ACUTE HAEMODYNAMIC EFFECTS OF THREE CARDIOACTIVE AGENTS: METOPROLOL, SOTALOL AND MILRINONE. INFLUENCE OF MYOCARDIAL CONTENT AND SYSTOLIC INTERVAL.

by

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SUMMARY

The acute effects of cardioactive agents are determined, at least in part, by the process of their uptake into the heart. However, for several drugs at least, there is evidence that effects are also modulated by inter-beat interval, leading to accentuation of haemodynamic effects of some agents during tachycardia. The potential for this phenomenon to be beneficial or deleterious is largely unknown, except for a few agents.

Utilizing a paired transcoronary sampling technique, serial determination of myocardial drug content was determined following intravenous bolus injection in patients undergoing diagnostic cardiac catheterization for the investigation of chest pain. During this procedure, serial determinations of various haemodynamic, electrocardiographic, and electrophysiological parameters were obtained. Examination of the potential for rate-related inotropic effects involved construction of a component of the mechanical restitution curve (MRC), utilizing atrial pacing with insertion of premature beats at progressively shorter diastolic intervals. MRC construction permits evaluation of a surrogate of tachycardia without significant risk of induction of ischaemia. A curve-fitting model for the component of the MRC associated with diastolic intervals shorter than those at spontaneous heart rate in man was developed, to facilitate accurate quantization of drug effects.

Three cardioactive agents were chosen for study:

(i) metoprolol, as a classical β₁-selective adrenoceptor antagonist, which has been associated with reduced mortality after acute myocardial infarction;

(ii) sotalol, a non-selective β-adrenoceptor antagonist which also possesses class III antiarrhythmic effects, and which appears to be the most effective agent currently available for the management of ventricular tachyarrhythmias; and

(iii) milrinone, a phosphodiesterase III inhibitor, which exerts both positive inotropic and vasodilatatory effects. Milrinone appears to increase risk of cardiac death during long-term administration. However, the mechanism of these deleterious effects is uncertain.
Metoprolol, a relatively lipophilic β-adrenoceptor antagonist, has a short elimination half-life (3-4h) and a reasonably high apparent volume of distribution. Following intravenous bolus administration (4mg), peak myocardial content was achieved within three minutes of injection. Conversely, peak haemodynamic and electrocardiographic effects were not observed until 5-10mins post administration, indicating a time lag between content and effect. Significant reductions in spontaneous heart rate and LV +dP/dt at constant heart rate were observed, accompanied by prolongation of PR intervals. However, the negative inotropic effects of metoprolol became progressively diminished with reductions in extrasystolic interval, indicating "reverse use-dependent" negative inotropic effects. Utilizing Langendorff-perfused rat hearts, the influence of a period of hypoxia on the uptake process of metoprolol was assessed: while myocardial uptake was not significantly modified by the hypoxic perfusion conditions, the efflux of the drug from the heart was impaired.

Sotalol, a relatively hydrophilic β-adrenoceptor antagonist, has a longer elimination half-life than metoprolol (≥7h) and a lower apparent volume of distribution. Despite this, following intravenous bolus administration (20mg), peak myocardial content was achieved less than one minute after injection. Peak haemodynamic, electrocardiographic and electrophysiologic effects were not observed until 10minutes post administration. Significant reductions in spontaneous heart rate and LV +dP/dt at constant heart rate were observed, accompanied by prolongation of PR and AH intervals, and atrioventricular nodal effective refractory periods. However, the negative inotropic effects of sotalol tended to be augmented during pacing-induced tachycardia, suggesting a small degree of use-dependence of sotalol's negative inotropic effects, in contrast to the reverse use-dependence exhibited for the electrophysiological effects of both the racemate and the d-enantiomer in vitro.

Milrinone, a phosphodiesterase inhibitor, has a short elimination half-life (1-2h) and a low apparent volume of distribution. Following intravenous bolus administration (1mg), peak myocardial content was also achieved less than one minute after injection. Again, peak haemodynamic effects were not observed until 7-10mins post administration. Significant in-
creases in spontaneous heart rate and LV+dp/dt at constant heart rate were observed, accompanied by reductions in PR intervals, LV systolic and mean arterial pressures. The positive inotropic effects of milrinone were significantly less marked with progressive reductions in systolic interval in isolated premature beats.

Thus, for all agents studied, acute drug uptake into the human heart precedes attainment of maximal effects. There was significant modulation of the haemodynamic effects of all three drugs according to changes in systolic interval. Therefore for some cardioactive agents, the relationship between myocardial drug content and acute effects is determined by baseline haemodynamic status.