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TITLE: EFFECTS OF NICARDIPINE HYDROCHLORIDE ON HEPATIC BLOOD FLOW AFTER LIVER TRANSPLANTATION

AUTHORS: M. Raucoules, M.D., C. Ichai, M.D., M. Drici, M.D., B.Goubaux, M.D.,J. Gugenheim, M.D., D. Grimaud, M.D

AFFILIATION: Anes. Dept. (Pr D. Grimaud), Nice, FRANCE.

Calcium channel blockers are often used to control acute hypertension in patients during the postoperative period after liver transplantation. The effects of these drugs on hepatic blood flow (HBF) are unknown. The aim of this study was to evaluate the effects of Nicardipine Hydrochloride (NH), used to control acute hypertension, on HBF after orthotopic liver transplantation.

After institutional approval and informed consent were obtained, eight patients (4 men, 4 women; age : 48.8 ± 2.2 years, mean ± sem) were studied in the postoperative period (10.2 ± 3.3 hours) after an orthotopic liver transplantation for chronic active hepatitis. Hypovolemia, hypothermia, cardiac or renal failure, acid-base disturbances and drugs that interfere with hepatic output were exclusion criteria. Systemic and splanchnic hemodynamic parameters and metabolic and pharmacokinetic parameters were measured at four phases: in the basal state (phase A) and five minutes (B) and 30 minutes (C) after the IV administration of 5 mg of NH to control acute hypertension. Parameters measured were: 1) mean arterial pressure and heart rate with an arterial line, CO by thermodilution, and pulmonary artery and wedge pressures with a Swan Ganz catheter. 2) HBF using the hepatic venous catheterization technic with a continuous infusion of indocyanine cardiogreen, wedged and free hepatic venous pressures. 3) metabolic parameters: arterial and hepatic venous blood glucose, lactates and pyruvates. 4) arterial and hepatic venous blood samples at the following times: 0, 3, 5, 10, 15, 20, 30, 45, 60 minutes after NH administration to determine the hepatic extraction ratio of Nicardipine. Capillary column gas chromatographic method and electron-capture detection were using for determining NH.[1] The cardiac index (CI), HBF index (HBFI), and the systemic and splanchnic vascular and pulmonary resistances were calculated. Statistical analysis was performed using Wilcoxon-U test, and linear regression (least squares method), ($p<0.05$). Values are mean ± SEM.

In phase A (table) we found the usual values in patients with cirrhosis: increase of CI and decrease of vascular resistances. The increase in CI probably explain the increase of HBFI. For phases B and C, there is no significant modification of systemic and splanchnic hemodynamic parameters after administration of NH. The lack of modification of CI and splanchnic parameters may explain the lack of modification of HBFI after NH. In phase D there is a statistically significant decrease of HBFI and HBFI/CI without changes in splanchnic pressures and resistances, but nevertheless, HBF remains in the normal range. This late relative decrease, two hours after the administration of NH, is probably independant of it, since its duration of action is only 45 minutes and there is no statistical relationship between arterial NH concentration and HBFI (r=0.10, N.S.)There is no change in the metabolic parameters. The hepatic extraction ratio of NH is stable during the study (0.37 ± 0.02) but is decreased by comparison with usual values in normal subjects (> 0.8).[2]

So we can conclude that Nicardipine, despite a decrease of its hepatic extraction ratio, has no adverse effects on cardiac and hepatic blood flow after liver transplantation.

References

1. Journal of chromatography 415:65-73, 1987
2. Xenobiotica 10:889-896, 1980

	A	B	C	D
CI l.mn-1.m-2	5.3 ± O.8	5.4 ± O.6	5.3 ± O.5	5.5. ± O.7
HBFI l.mn-1.m-2	1.42 ± O.19	1.42 ± O.16	1.46 ± O.21	1.19 ± O.14*
HBFI/CI	O.25 ± O.07	O.26 ± O.O6	O.27 ± O.O7	O.20 ± O.O6*

TABLE : SYSTEMIC AND SPLANCHNIC PARAMETERS AT DIFFERENT PHASES (A/B, C, D) * p < O..O5

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TITLE: PREVENTION OF HEPATIC ISCHEMIC INJURY-INDUCED CORONARY VASOCONSTRICTION WITH MANNITOL OR LAZAROID (U74006F).

AUTHORS: E.A.PRETTO M.D., K. DORKO B.S.

AFFILIATION: International Resuscitation Research Center and Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh, PA 15260

In a previous report, we described coronary vasoconstriction after 90 min of hepatic ischemia-anoxic and reperfusion injury, in a new experimental liver-heart cross-perfusion (LHCP) rat model (1). We concluded that metabolite(s) from postischemic rat livers may be responsible for this phenomenon. In the present study we sought to determine whether this finding was reproducible and linked to free radical mediated mechanisms. We theorize that both xanthine oxidase and hypoxanthine produced by the postischemic rat liver could cause free radical mediated-injury of the heart in our model. To prove this hypothesis we repeated our experiments in the presence of mannitol (a hydroxyl radical scavenger) or a 21-aminosteroid (inhibitor of lipid peroxidation).

Methods: The LHCP model consists of an isolated perfused rat liver at a perfusion pressure of 13 mmHg connected via glass and tygon tubing to an isolated non-working rat heart or Langendorff preparation at a mean coronary perfusion pressure fixed by gravity at 50 mmHg both perfused with a modified Krebs-Henseleit solution containing 2% bovine albumin at 38°C. The prep is oxygenated with a membrane oxygenator (PaO_2>500, CO_2=35-40). Both are capable of independent or LHCP. Livers or hearts from 112 Sprague-dawley rats (350-400 g) were isolated and perfused in this manner. After 30 min of equilibration, 4 groups of LHCP experiments were performed. Group 1 (n=13) livers were exposed to 120 min of normothermic ischemia by stopping portal flow followed by reperfusion with LHCP for 60 min. Group 2 (n=11), were sham (no liver insult) with LHCP for 60 min. Groups 3 (n=12) and 4 (n=12) were identical to group 1 except that Lazaroid 10 ug/ml (L) or Mannitol 3% (M) were mixed in the buffer at the beginning of reperfusion. Myocardial function variables such as LVP, dp/dt, and coronary flow (CF) were measured throughout the experiments. LFTs, lytes and lactate were measured at baseline and at 30 and 60 min following reperfusion. Liver bile flow was measured continuously. Data was analyzed with ANOVA and Student-Newman-Keuls for significance at $p<.05$.

Results: CF decreased gradually over 60 min of reperfusion in all LHCP experiments compared to baseline values. However, CF in the M (15.5 ± 2.6 ml/min, $p<.05$) and L (15.1 ± 1.4, $p<.05$) groups was significantly preserved compared with group 1 (12.6 ± 3.0) at the end of reperfusion.

Conclusions: We conclude that hepatic ischemia and reperfusion injury can adversely affect CF of spontaneously beating non-ischemic rat heart in this model. This study provides indirect evidence that this phenomenon may be mediated by a yet to be determined free radical/mediated-injury mechanism.

1) Crit Care Med 18(4):S180, 1990.