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 peri-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.
demonstrated that mild elevation of the pulmonary arterial hypertension is an uncommon complication of cirrhosis. In contrast, Portopulmonary hypertension is an increased cardiac output and/or systemic shunt. This is related to the increased venous return through his porto-systemic 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 hypertension in the face of PPH. 

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. 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. However these investigations lack sufficient sensitivity to serve as screening tools for the detection of PPH in those being considered for liver transplantation. 

Echocardiography is the non-invasive diagnostic tool of choice, and may reveal an enlarged, dilated right atrium and ventricle with tricuspid regurgitation. 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. 

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. 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. 

Work by Krowka and Herve 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. The obvious limitation of epoprostenol is its mechanism of administration, i.e. intravenously, however other inhalers have also been shown to be beneficial in the treatment of PPH.

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 has lead to the use of the endothelin receptor antagonist, bosentan, in portopulmonary hypertension. 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 bosentan.

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. This is related to the increased cardiac output and/or blood volume seen in those with advanced liver disease. In contrast, Portopulmonary hypertension is an uncommon complication of cirrhosis.
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 porto-systemic 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.

References


