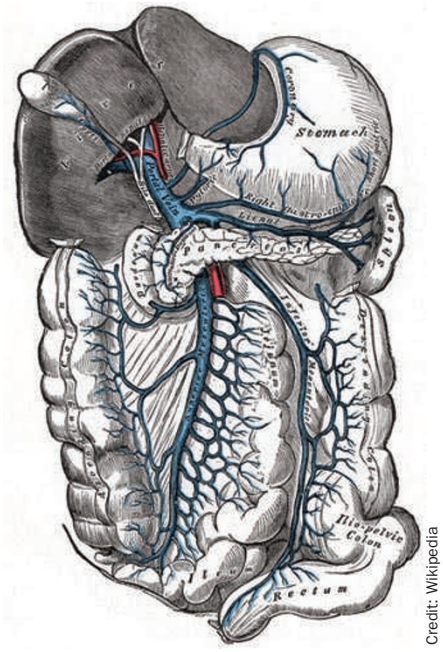
LIVER

Simvastatin might be an effective therapy for portal hypertension in cirrhosis

Simvastatin could be an effective therapy for portal hypertension, according to a study by Abraldes and colleagues, which shows that the drug decreases portal hypertension and improves liver perfusion in patients with cirrhosis.

Complications of portal hypertension include the development of esophageal varices, ascites, hepatic encephalopathy, hepatorenal syndrome and splenomegaly. Such complications are a major cause of morbidity and mortality in patients with cirrhosis and the majority of indications for liver transplantation are attributable to the consequences of portal hypertension. Treatment for portal hypertension in patients with cirrhosis is based on the use of β-blockers with or without organic nitrates; however, these agents are effective in less than 50% of patients and a proportion of patients with cirrhosis cannot tolerate β-blockers. The limitations of this therapeutic strategy have stimulated research for alternative drugs that are effective for the long-term treatment of portal hypertension. An ideal drug for this condition would reduce portal pressure while maintaining or improving hepatic blood flow.

Portal hypertension in cirrhosis is mainly the result of increased resistance to portal blood flow in the liver. Around 30% of this increased resistance is due to increased hepatic vascular tone, which is partly caused by defective release of nitric oxide (NO) into the intrahepatic circulation. Previous work by this group of researchers in animals and humans with cirrhosis revealed that short-term administration of simvastatin increases the release of NO into the intrahepatic circulation. As a consequence of this increase in NO, intrahepatic resistance to blood flow within the liver is significantly reduced, which results in improved perfusion and reduced portal pressure. This initial research identified an unrecognized beneficial effect of simvastatin. "The next step was to explore whether long-term administration of simvastatin could reduce portal pressure in patients with cirrhosis without further impairing the hepatic circulation and liver function", explains Bosch, who was a member of the research team on this project.



Credit: Wikipedia

Their double-blind, randomized, controlled trial was performed at three Spanish hospitals and included 59 patients with cirrhosis and severe portal hypertension (hepatic venous pressure gradient [HPVG] ≥12 mmHg). Eligible patients were randomly allocated to simvastatin (20 mg daily for the first 14 days and 40 mg daily thereafter) or placebo for 1 month. Allocation of therapy was also stratified according to whether an individual was receiving β-blockers. The main end point was the change in portal pressure. HVPG was determined before and after treatment by insertion of a catheter into the main right hepatic vein to measure wedged and free hepatic vein pressures. As Bosch comments, "it is important to remember that HVPG is considered to be the closest optimal surrogate outcome measurement in chronic liver diseases". Systemic hemodynamics were also monitored and quantitative liver function tests (hepatic clearance of indocyanine green, fractional clearance and hepatic intrinsic clearance) were performed.

The main findings of the study were that simvastatin significantly lowered portal pressure, by 8.3%. This decrease in portal pressure was observed both in patients on simvastatin alone and in those on simvaststin and β-blockers, which suggests an additive effect of simvastatin. Quantitative liver function parameters were significantly improved by administration of simvastatin. Safety is an important concern when considering the use of statins in patients with cirrhosis, owing to their potential for inducing toxic effects in the liver. Treatment was, however, well tolerated and none of the safety parameters assessed in this trial differed between the placebo and active-treatment groups.

"Our results indicate that simvastatin has a clear potential for the treatment of portal hypertension in patients with cirrhosis and may be a useful adjunct to standard pharmacological treatment", concludes Bosch. "The next step is to perform a large-scale, long-term clinical trial with clinical end points, for example, complications of portal hypertension, survival, to confirm the potential of this drug for the long-term management of portal hypertension in this population".

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