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Case Report

The use of sildenafil to treat portopulmonary hypertension prior to liver transplantation

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Abstract

Portopulmonary hypertension (PPH) is an infrequent, but well-recognized complication of liver cirrhosis. PPH in those with end-stage liver disease has a significant impact on per-operative and intra-operative mortality, with liver transplantation being contraindicated in those individuals with mean pulmonary artery pressure exceeding 50 mmHg. Vasodilatory therapy is the mainstay of pharmacotherapy for PPH, although the evidence of benefit is largely extrapolated from the pulmonary hypertension literature. We report the use of the phosphodiesterase inhibitor, sildenafil, in a patient with end stage liver disease and PPH, with a pulmonary artery pressure before transplantation of 75 mmHg, to reduce pulmonary artery pressure prior to a successful liver transplant.

Key words: Liver transplantation, sildenafil, cirrhosis, pulmonary hypertension, portopulmonary.

Introduction

Portopulmonary hypertension (PPH) is an infrequent, but well recognized complication of liver cirrhosis. The pre-requisites for its diagnosis are a mean pulmonary artery pressure (PAP) exceeding 25 mmHg at rest (or > 30 mmHg with exercise) in the setting of a normal pulmonary artery wedge pressure (*i.e.* < 15mmHg) in a patient with portal hypertension.[1,2] Other secondary causes of pulmonary hypertension must also have been excluded.[1,2] Depending upon the source, the literature suggests the incidence of PPH amongst those with cirrhosis to be somewhere between 0.25% and 3%.[3-6] This rises to 8.5% for those individuals undergoing liver transplantation.[7]

The significance of PPH in those with end stage liver disease is its impact on peri-operative and intra-operative mortality.[7] Those who exhibit pulmonary artery pressures in the 35–50 mmHg range have operation-related mortality approaching 50% according to work by Krowka *et al.*[8] Moreover, liver transplantation is contraindicated in those individuals with mean PAP exceeding 50 mmHg.[8] In view of this, it is mandatory to reduce the PAP prior to proceeding to liver transplantation.[8]

We report the case of a 51 year old man with end stage liver disease due to Hepatitis C, complicated by PPH, who underwent orthotopic liver transplantation following treatment with sildenafil to reduce pulmonary arterial pressure.

Case report

A 51 year old man presented to our institution with vomiting and abdominal pain. An abdominal CT scan was performed which demonstrated features in keeping with liver cirrhosis. Subsequent investigation determined the aetiology of his liver disease to be Hepatitis C (genotype 1b). The mechanism of contraction of the virus was unclear given that the patient did not use intravenous or intranasal drugs and reported no previous exposure to blood products.

The patient began to complain of shortness of breath and reduced exercise tolerance. Physical examination did not reveal any abnormalities in the cardiovascular, respiratory or gastrointestinal systems. An echocardiogram was carried out demonstrating mild pulmonary hypertension, with an estimated PAP of 43 mmHg. The right heart structures were normal and there was no evidence of intra-pulmonary shunting on a contrast study.

Ten months later, the patient was again admitted to our institution with a presumed variceal haemorrhage

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(his second in several months). Endoscopy revealed a large amount of blood in the stomach, however no source of bleeding was identified. Subsequent endoscopy the following day showed large gastric varices. In an effort to control these gastric varices the patient proceeded to the formation of a medium aperture mesocaval shunt. Interestingly, at the time of shunt insertion, an elevated IVC pressure of 38mmHg was recorded.

Following insertion of the mesocaval shunt the patient complained of increasing fatigue and gradually decreasing exercise tolerance with dyspnoea after walking one city block. In view of this, his echocardiogram was repeated a few months later and this demonstrated a significant increase in his pulmonary hypertension with the PAP estimated now at 62 mmHg. In contrast to the previous study there was now bi-atrial enlargement with enlargement of right ventricle and a moderate degree of tricuspid regurgitation. The patient proceeded to cardiac catheterization which confirmed pulmonary hypertension with a PAP of 75 mmHg. The patient was diagnosed with portopulmonary hypertension which had been exacerbated by the increased venous return through his portosystemic shunt.

By this stage the patient's liver disease had progressed to a point where transplant assessment was considered necessary. The patient was commenced on sildenafil 50 mg twice daily in an effort to reduce his pulmonary artery pressure. He was on no other pharmacotherapy at that time, other than the herbal product, milk thistle, which he had been taking for several months. After three months his echocardiogram was repeated and demonstrated a degree of improvement with the PAP having fallen to 50 mmHg. Additionally, the previously noted bi-atrial and right ventricular enlargement had resolved and there was a decrease in the degree of tricuspid regurgitation. The patient tolerated sildenafil therapy well and was maintained on the initial dose of 50 mg daily.

The patient was subsequently listed for liver transplantation. He underwent an uneventful orthotopic liver transplant. Following his surgery his sildenafil was recommenced. A repeat echocardiograhic study 1 year after transplantation has demonstrated that the estimated pulmonary pressure had fallen to 39 mmHg in keeping with mild pulmonary hypertension. The patient remains clinically well more than 2.5 years post-transplant.

