CLINICAL AND PHARMACOKINETIC PROFILES OF DIGOXIN IMMUNE FAB IN FOUR PATIENTS WITH RENAL IMPAIRMENT

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Minimal pharmacokinetic data on digoxin immune Fab are currently available, especially in patients with impaired renal function. The serum concentration-time profiles of total digoxin, free digoxin, and digoxin immune Fab in four patients with moderate to severe renal impairment who received digoxin immune Fab are presented. The calculated elimination $t_{\frac{1}{2}}$ of digoxin immune Fab was 25 to 73 hours. The calculated elimination $t_{\frac{1}{2}}$ of total digoxin was 24 to 72 hours. Free digoxin concentrations rebounded to a peak level of 1 to 2.9 ng/ml 44 to 97 hours after the administration of digoxin immune Fab. The area under the curves for digoxin immune Fab were 213 to 1026 mcg·hr/ml, and total body clearance was 2.3 to 7.1 ml/min. The total digoxin concentrations peaked at 14 to 33 times the pre-Fab digoxin concentrations 5 to 36 hours after digoxin immune Fab administration. In comparing these data with data available from patients with normal renal function, the $t_{\frac{1}{2}}$ of digoxin immune Fab and total digoxin is longer, the peak total digoxin concentration occurs later, the ratio of total digoxin concentration to pre-Fab digoxin concentration is larger, and the rebound in free digoxin occurs later in patients with renal impairment. The Fab dose does not need to be reduced in patients with renal impairment, however, post-Fab monitoring should be extended to compensate for the prolonged $t_{\frac{1}{2}}$ of Fab and later rebound of free digoxin.

EFFICACY OF TRANSDERMAL NITROGLYCERIN IN COMBINATION WITH AN ACE-INHIBITOR IN PATIENTS WITH CHRONIC STABLE ANGINA PECTORIS

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We have previously shown that transdermal nitroglycerin may induce an increase in the activity of the adrenergic and the renin-angiotensin-aldosterone systems (SRAA) in patients with chronic stable angina pectoris (SA); when the activation of these systems is more pronounced, the antianginal effect of this drug seems to be reduced. Aim of this study was to evaluate the antianginal efficacy of transdermal nitroglycerin administration (TTS-NG 10 mg/ 24hrs) in combination with an ACE-inhibitor without sulphydryl groups (BNZ, benazepril 10 mg bid) in respect to placebo (PI), or to TTS-NG or to BNZ administered as monotherapy. Twentyfour patients (20M, 4F) were admitted to this multicenter, randomized, double blind, latin square, placebo controlled study. Patients received all the treatments (PI, TTS-NG, BNZ and BNZ+TTS-NG) each for one week; at the end of each week patients performed two exercise tests 4 and 24 hours post-dosing. Two hrs postdosing exercise duration at 1 mm ST depression was significantly increased in respect to PI during TTS-NG (+21%,p<.05) and TTS-NG+BNZ (+25%,p<.05) treatments. Two hrs postdosing exercise duration at angina was also increased in respect to PI during TTS-NG (+ 16%, p<.05) and TTSNG+BNZ (+25%, p<.05); 24 hrs postdosing the increase of exercise duration was significant only during TTS-NG+BNZ treatment (+15%,p<.05) in respect to PI, but not in respect to TTS-NG given alone. Heart rate at 1 mm ST depression was significantly increased 2 hrs postdosing during TTSNG and TTSNG+BNZ treatments (p<.05), while no significant differences were observed within treatments for heart rate, systolic blood pressure and rate-pressure product.
In conclusion, these results suggest that ACE inhibitor administration given in combination with TTS-NG can induce a statistically significant increase of exercise duration in stable angina patients, in respect to placebo, 24 hours postdosing. The clinical significance of this finding must be evaluated in further studies.

COMPARATIVE EFFICACY AND SAFETY OF NITROGLYCERIN, VERAPAMIL AND NICORANDIL DURING CORONARY ANGIOPLASTY

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To determine and compare the efficacy and safety of the cardioprotective agents during coronary angioplasy (PTCA), we studied the effects of nitroglycerin (NTG,0.2mg/5ml), verapamil (VP,5mg/5ml) and nicorandil (NR,4mg/5ml) during coronary occlusion (oc) on the intracoronary-ECG (ic-ECG) and hemodynamic variables. PTCA was performed in 40 pts with proximal epicardial coronary stenosis. After two 30 sec oc, the patients recieved one of these agents or an equivalent volume of saline (4 groups ã 10). Five min after injection, the 3rd oc was performed.
[Results]

	ST (mV) after 30 sec oc			Time (sec) to .1mV ST Elev.		
	oc #1	oc #2	oc #3	oc #1	oc #2	oc #3
saline	.65±.13	.63±.24	.60±.18	18±3	17±2	19±4
NTG	.62±.11	.63±.20	.60±.20	19±3	18±4	18±3
VP	.63±.21	.64±.24	.49±.19*	19±4	19±5	25±3*
NR	.64±.16	.65±.19	.30±.22*	18±2	18±4	31±5*

(mean±SD, *: p<.01 as compared to saline)

The incidence of negative U waves during PTCA was significantly reduced by VP (30%) and NR (20%) as compared to that of saline (60%) and NTG (50%). NTG produced a significant fall in pulmonary wedge pressure (PWP) and pressure-rate-product (PRP). VP significantly reduced PRP but had no effect on PWP. Bradycardia (incl. AV block) and/or hypotension was occasionally observed in both NTG(20%)- and VP(30%)-treated groups. In contrast, NR did not significantly change systemic hemodynamic variables and no adverse effect was noted. These results show both VP and NR reduce the extent of myocardial ischemia during brief oc.; however, NR is more safe and efficacious than VP.

CORONARY HEMODYNAMICS FOLLOWING AMINOPHYLLINE IN CORONARY ARTERY DISEASE.

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The present study was undertaken to investigate coronary hemodynamics after aminophylline (A) (7 mg/kg i.v. over 10 min) in 12 pts with stable angina (SA). Of these, 6 pts (G1) presented with a < 90% and 6 (G2) with a ≥ 90% stenosis of the left anterior descending coronary artery; 6 pts with atypical chest pain as well as normal coronary arteries served as controls (G3). Great cardiac vein flow (GCVF; thermodilution technique) and anterior coronary resistance (ACR) were assessed every 5 min for 2 hrs following A. This drug increased GCVF in G1 (from 110±34 to 135±16 ml/min; p < 0.05) and in G3 (from 90±14 to 122±17 ml/min; p < 0.001). The opposite occurred in G2 (from 127±27 to 95±25 ml/min; p < 0.001). Changes in ACR inversely paralleled those in GCVF in all pts, i.e. it significantly decreased in G1 (from 0.89±0.21 to 0.68±0.08 mmHg/ml.min; p< 0.05) and in G3 (from 0.93±0.25 to 0.70±0.16 mmHg/ml.min; p < 0.005) but increased in G2 (from 0.71±0.09 to 0.91±0.18 mmHg/ml.min; p < 0.005). The mean duration of the hemodynamic changes was 32±7 min and did not differ among groups. Thus: (1) A increases GCVF in normal subjects; (2) conversely, the response in SA is heterogeneous,in that GCVF increases in pts with moderate (< 90%), but decreases in those with severe (≥ 90%) coronary stenoses; (3) a coronary steal phenomenon is suggested in pts with severe coronary artery disease.