ELSEVIER

Attenuation of Ischemic Liver Injury by a Non-Selective Endothelin Receptor Antagonist

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THE ability of the liver to recover from ischemia/reperfusion (I/R) injury depends on the integrity of the microcirculation.[1] It has been recently reported that endothelin (ET) plays a major role in the regulation of hepatic microcirculation.[2] The aim of this study is to determine whether inhibition of the binding of endothelin to its receptors by a non-selective (ET_A, ET_B) receptor antagonist, TAK-044[3] can lessen liver injury after 2 hours of warm ischemia.

MATERIALS AND METHODS

Two-hour complete hepatic ischemia was induced in adults female beagle dogs by clamping the vena cava (above and below the liver) and the portal triad. Splanchnic and inferior systemic venous beds were decompressed using veno-venous bypass. TAK-044 (donated by Takeda Chemical Industries, Ltd, Osaka, Japan), dissolved in normal saline and given to animals at a dose of 5.0 mg/kg, was given as a continuous intravenous infusion (via a peripheral vein) over 30 minutes, just before hepatic ischemia (Group 2, n = 5). Control animals (Group 1, n = 10) received a 30-minute infusion of normal saline.

Serial arterial aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bile acid (BA) levels and hepatic venous immunoreactive endothelin-1 (irET-1) levels were determined. Intraoperative hepatic tissue blood flow (HTBF) was measured serially using a laser-doppler flow meter (ALF21; Advance, Co, Ltd, Tokyo, Japan). Post-ischemic liver tissues (wedge biopsies) were stained with hematoxylin and eosin for histological analysis. Results are presented as the mean ± the standard error of the mean. Statistical analysis of the results was performed using the Log Rank test (for survival), and the Mann-Whitney U test (all others). A P value less than .05 was considered significant.

RESULTS

Two-week animal survival in Group 2 (100%) was significantly better than Group 1 (30%). Peak AST and ALT levels in Group 1 were significantly higher than AST and ALT levels in Group 2. The AST and ALT of Group 1 livers 12 hours after reperfusion were 1152 ± 1014 U/L and 13563 ± 1379 U/L, respectively, while AST and ALT of Group 2 livers at 12 hours were 3407 ± 420 U/L and 4228 ± 1167 U/L, respectively. Bile acid levels in Group 1 increased after reperfusion, and peaked at 175 ± 39 mmol/L 24 hours after reperfusion. On the other hand, bile acid levels in Group 2 peaked 58 ± 21 mmol/L 1 hour after reperfusion, and returned to normal levels 12 hours after reperfusion.

Neither the infusion of TAK-044 (Group 2), nor the normal saline (Group 1), caused any change in hemodynamics. Reperfusion caused a significant hemodynamic change in animals of both groups; however, the change was significantly less pronounced in Group 2 (60% of pre-ischemia MAP) than Group 1 (40% of pre-ischemia MAP). Conversely, peak portal vein pressure after reperfusion was significantly higher in Group 1 (12.7 ± 1.9 mm Hg) than in Group 2 (4.2 ± 0.9 mm Hg). Most importantly, however, hepatic tissue blood flow after reperfusion was significantly better in Group 2 (51.4 ± 1.6% of normal) than in Group 1 (26.8 ± 1.7%).

Two hours of complete normothermic hepatic ischemia caused a 20-fold increase in irET-1 levels in the hepatic venous blood of Group 1 (pre-ischemia: 0.8 ± 0.2 pg/mL vs post-ischemia: 17.6 ± 6.3 pg/mL). The increase of irET-1 was further enhanced by TAK-044 treatment (47.8 ± 10.4 pg/mL).

Histological analysis of post-ischemic liver tissue revealed that microthombi formation and heterotopic blood in sinusoid were significantly worse in Group 1 than in Group 2.

DISCUSSION

The infusion of TAK-044, a nonselective $ET_{A/B}$ receptor antagonist, before prolonged complete hepatic ischemia improved post-reperfusion hemodynamics, hepatic tissue blood flow, liver function, and tissue histology. As described in other studies,[2] our results suggest that endogenous endothelin influences hepatic microcirculation, and can induce microcirculatory disturbances after ischemia and reperfusion. Our results also suggest that the inhibition of endothelin binding to its receptors by the non-selective $ET_{A/B}$ receptor antagonist, TAK-044, provides effective protection against ischemia and reperfusion injury to the liver.

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