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Review

Oral sildenafil: Potential role in heart transplantation. Review of the literature and personal experience

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Summary Early right ventricular dysfunction after heart transplantation (HTx) is a major complication especially in patients with pre-transplant pulmonary arterial hypertension (PH). The possibility to reverse secondary PH using sodium nitroprusside (NPS) or inhaled nitric oxide has been already established and there is a well-known stratification of the incidence of early death after HTx related to the reversibility of PH. Despite this, in a group of patients with irreversible disorders of the pulmonary vascular bed, conventional therapy may not be useful. However, the decision to disqualify non-responsive HTx candidates may be inappropriate, considering that PH unresponsiveness to NPS does not exclude the possibility to decrease pulmonary pressures with other medications. In case of non-responsive patients, the debate regarding the role of new selective pulmonary vasodilators is still open and oral sildenafil use in cardiac transplant candidates and recipients is growing. Despite this, there are many reports of the use of phosphodiesterase 5 inhibitors in patients with chronic heart failure and several studies describe the positive effects of sildenafil in reducing pulmonary vascular resistance and pulmonary arterial pressure and in increasing cardiac output. Oral sildenafil use in cardiac transplant candidates or recipients is still limited.

Contents

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Introduction

In chronic heart failure, the elevated left ventricular end-diastolic pressure may lead to pulmonary arterial hypertension (PH) either by indirect ''reactive'' pulmonary vasoconstriction or by retrograde direct transmission of the increased pressure to the lungs. PH is present when mean pulmonary artery pressure (mPAP) is greater than 25 mmHg at rest or greater than 30 mmHg with exercise [1]. It is characterized by complex vascular changes with the final result of an increased PAP and pulmonary vascular resistance (PVR). This modification is initially reversible but progressively collagen deposition in the pulmonary arteries leads to irreversible structural changes. At this stage PH and PVR become non-reactive to common pulmonary vasodilators.

The ''milestone'' in the treatment of PH is inhaled nitric oxide (iNO) that causes pulmonary vasodilatation increasing cyclic guanyl monophosphate (cGMP) levels in pulmonary vessels. iNO is inactivated directly in the lumen of the vessel limiting its effect to the vascular smooth muscle adjacent to the alveolar unit. Although iNO is the most effective and selective pulmonary vasodilator, its use is limited because of the complicated delivery system that requires mechanical ventilation, the high costs of the medical form of NO gas, the necessity of invasive monitoring system, and the very short half-life. Despite these limitations, iNO is considered the gold standard in pre-transplant evaluation of patients with PH [2,3] and some authors [4] suggested the use of iNO immediately after heart transplantation to prevent early right ventricular dysfunction (RVD). Moreover, iNO is the only selective pulmonary vasodilator that does not require the use of a vasoconstrictor to support systemic blood pressure. However, the debate regarding the role of new selective pulmonary vasodilators is still open [5,6] and oral sildenafil use in cardiac transplant candidates and recipients is growing up [7—11].

Many other drugs have been used for the treatment of PH such as:

- *Isoproterenol*: nonselective β receptor agonist that induces pulmonary and systemic vasodilatation increasing cardiac output (CO). Its short half-life should induce acute increase of PVR after therapy discontinuation with bad prognosis.
- *Dobutamine*: selective β2 receptors agonist with vasodilator effect, ideal in case of heart failure associated with high PVR. It should increase myocardial oxygen demand.
- *Phosphodiesterase III inhibitors (milrinone)*: inotropic drug with a vascular smooth muscle-relaxing effect mediated by cyclic adenosine monophosphate pathway. It should be used in association with β2 receptors (dobutamine) because of their different but synergistic mechanisms of action.
- *Prostaglandin E1 and prostacyclin*: they are potent pulmonary vasodilators unfortunately with significant systemic effects. They have very short half-lives due to quick degradation in lungs and liver.

In addition to using these drugs, some authors believe that the use of oversized donor in case of preoperative PH should improve the adaptation of the organ implanted to high PAP [12], but other investigators [13] demonstrated that the outcome of recipients was not related to the heart size.

However, the recent introduction of new selective pulmonary vasodilators added new resources in the treatment of PH: many reports suggested that non-responders to sodium nitroprusside (NPS) or iNO tests, should be favored by the use of other vasodilators as inhaled or intravenous iloprost, endothelin receptor inhibitors [2,3], and in recent years by phosphodiesterase 5 inhibitors (PDE-5i).

Sildenafil and pulmonary arterial hypertension

The effects of sildenafil on pulmonary vessels were investigated during recent years when initial reports describing hemodynamic results with PDE-5i were presented. Pulmonary vasodilatation is caused by the increased levels of cGMP in vascular smooth muscle cells [14]. cGMP has a short life because of its degradation by phosphodiesterase 5 (PDE-5), which is the active iso-form in the lung [15]. All the processes able to enhance the effects of PDE-5 or reduce cGMP levels, like hypoxia, may cause pulmonary vasoconstriction and then PH.

