

HIDDEN CARDIOTOXICITY - CARDIAC SAFETY TESTING IN ISCHEMIC AND COMORBID CONDITIONS: DEVELOPMENT OF PRECLINICAL TEST PLATFORMS

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Unexpected cardiac adverse events are one of the leading causes of interruption of clinical trials and drug withdrawals. It has been shown that cardiovascular risk factors and comorbidities (such as aging, metabolic diseases, etc) and their medications (e.g. nitrates, antidiabetic drugs, statins, etc) may interfere with cardiac ischemic tolerance and molecular signaling of endogenous cardioprotection. Indeed certain drugs may exert adverse events on the diseased heart that is hidden in the healthy myocardium. Hidden cardiotoxic effects of drugs may occur due to (i) enhancement of unwanted signaling due to ischemia/reperfusion injury and/or the presence of risk factors and/or (ii) inhibition of cardioprotective signaling pathways, both of which may lead to ischemia-related cell death and pro-arrhythmic events. This led to novel concept of “hidden cardiotoxicity”, i.e. cardiotoxicity seen only in the diseased heart, i.e. ischemia/reperfusion injury and/or its major comorbidities (Ferdinandy et al, Eur Heart J, 2018). Hidden cardiotoxicity cannot be revealed by the routinely used cardiac safety testing methods in “healthy” test systems, moreover, the mechanism of hidden cardiotoxicity is largely unknown. Therefore, we aimed to develop a preclinical in vivo and vitro platform and test already withdrawn drugs with hidden cardiotoxic properties (Brenner et al, Cells, 2020; Weber et al, Pharmaceuticals, 2022) and new drugs with potential cardiotoxic properties. Here we summarize the current knowledge on hidden cardiotoxicity and urge the need for development of novel cardiac safety testing platforms for early detection of yet “hidden” cardiotoxicity.