

DEVELOPMENT OF A TRANSLATIONAL MODEL OF HUMAN HEART FOR MONITORING TOXIC METABOLIC INTERACTIONS OF DOXORUBICIN OR EPIRUBICIN WITH PACLITAXEL OR DOCETAXEL

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The anthracyclines doxorubicin (DOX) and epirubicin (EPI), and the taxanes paclitaxel (PTX) or docetaxel (DCT), are highly active in breast cancer; unfortunately, however, DOX-taxane combinations may cause a higher than expected incidence of anthracycline-related cardiotoxicity. EPI-taxane combinations are more cardiac tolerable, but a mechanistic foundation for replacing DOX with EPI is lacking. The cardiotoxicity of DOX-taxane combinations was attributed to vehicle-mediated or reciprocal drug interactions that increased the plasma exposure to DOX and its toxic secondary alcohol metabolite DOXOL. Intramyocardial events like a stimulated conversion of DOX to DOXOL and reactive oxygen species (ROS) were also considered. Because animal models do not adequately reproduce the human pattern of anthracycline metabolism, we developed a translational model of human heart that screened the main determinants of the safety/toxicity of anthracycline-taxane schedules (1). Human myocardial strips were incubated in plasma added with anthracyclines and PTX-Cremophor EL or DCT-polysorbate 80 formulations. An analysis of 160 myocardial strips showed that secondary alcohol metabolites never diffused from plasma in myocardium or *viceversa*. Taxane-vehicle formulations did not alter the myocardial uptake/efflux of DOX or EPI, nor did they change the relative amount of anthracycline that yielded ROS in mitochondria or accumulated in secretory vesicles. However, both PTX and DCT *per se* improved the V_{max}/K_m value with which cytoplasmic aldehyde reductases converted DOX to DOXOL, leading to higher steady-state levels of DOXOL in myocardium. Aldehyde reductases converted EPI to its alcohol metabolite EPIOL, but PTX and DCT failed to increase the V_{max}/K_m value and steady-state concentrations of EPIOL. Moreover, EPI underwent a taxane-insensitive reduction/deglycosidation to an EPIOL aglycone that diffused from myocardium in plasma. These results identify an accelerated intramyocardial formation of DOXOL as the main determinant of cardiotoxicity induced by DOX-taxane schedules. The cardiac safety of EPI-taxane schedules is attributable to the lack of EPI-taxane metabolic interactions and to a previously unrecognized cardiac clearance of EPI in the form of an EPIOL aglycone. This translational model of human heart should prove useful to screen toxic interactions of anthracyclines with many other new generation drugs.

1. Salvatorelli E., Menna P., Cascegnà S., Liberi G., Calafiore A., Gianni L. and Minotti G (2006) *J Pharmacol Exptl Ther* 318: 424-433.