

COMPARATIVE EVALUATION OF SUBLINGUAL LONG ACTING NITRATES IN ANGINA PECTORIS

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Ten patients with angina performed two exercise tests on five consecutive days to determine the efficacy and duration of action of three sublingual long acting nitrates (LAN): isosorbide dinitrate 5 mg (ISD), erythrityl tetranitrate 10 mg (ETN), and pentaerythritol trinitrate 10 mg (PET). In a double blind protocol the mean duration of exercise 45 and 100 minutes after administration of LAN were compared with the mean duration of exercise 45 minutes after placebo and also 4 and 50 minutes after nitroglycerin 0.4 mg. Mean duration of exercise 4 minutes after nitroglycerin was 89.3 seconds compared to 60.5 seconds after placebo ($p < 0.001$); no difference from placebo was found 50 minutes after nitroglycerin. Mean duration of exercise 45 minutes after ETN, ISD, and PET were 89.1, 87.5 and 87.5 seconds respectively and were all different from placebo ($p < 0.01$). Mean duration of exercise for the group 100 minutes after each LAN was not significantly different from placebo but 5 of the 10 patients had prolongation at 100 minutes equal to that at 45 minutes with at least one LAN. Sublingual LAN significantly improve exercise capacity at 45 but not at 100 minutes after administration. While these drugs appear to be useful as a prophylaxis for angina they should not be given on a fixed schedule 3 to 4 times a day as is currently the practice.

THE ANTI-FIBRILLATORY EFFECT OF DIMETHYL QUATERNARY PROPRANOLOL (UM-272).

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UM-272, (N,N-Dimethyl-1-isopropylamino-3- I-naphthyl oxy propan-2-ol), a quaternary derivative of propranolol, lacks both α -adrenergic receptor blocking activity and local anesthetic activity. UM-272 demonstrates anti-arrhythmic effectiveness against digitalis-induced arrhythmia, and ectopic ventricular rhythms occurring 48 hrs. after two-stage coronary ligation. The anti-fibrillatory effectiveness of the agent, in acute coronary artery ligation studies and fibrillation threshold measurements were performed in anesthetized mongrel dogs. Pretreatment with UM-272, 10 mg/kg, lowered the incidence of ventricular fibrillation after a 20 min. single-stage coronary artery ligation from 100% to 40% in the treated group. The incidence of premature ventricular contractions after treatment, was reduced to 20% from a control value of 100%. The vulnerability to fibrillation was assessed using trains of 60 Hz square wave pulses of 5 mA in intensity and 2 msec in duration. UM-272, 5 mg/kg, raised the mean fibrillation threshold from $322 \text{ msec} \pm 20 \text{ SEM}$ to $599 \text{ msec} \pm 76 \text{ SEM}$, an increase of 185%. After a total dose of 10 mg/kg, none of the five experimental animals fibrillated utilizing the same test parameters. When the strength of the 60 Hz pulse was raised to 10 mA, only short bursts of ventricular tachycardia were observed. The time course of vulnerability to fibrillation after experimental coronary occlusion was studied in the presence and absence of UM-272. In control experiments, occlusion produced a 64% decrease in the duration of the train necessary to induce ventricular fibrillation. This was raised to 124% of control after UM-272, 5 mg/kg. The results indicate that UM-272 possesses potent anti-fibrillatory properties.

EFFECTS OF SYMPATHETIC NERVE BRANCH STIMULATION ON VENTRICULAR RECOVERY PROPERTIES AND CARDIAC RHYTHM

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The cardiac distribution of right and left stellate fibers has been shown to differ, providing an explanation for ECG neurogenic ST-T abnormalities. In the present study in 27 dogs distribution of individual nerves was determined by refractory period (RP) changes induced by stimulation of nerves distal to the stellate ganglia (SG). Basic and premature stimuli twice threshold voltage were applied sequentially at 20 ventricular epicardial or several septal sites. RP was taken as the earliest premature stimulus resulting in propagated activation. On the left, stimulation of the ventrolateral cardiac nerve (VLCN) shortened RP's by 10 msec or more on the posterior cardiac surface and the ventromedial cardiac nerve (VMCN) affected anterior and posterior surfaces with varying distribution and also shortened RP's in the septum. On the right, the recurrent cardiac nerve (RCN) shortened RP's in the septum and on the anterior surface, mainly of the right ventricle. Other nerve branches had inconsistent effects. RP changes were associated with T wave changes in an ECG Y lead. Right SG, RCN, and VMCN stimulation inverted T waves and left SG and VLCN elicited more upright T waves, findings which are predictable from the RP data. Rhythm changes included sinus tachycardia during right SG and stellate cardiac nerve stimulation and AV junctional tachycardia during left SG, RCN, and VLCN stimulation. Findings demonstrate localized but overlapping cardiac distribution of individual nerves, providing a mechanism for localized electrophysiologic and contractile effects of sympathetic activity. New information includes the localization of sympathetic efferent pathways distal to the SG and the identification of efferent pathways to the interventricular septum.

PROGNOSTIC FACTORS AFTER MYOCARDIAL INFARCTION IN THE CORONARY DRUG PROJECT (CDP)

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In the CDP, a National Heart and Lung Institute Collaborative Trial, the natural history of infarction was studied in 2035 placebo-treated men, among which 265 died in 3 years follow-up. A ranking procedure identified the 1st 5 entry characteristics having the strongest independent contribution to mortality prediction: ST segment depression in the resting ECG, cardiomegaly, diuretic therapy, ventricular conduction defects and intermittent claudication. The next 5 in rank were ventricular premature beats, functional NYHA class, serum cholesterol level, size or extent of Q waves and resting heart rate.

A multivariate risk score based on 5 factors discriminated those who eventually died as well as did one using 10, 20, or 40 characteristics. Only 19 deaths actually occurred among men in the lowest quintile of predicted risk while 117 occurred in the upper quintile, a risk ratio of 6.2. 48% of eventual deaths were concentrated in men identified in the upper 20% of predicted risk.

The validity and universality of the risk score was established in an independent population. Application of the score to a geographically different population of infarct patients achieved similar predictive results. It allowed discrimination between men with 7-fold different risk of dying in a given period. This prognostic index should prove useful in several ways: effective classification of infarction patients for controlled therapeutic trials, identification of individuals at excess risk for closer monitoring, and--to the degree that risk can be modified--prevention of recurrent myocardial infarction.