On this basis, the possibility of using PDE-5i to induce pulmonary vasodilatation (enhancing the levels of intracellular cGMP) was considered and a drug everywhere used for erectile dysfunction [16] was investigated for its activity on PVR in patients with PH [17,18] or in case of hypoxia-related pulmonary vasoconstriction [19].

Supported by these preliminary data and considering the similar mechanism of action of PDE-5i and iNO, Michelakis et al. [20] reported their initial experience with oral sildenafil in patients evaluated for heart and lung transplantation and compared the data on sildenafil therapy with those obtained with iNO. This paper was the first evidence of the effects of PDE-5i on pulmonary circulation: a single dose of oral sildenafil (75 mg) is a potent and selective pulmonary vasodilator compared with iNO (80 ppm). Sildenafil is superior in decreasing the mPAP and equally effective and selective in reducing PVR and it causes a significant increase in cardiac index. Sildenafil resulted in a higher reduction of pulmonary artery wedge pressure (PAWP) than iNO and this has positive effects on the patients' symptoms with end-stage heart failure and it may prevent pulmonary edema (rare complication during iNO therapy). In that paper the effects of oral sildenafil and iNO were at least comparable: furthermore, their actions are synergistic and this

is a new opportunity in the treatment of low-responsive patients.

The effects of sildenafil in patients both with idiopathic PH and with secondary PH were investigated by Ghofrani et al. [21]. They reported that 120 or 180 min after low/or high doses of oral sildenafil (12.5 or 50 mg) alone or in combination with inhaled iloprost, there was a significant decrease in PVR and PAPs with increase of CO and improvement in symptoms. This report confirmed the additive effects of PDE-5i with inhaled iloprost. Another study by Ghofrani et al. [22] confirmed the data reported above in patients with lung fibrosis.

Sildenafil and heart transplantation

Sildenafil use in heart transplantation (HTx) started about 5 years after the first use of sildenafil in non-transplant patients with PH. The major limitation of its use in HTx was related to the possible interferences with immunosuppressive drugs and the possibility of negative effects on the implanted organ. Considering that PVR from 3 to 5 Wood units and transpulmonary gradients >15 mmHg have accounted for a 3—5-fold increased risk of mortality within the initial 30 days after heart transplantation [23] and many vasodilators as iNO, prostacyclin, nitroglycerine, and NPS have been used with varying success to treat RVD due to PH [24], many authors started to be interested in the use of oral sildenafil in heart transplant candidates or recipients with PH because of its easiness of administration, its low cost, its safety, and its additive effects with all the other vasodilators.

Acute RVD remains a difficult and ever-present clinical syndrome in the transplant recipient. Avoidance of RVD after HTx is unfortunately, not possible. Goals in the treatment of this clinical problem include: coronary perfusion maintaining high systemic blood pressure, reducing RV preload with diuretics and RV afterload by decreasing PVR, avoidance of pulmonary vasoconstriction using high inspired oxygen concentrations and increased tidal volume.

In the last few years, the effects of oral sildenafil in heart transplant patients started to be investigated and many authors reported their preliminary experience.

An interesting study published in 2003 [25] described the use of 50 mg of sildenafil in heart transplant recipients with erectile dysfunction: the authors concluded that sildenafil is well tolerated in these patients avoiding hypotension and by decreasing the amplitude of the reflected pressure wave and delaying its return to the heart, sildenafil reduces left ventricular afterload and systolic stress. Moreover, some other authors suggested that the use of sildenafil in hypertensive transplanted patients should have a synergistic role in reduction of systemic blood pressure, improving heart function [26].

Many authors focused their attention on the role of sildenafil in pre-transplant candidates. An interesting paper published in 2007 described the experience with six patients with PH awaiting HTx: in five of these patients PH was reversed and they were enrolled on the waiting list for HTx. Despite this, the major limit of this study is that the patients described were not yet transplanted and this does not allow evaluating the role of pre-transplant therapy with sildenafil on the overall mortality after heart transplantation. The authors concluded that sildenafil can be effectively used to treat secondary irreversible PH among potential heart transplant candidates, allowing qualification for HTx [10].

Moreover, some authors use oral sildenafil as a vasodilator drug for preoperative evaluation in patients with PAH. They reported that sublingual sildenafil causes a rapid and selective decrease in mean transpulmonary gradient, mPAP, and PVR in HTx patients with PH due to left ventricular systolic dysfunction, without significant changes in mean pulmonary wedge pressure, CO, and systemic vascular resistance. They concluded that sublingual sildenafil is a simple acute vasodilator test in heart transplant candidates with PH [27].

