REDUCTION OF THE TOXICITY OF ADRIAMYCIN TO BEATING HEART CELLS BY FREE-RADICAL SCAVENGERS

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Adriamycin is a useful and wide-spectrum antineoplastic compound, but it shows dose-dependent, cumulative cardiomyopathy. Previous reports by several groups have failed to elucidate the mechanism of toxicity. It appears not to be associated with the anti-tumour effect, which is probably mainly by inhibition of DNA synthesis. We have therefore investigated the reduction of the toxicity in the hope of extending dose schedules without heart failure supervening.

We have previously reported a protective effect by ATP (Dawson & Abdul-Jabar 1981), but this was not a complete explanation and we now report the effects of superoxide dismutase, catalase, sodium ascorbate and α-tocopherol acid succinate, the rationale of this work being a report by Myers (1977) who said the cardiotoxicity involved lipid peroxidation.

Our test material was chick embryo heart cells, prepared in a uniformly beating condition as previously described (Dawson & Abdul-Jabar 1980). The test materials were added as freshly prepared solutions in cell culture medium. The flasks of cells were held on the microscopes in specially designed jackets which kept them at constant temperature and enabled individual cells to be re-located. Beating was measured by eye, by filming or by an apparatus measuring transmitted light.

Adriamycin (5×10^{-5}M) stopped beating in 90% of the cells within an hour. Superoxide dismutase (200μg/ml), which scavenges super-oxide free radical with the production of hydrogen peroxide, caused no improvement, but when used together with catalase (200 μg/ml) to detoxify H_2O_2, only 60% of the cells stopped beating within an hour. Heart cells are notably low in catalase. The effect was significant ($P < 0.001$), and greater than that shown by catalase alone (Cope & Dawson 1980). Therefore part of adriamycin's toxicity is caused by superoxide production.

Tocopherol acid succinate (300 μg/ml), a more general free radical scavenger, resulted in 98% of the cells still beating after 1 hour. Also sodium ascorbate (200 μg/ml) + catalase (200 μg/ml) resulted in 50% still beating.

The results indicate therefore that superoxide production is partially responsible for the cardiotoxicity of adriamycin. Further, it appears that hydrogen peroxide, produced by the dismutation of the superoxide radical, plays a large part in the toxicity. Since tocopherol is a less specific scavenger than superoxide dismutase, it may be that free radicals other than superoxide are also involved, or it may be that the greater lipid solubility of tocopherol enables it to associate more closely with membrane lipid to provide protection nearer the site of peroxidative attack.

We conclude that the concurrent clinical administration of tocopherol with adriamycin is worthy of further investigation.

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