Pharmacological effects are model specific in animal models of portal hypertension

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Portal hypertension is responsible for a major part of complications of liver disease. The increase in portal pressure is attributable to an enhanced vascular resistance followed by an increase in portal venous inflow. The causes of the increase in portal resistance can be prehepatic (i.e., portal venous thrombosis), intrahepatic (most often cirrhosis), or posthepatic (Budd-Chiari syndrome). Furthermore, intrahepatic portal hypertension can be classified as presinusoidal, sinusoidal, and postsinusoidal; the last type being characteristic for human cirrhosis.

The increase in portal resistance is accompanied by severe disturbances of the systemic and splanchnic circulation and activation of vasoactive hormones leading to plasma volume expansion, increased cardiac output, systemic hypotension, vasodilatation, and increased portal venous inflow, often mentioned as the hyperdynamic circulatory dysfunction.

One of the most frequent and serious complications of portal hypertension is bleeding from esophageal or gastric varices. The risk and prognosis depend on the degree of portal hypertension, endoscopic characteristics, and liver dysfunction. Treatment aims at reducing portal pressure or obliterating varices by endoscopic ligation. A nonselective β -blocker (propranolol, nadolol, or timolol) is the pharmacologic treatment most often used as primary or

secondary prophylaxis against variceal bleeding. The effect of propranolol is a combination of a β -1 effect, with a decrease in cardiac output and thereby a decrease in portal venous inflow, and a β -2 effect inducing an increase in portocollateral resistance, which reduces the flow in the varices evidenced by a decrease in azygos venous blood flow [1]. The effect of propranolol varies and only approximately 40% of treated patients achieve a reduction of the hepatic venous pressure gradient (HVPG) to values below 12 mmHg or a reduction of HVPG of more than 20%, which seem to be crucial for the prevention of bleeding from varices. Although treatment with a β -receptor blocker is efficacious as primary and secondary prophylaxis against variceal bleeding, recent studies indicate lack of effect as pre-primary prophylaxis on the development of varices.

A major part of our understanding of the pathophysiologic mechanisms of portal hypertension has been based on animal models, particularly in rats [2]. The most extensively studied rat models have been conducted using partial portal vein ligation, which is a presinusoidal portal hypertension model, and common bile duct ligation (CBDL) and carbon tetrachloride (CCL₄)-induced cirrhosis, which both resemble sinusoidal portal hypertension. Because of difference in etiology and type of the experimental portal hypertension model, pharmacologic effects may differ between these models [3].

In the present issue of the journal, Fizzanne et al. [4] investigated the hemodynamic effects of propranolol in CBDL and CCL₄ rats. Apart from having sinusoidal portal hypertension, rat models differ from cirrhosis in humans, who have postsinusoidal hypertension, with respect to developments of portosystemic collaterals, which are mainly an esophageal venous network in humans and splenorenal shunts in rats.

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The authors randomized 44 rats with CBDL and 42 rats with CCL₄-induced cirrhosis to either placebo or propranolol. CBDL rats showed more severe signs of systemic hemodynamic abnormalities with a higher cardiac output and decreased MAP and SVR in the placebo group than the rats receiving placebo in the CCL₄ group. Heart rate, cardiac index, portal pressure, and splenorenal shunt flow all decreased significantly after propranolol in comparison with placebo in the CCL₄-treated rats, whereas propranolol showed no effect on any of the hemodynamic parameters in the CBDL rats. The discrepancy in effects in the two rat models could be due to several factors. In the CBDL model, there is a high risk of development of biliary cysts, which seemed not to be the case in the present study. Furthermore, the bile excretion is interrupted in the CBDL model, which might have an influence on pharmacokinetics of pharmacologic agents that are metabolized in the liver, which is the case for propranolol, and an enhanced plasma elimination of propranolol has previously been demonstrated in BDL rats [3]. Another difference is the development of severe biliary fibrosis in CBDL rats, and cirrhosis is seldom observed. The CCL₄ rats develop cirrhosis in most cases after 12–15 weeks, whereas only approximately 50% have signs of portosystemic shunting. Other differences in the models, which may interfere with hemodynamic results as stated in the discussion, are the potential influence of bile acids in the CBDL model and higher risk of bacterial translocation in this model, which may alter hemodynamics. The same group confirmed in a previous study that propranolol was without effect on the

prevention of development of portosystemic shunts and did not decrease portal pressure in bile duct-ligated rats [5]. The present data indicate that the CBDL rat model is not optimal for studies, which aim to evaluate potential drugs for future treatment of portal hypertension.

In conclusion, the results of this experimental study emphasize that pharmacologic hemodynamic effects are model specific, and one should therefore be cautious to draw firm conclusions as to the efficacy in humans based on animal studies.

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