Screening for potential hazard effects from a multitarget anthracycline on the cardiovascular system

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Conjugation of doxorubicin (DOX) with NO-releasing groups gives rise to novel multitarget anthracyclines, such as nitrooxy-DOX (NitDOX), capable to overcome drug resistance by decreasing the activity of ABC transporters *via* nitration of critical tyrosine residues on the pumps (1). In addition, NitDOX preferentially accumulates in mitochondria and affects their function, thus representing a prototype multifunctional anthracycline, which have cellular targets different from, and greater efficacy against drug-resistant tumor cells than the parent compound (2). The widely described anthracyclines toxicity, however, might limit their use. Therefore, the aim of this study was to investigate the NitDOX-induced cardiovascular effects, as potential hazard, by studying its effects on the mechanical activity of fresh and cultured rat aorta rings (3, 4 Murata), on L-type Ca^{2+} current [$I_{Ca(L)}$] of A7r5 cells (5) as well as its cytotoxicity on A7r5 and EA.hy926 cells. DOX was used as reference compound (6).

At concentrations ≥ 1 μM, NitDOX partially antagonized phenylephrine-induced contraction in fresh, endothelium-denuded rings, while DOX was ineffective. Conversely, in endothelium-intact rings both drugs were ineffective. NitDOX and DOX did not significantly affect the concentration-response curve to KCl. In arteries cultured with both drugs for 7 days, NitDOX blocked both phenylephrine- and high KCl-induced contractions at a concentration 10-fold higher than that of DOX.

NitDOX, at the maximum concentration tested of 10 μM, exhibited weak Ca^{2+} antagonist properties in single A7r5 cells. Moreover, preliminary results suggest that DOX significantly reduced left ventricular pressure, coronary perfusion pressure and heart rate in Langendorff perfused rat heart. The cardiac effects of NitDOX are currently under investigation.

NitDOX was less toxic than DOX in human endothelial cells at concentrations comparable to those effective to exert antitumor activities and to accumulate in drug-resistant cells. Both NitDOX and DOX, however, promoted similar cytotoxic and apoptotic effects in A7r5 cells.

In conclusion, NitDOX is a NO-releasing anthracycline with a more favourable toxicity profile and a better efficacy against drug-resistant cells than the parent compound. In the context of earlier attempts to use NO delivery strategies in cancer therapy, NitDOX is worthy of further investigations in preclinical and clinical settings.

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