In 2004, the first report of Kulkarni et al. [11] described the use of oral sildenafil in a young transplant recipient with post-transplant PH complicated by RVD and tricuspid regurgitation: oral sildenafil (0.5 mg/kg every 4 h), added to inotropes and vasodilators (milrinone and nitroglycerine) on 2nd postoperative day, enabled quick decrease in PAP, PAWP, PVR, and central venous pressure and a fast improvement in urine output allowing a fast weaning of intravenous inotropes and vasodilators.

In 1971, Griepp et al. [28] first reported the relationship between elevated preoperative PVR and the risk of death from acute RVD after heart transplantation. Numerous other studies confirmed this association [29—31].

Personal experience

We have analyzed the data obtained from patients with RVD after heart transplantation [32]: in our experience about 10—15% of all transplant recipients suffered for RVD at different time after transplantation. We treated patients suffering from RVD after HTx with conventional therapy including inotropes, iNO, and intravenous NPS: they received oral sildenafil in the postoperative period in order to stop the inhaled and intravenous drugs administration. RVD diagnosis was assessed by:

- direct inspection during cardiopulmonary by-pass weaning with the evidence of right ventricular dysfunction and dilatation;
- transesophageal echocardiography with the evidence of right ventricular hypokynesia and dysfunction;
- hemodynamic parameters measured using Swan Ganz catheter;
- clinical evaluation such as signs of good peripheral perfusion, diuresis, hepatic and pulmonary function.

In order to offer the possibility of weaning from intravenous or inhaled drugs administration, we added oral sildenafil during intensive care unit (ICU) stay: the principal aim of this approach was to reduce time of intubation and ICU stay. Early hemodynamic data (during conventional therapy alone) were compared with late hemodynamic results (oral sildenafil therapy alone). The main result of our analysis was the evidence of a significant reduction in PAP values after inotropes weaning and introduction of oral sildenafil. However, it is not possible to demonstrate that the hemodynamic improvement is completely related to oral sildenafil

considering that the physiologic hemodynamic resetting of the new heart in the recipient should play a role. Our results, although in a limited number of patients, show the efficacy of sildenafil in reducing PAP and increasing CO in patients suffering from RVD after HTx and suggest that oral administration of sildenafil may be safe and feasible.

Discussion

Right ventricular function immediately after HTx is the strong determinant of heart transplant recipient outcome: in fact, RVD is caused by different causes and it has a negative impact on heart transplant recipient survival. Many strategies have been proposed to prevent and to treat RVD after HTx such as the use of drugs like isoproterenol, NPS, prostaglandin E1, prostacyclin, or the use of mechanical support of right ventricular function. From one side, the use of these drugs induces pulmonary vasodilatation, but the side effect of systemic hypotension should be always considered. Many efforts have been focused in order to develop the ideal pulmonary vasodilator. At the moment, NO is the most effective and selective pulmonary vasodilator: it is produced in the lung by NO synthase and it is a powerful, rapidly acting, and selective pulmonary vasodilator. iNO selectively dilates pulmonary vessels, decreasing PVR and PAP without affecting systemic vascular resistance. The major limitation of its application is the complicated delivery system that requires mechanical ventilation and needs orotracheal intubation.

Sildenafil is an oral inhibitor of PDE-5. Pulmonary vasodilation is caused by increase of the levels of cGMP in vascular smooth muscle cells [14]. cGMP has a short life because of the degradation by PDE-5, which is the active iso-form in degrading cGMP in the lung [15]. All the processes able to enhance the effects of PDE-5 or reduce cGMP levels, like hypoxia, may cause pulmonary vasoconstriction and then PH. PDE-5 is the pulmonary iso-form of PDE-5i and inhibition of PDE-5 by sildenafil leads to a selective pulmonary vasodilatation with minimal systemic side effects. The use of oral sildenafil after HTx has not been well established because of the suspect of drug interaction between PDE-5i and immunosuppressive drugs: sildenafil in the postoperative period after HTx as treatment of RVD may be quite common in centers performing HTx, but its use has not yet been clearly recommended. In our experience the use of oral sildenafil allowed a gradual weaning from inotropic and pulmonary vasodilator drugs, iNO and mechanical ventilation in all patients suffering from RVD after HTx. This strategy presents several advantages. First a shorter need for iNO allows a faster weaning of the patients from mechanical ventilation. PDE-5i facilitates gas exchange and improves ventilation efficiency because they preferentially dilate vessels in well-ventilated areas of the lung reducing vascular resistance and improving overall oxygenation (''re-matching'' drug). A shorter ventilation time may lead to a reduced risk of ventilator associated pulmonitis. Considering the known effect of sildenafil on PH and the relation between the reduction in PAP and the improvement in right ventricular stroke work, this drug may allow right ventricular recovery. Another important aspect is the relative low cost of sildenafil if compared with other therapies for PH.

Conclusion

On the basis of the data reported in literature and our experience we can affirm that oral sildenafil represents an attractive alternative in the treatment of PH and RVD. Its low cost and oral administration are two important advantages in comparison with other therapies nowadays available.

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