Discussion

Work carried out by Castro *et al* and Herve *et al* has demonstrated that mild elevation of the pulmonary arterial pressure is a common finding in cirrhotic patients.[9,10] This is related to the increased cardiac output and/or blood volume seen in those with advanced liver disease.[9,10] In contrast, Portopulmonary hypertension is an uncommon complication of cirrhosis.

The presentation of individuals with PPH can be varied. Subjects may be asymptomatic or present with a spectrum of symptoms ranging from exertional dyspnoea and fatigue (as seen in our patient) to syncope and symptoms of right sided heart failure.[5,11] The presence of right ventricular hypertrophy, right axis deviation or right bundle branch block on electrocardiogram, or cardiomegaly and prominent pulmonary arteries seen on chest radiograph should raise the suspicion of pulmonary hypertension.[12] However these investigations lack sufficient sensitivity to serve as screening tools for the detection of PPH in those being considered for liver transplantation.[13] Echocardiography is the non-invasive diagnostic tool of choice, and may reveal an enlarged, dilated right atrium and ventricle with tricuspid regurgitation.[12] The presence of tricuspid regurgitation allows estimation of the right ventricular systolic pressure, however due to difficulties ascertaining precise values, right heart catheterization is recommended as the gold standard investigation to confirm the diagnosis of PPH.[14]

The significance of PPH is its effect on patient survival. Liver transplantation in the face of PPH is associated with high operative mortality (70-80%) without prior attempts to reduce pulmonary pressure, with the patients' demise commonly resulting from right ventricular failure.[15-17] Vasodilatory therapy is the mainstay of pharmacotherapy for PPH, and most of the regimens explored have been extrapolated from data relating to the treatment of pulmonary hypertension.[1,2,18] Pulmonary artery hypertension can be reduced using calcium channel blockers; however Rich *et al* suggested that as few as 25% respond and those that do require high doses, thereby risking side effects.[19]

The use of intravenous epoprostenol, a potent vasodilator, has been reported for the treatment of portopulmonary hypertension.[12] Indeed it has been used successfully as a bridge to transplantation in several patients.[20] Work by Krowka *et al* detailing the experiences of a number of liver transplant centres suggests a survival benefit in 4 out of 5 liver-transplanted patients receiving this agent.[21] The obvious limitation of epoprostenol is its mechanism of administration, *i.e.* intravenously,[22] however other inhaled prostaglandin preparations, such as iloprost, have also been shown to be beneficial in the treatment of PPH.[23,24]

A number of other agents have also been used in an attempt to reduce PAP in those with PPH. The demonstration of elevated endothelin-1 (ET-1) levels in subjects with PPH[12] has lead to the use of the endothelin receptor antagonist, bosentan, in portopulmonary hypertension.[25-27] Investigators have reported clinical, functional and haemodynamic improvements in individuals with portopulmonary hypertension receiving bosentan. However, the elevation of serum transaminases associated with it, although seen only in a minority of patients with pulmonary arterial hypertension, has limited the use of bosen-

tan to experienced centres and made its use difficult in a population with decompensated liver disease.[28]

Phosphodiesterase (PDE) inhibitors have recently been suggested as an alternative therapeutic approach for the management of PPH.[22,29,30] These agents enhance the effect of nitric oxide on vascular smooth muscle by inhibiting cyclic GMP breakdown.[12,22] The overall effect of this is to promote pulmonary vasodilatation and inhibit the proliferation of vascular smooth muscle.[12] Sildenafil is an inhibitor of PDE type V (PDE-V), used initially in the management of male sexual dysfunction.[22] However, a number of case reports have described its use in PPH.[22,29-32] Moreover, a Finnish group reporting the use of sildenafil to reduce PAP in an individual with PPH who subsequently underwent liver transplantation for primary biliary cirrhosis related end stage liver disease.[29] In this case report, a significant improvement in PAP was achieved with sildenafil in concurrence with that demonstrated in our patient.[29] Wang *et al* have suggested that, given that PDE-V is also present in the mesenteric vessels, sildenafil may cause splanchnic vasodilatation. This may ultimately cause an increase in splanchnic blood flow thereby exacerbating pre-existing portal hypertension,[22] an hypothesis supported by work on an animal model of cirrhosis.[33] Indeed, Charalabos *et al* have reported a case of oesophageal variceal haemorrhage related to the use of sildenafil.[34] However, this unfortunate complication was not seen in either the case described here or by Makisalo *et al*.[29] It is possible that the portosystemic shunt present in our patient protected him from any sildenafil-associated increases in portal pressure.

Conclusion

Portopulmonary hypertension is a rare, but serious complication of end stage liver disease which, if severe, is a contraindication to liver transplantation. To date pharmacotherapy has been limited by poor efficacy, the side effect profiles and the modes of delivery of the various agents. Several anecdotal reports have shown that the phosphodiesterase type V inhibitor, sildenafil, has promise in the management of portopulmonary hypertension. The results of large, randomized controlled trials are awaited before sildenafil can be considered as an established therapeutic option for this challenging condition.

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