EFFECT OF UNITHIOL ON ACUTE ADRIAMYCIN CARDIOTOXICITY IN RAT

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The protective action of dexrazoxane (ICRF-187) against anthracycline cardiotoxicity has been both experimentally and clinically well documented. However, in higher doses (more than 600-750 mg/m^2) it may cause myelotoxicity. Unithiol (dimercaptopropane sulfonate) - chelating agent used in heavy metal poisoning - is well tolerated, but its possible use as a cardioprotective agent in anthracycline cardiotoxicity has not been studied as yet. At first, we studied effect of unithiol (cummulative dose of 350 mg/kg i.p.) on acute adriamycin cardiotoxicity (single dose of 6 mg/kg i.v.) in the rat. Haemodynamic and electrocardiographic measurements were performed the 7th day following i.v. adriamycin administration (a peak of the acute cardiotoxic changes). Results indicate that unithiol normalized increased contractility (dP/dt_{max}) accompanying acute phase of adriamycin cardiotoxicity, possibly by chelating of Ca^{2+} released by adriamycin and/or its metabolites in the cardiac cells. Futher experiments are carried out to verify cardioprotective action of unithiol in chronic anthracycline cardiotoxicity.

INVESTIGATION OF THE MECHANISM BY WHICH KETANSERIN INCREASES CARDIAC ACTION POTENTIAL DURATION.

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In order to elucidate the proarrhythmic properties of ketanserin, *in vivo*, we investigated the cellular electrophysiological effects of the drug, *in vitro*. Action potentials were recorded in guinea-pig isolated papillary muscles by conventional "floating" microelectrode techniques; and potassium currents were measured in guinea-pig isolated cardiomyocytes in the whole cell patch-clamp configuration. Ketanserin (0.1 - 10μM) concentration-dependently increased action potential duration (APD) to 50 and 90% repolarization levels (EC50 3.1 ± 2.7 μM, n=6 for APD90) without affecting resting potential, maximum upstroke velocity (Vmax) or action potential amplitude. Ritanserin and ICI 170809 (both 0.1 - 10μM), two 5-$HT_{2A/2C}$ receptor antagonists chemically distinct from ketanserin, failed to increase APD. In isolated cardiomyocytes, ketanserin (0.1 - 10μM) concentration-dependently reduced the delayed outward current (IK), specifically IK_r from 1μM ($p<0.01$, n=6), whereas IK_1 was not significantly affected. The results demonstrate that ketanserin reduced IK, which could explain the APD lengthening effects of the drug, and therefore its proarrhythmic properties. Furthermore, ketanserin-evoked increases in APD do not appear to involve 5-$HT_{2A/2C}$ receptors.

CARDIAC ELECTROPHYSIOLOGICAL EFFECTS OF CALCITONIN

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Calcitonin has been found exerting some cardiovascular actions (1,2) but there are also other data (3) which could not confirm this effect. It has been demonstrated that calcitonin gene related peptide plays an important role in the regulation of cardiac calcium current (4). The purpose of this work was to study the effects of salmon calcitonin (CT) on the transmembrane action potentials (AP) of guinea pig left auricle and right ventricular papillary muscles. CT (0.5, 1, 2.5 nM) significantly increased the amplitude of AP (APA) and the magnitude of the overshoot (OS) in both preparations without changing the resting membrane potential and the maximum rate of depolarization phase. While the increase of ventricular OS was concentration dependent (34, 38 and 44%, respectively), in atrial preparation the highest effect on OS occurred at 1 nM of CT. CT caused a significant and concentration dependent decrease of the duration of atrial AP (APD) measured at 20 and 50% repolarization, but it did not modify the ventricular APD. The K^+channel antagonist 4-aminopyridine (1 mM) prevented the shortening effect of CT (2.5 nM) on the atrial repolarization phase. These results suggest that calcitonin may increase the inward Ca^{2+}current, Ca^{2+}channel activity, but its enhancing effect on K^+currents can not be excluded either.

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EFFECT OF DIMETHYL SULFOXIDE ON THE ECG IN FREELY MOVING MALE Balb/c MICE

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A wide range of pharmacological actions of dimethyl sulfoxide (DMSO) has been documented in laboratory studies. Several applications of DMSO in clinical medicine have been suggested. Moreover, the compound has been recommended as a vehicle for the administration of various drugs. Since it promotes tissue penetrations, it is also used as a carrier for antitumor drugs. The agents are dissolved in 85%-100% concentrations of DMSO. DMSO has no carcinogenic action of its own. We wanted to use DMSO as a solvent for protective agents tested against the cardiotoxicity of doxorubicin We therefore investigated the effect of a daily administration of DMSO on the telemetrically obtained electrocardiogram (ECG) in freely moving male Balb/c mice. During treatment with 4.5 ml 100% DMSO/kg i.p. five days per week during three weeks, DMSO caused substantial cardiotoxicity. The ST-interval increased significantly after one week by 2.2 ± 1.3 msec and also the ECG wave form changed completely in time. During treatment with 4.5 ml 50% DMSO/kg i.p. five days per week during three weeks, no significant difference was observed compared with the control animals. During the entire study the maximal heart rate and body weight remained constant in all treated groups. The data indicate that DMSO can not be used in a 100% concentration to dissolve compounds that are tested for protection against the cardiotoxicity of cytostatics.