1]

[1]Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary;
[2]Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary;
[3]Pharmahungary Group, Szeged, Hungary

Unexpected ischaemia-induced cardiac adverse events are major contributors to clinical trial discontinuation and drug attrition. However, the proarrhythmic effect of drug candidates is exclusively studied in healthy cells, tissues, or in healthy experimental animals. Thus, the aim is to develop a sensitized animal model that can reliably screen for the arrhythmogenic effects of a compound. Here we show that the selective COX- 2 inhibitor rofecoxib possesses cardiac electrophysiological adverse effects only revealed during ischaemia/reperfusion, a phenomenon we termed “hidden cardiotoxicity”. Our group has previously reported the hidden cardiotoxic effect of rofecoxib on rat ventricular preparations. Given the significant differences in cardiac electrophysiological properties between rats and humans, the human extrapolation of arrhythmological results obtained from rats is limited, so our aim was to investigate the proarrhythmic effect of rofecoxib in a sensitized rabbit model.
Action potentials were registered from rabbit right ventricular papillary muscles using the conventional microelectrode technique and the effects of 10 μM rofecoxib upon test ischaemia and reperfusion were investigated.
Rofecoxib (10 μM) did not alter electrophysiological parameters in normoxic conditions. However, following 30 minute ischaemia the APD_{90} was significantly decreased during reperfusion compared to APD_{90} in the vehicle-treated group. Following sI/R, a decrease in impulse conduction velocity was also measured in the rofecoxib- treated group, but the differences were not statistically significant.
Under pathological conditions, rofecoxib may increase the incidence of reperfusion arrhythmias. Consequently, the sensitized rabbit model may be suitable for investigating the "hidden cardiotoxic" effect of a drug candidate compound. Significant differences were observed in the effect of rofecoxib on repolarization between the rat and rabbit models. However, due to the well- known electrophysiological differences between the two species, the human relevance of the results obtained in rabbits is more reliable.

Keywords: hidden cardiotoxicity, proarrhythmia, ischaemia/reperfusion