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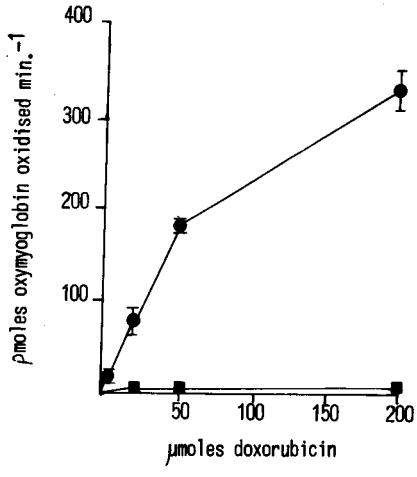
OXIDATION OF OXYMYOGLOBIN BY DOXORUBICIN AND ITS EFFECT ON HEART SARCOSOMAL LIPID PEROXIDATION

T.J. Lavelle and L.H. Patterson, School of Pharmacy, Leicester Polytechnic, Leicester LE1 9BH.

The cardiotoxicity associated with the use of doxorubicin as an antitumour agent is considered to be mediated, at least in part, via free radical formation. This involves metabolic activation of doxorubicin to a free radical intermediate which via the production of reactive oxygen species initiates cell damaging lipid peroxidation (Olsen et al, 1981. In heart tissue the biological mechanism responsible for reductive activation of doxorubicin has not been fully elucidated. The reductive enzymes suggested to be involved (Bachur et al, 1979) are either not specific to heart tissue or are barely detectable in heart subcellular fractions. In this study the involvement of the haemoprotein myoglobin was investigated as a biological reductant for doxorubicin activation in heart tissue.

Oxymyoglobin ($MbFe^{2+}O_2$)and metmyoglobin ($MbFe^{3+}$) were prepared as described by Taylor and Hochstein,1978 and the effect of doxorubicin (1-200μM) on them monitored spectrophotometrically between 500-600nm. Superoxide formation in the presence of doxorubicin and $MbFe^{2+}O_2$ was measured by the adrenochrome assay as described by Basra et al, 1985. Doxorubicin mediated heart sarcosomal lipid peroxidation was measured using the malondialdehyde-thiobarbituric acid adduct method (Patterson et al, 1983).



Doxorubicin was shown to generate $MbFe^{3+}$ when incubated with $MbFe^{2+}O_2$. This resulted in a doxorubicin dependent superoxide anion formation as indicated by a 23% increase ($p<0.05$) in adrenochrome formation over controls and greater than 90% inhibition of $MbFe^{2+}O_2$ conversion in the presence of the reactive oxygen scavengers superoxide dismutase (SOD) + catalase (see figure 1). Furthermore $MbFe^{2+}O_2$ stimulated doxorubicin mediated heart sarcosomal lipid peroxidation by up to 271% ($p< 0.05$) compared to controls by a process that was doxorubicin dose dependent.

Fig.1 Effect of doxorubicin without (●) and with SOD+Catalase (■) on $MbFe^{2+}O_2$

The results show that $MbFe^{2+}O_2$ can interact with doxorubicin to produce reactive oxygen and concomitantly heart tissue lipid peroxidation. An electron transfer process from myoglobin to unbound oxygen is suggested in which a doxorubicin free radical mediates. A further consequence is the production of metmyoglobin which cannot function as an oxygen transport protein.

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