Case Report

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Successful switch from long-term intravenous iloprost to non-invasive combination therapy in idiopathic pulmonary arterial hypertension*

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Erfolgreiche Umstellung einer intravenösen Langzeittherapie mit Iloprost auf eine nicht invasive Kombinationstherapie bei idiopathischer pulmonal arterieller Hypertonie

Zusammenfassung. In Europa stellt die intravenöse (i.v.) Gabe von Iloprost, als Alternative zu Epoprostenol, eine anerkannte Therapie bei Patienten mit einer schweren idiopathischen pulmonal arteriellen Hypertonie (IPAH) dar. Nach Einleitung einer solchen Therapie wird diese meist lebenslang oder bis zur Transplantation durchgeführt.

In der vorliegenden Arbeit beschreiben wir zwei Patientinnen mit IPAH, die sich unter einer kontinuierlichen i.v. Iloprost Monotherapie beziehungsweise unter einer Kombinationstherapie mit i.v. Iloprost plus oralem Bosentan funktionell in der World Health Organisation (WHO) Klasse II beziehungsweise III befanden. Die Dauer der i.v. Iloprosttherapie betrug 4,5 beziehungsweise 2,5 Jahre. Auf Grund lebensbedrohlicher und wiederholter Katheter-assoziierter Komplikationen der i.v. Langzeittherapie mit Iloprost erfolgte eine Therapieumstellung auf eine nicht invasive Kombinationstherapie bestehend aus oralem Bosentan plus inhalativem Iloprost (Patient 1) beziehungsweise aus oralem Bosentan plus inhalativem Iloprost plus oralem Sildenafil (Patient 2). Vier Wochen nach Beginn der Bosentantherapie konnte bei der Patientin in der WHO Klasse II die intravenöse Iloprost Therapie innerhalb von 8 Stunden nach Einleitung der Inhalationstherapie mit Iloprost ausgeschlichen werden. Bei der Patientin in der WHO Klasse III wurde das i.v. Iloprost nach Beginn der nicht invasiven Dreifachkombinationstherapie innerhalb von 5 Tagen reduziert und beendet. Beide Patientinnen konnten unproblematisch von i.v. Iloprost zu nicht invasiven Kombinationstherapien wechseln und die WHO Klasse änderte sich seit nun mindestens 12 bzw. 14 Monaten nicht. Diese Daten weisen darauf hin, dass ausgewählte Patienten mit Komplikationen durch eine intravenöse Langzeittherapie mit Iloprost auf eine nicht invasive Kombinationstherapie umgestellt werden können.

Summary. In Europe intravenous (IV) iloprost, an alternative to epoprostenol, is an accepted treatment option for severely compromised patients with idiopathic pulmonary arterial hypertension (IPAH). Once initiated, this therapy usually has to be continued lifelong or as bridging to transplantation.

In our paper we describe two patients with IPAH in World Health Organisation (WHO) functional classes II and III while on treatment with continuous IV iloprost monotherapy or combination therapy with continuous IV iloprost plus oral bosentan, respectively. The duration of IV iloprost therapy was 4.5 and 2.5 years, respectively. Because of life-threatening or recurring catheter-related complications during long-term IV iloprost therapy, these patients were switched to non-invasive combination therapy consisting of oral bosentan plus aerosolized iloprost (patient 1) and oral bosentan plus aerosolized iloprost plus oral sildenafil (patient 2), respectively. After four weeks of additional bosentan therapy, stepwise reduction and discontinuation of IV iloprost were performed within eight hours in the patient in WHO class II, and within five days in the patient in WHO class III. Simultaneously, therapy with aerosolized iloprost was started in the first patient and with aerosolized iloprost plus sildenafil in the second patient. Both patients were safely switched from IV iloprost to non-invasive combination therapy while WHO classification of functional status remained unchanged for at least 12 and 14 months, respectively. These data suggest that selected patients with complications due to IV iloprost treatment can be safely switched to non-IV combination therapies.

Key words: Bosentan, iloprost, pulmonary hypertension, idiopathic pulmonary arterial hypertension, sildenafil.

* This work was performed at University Hospital Carl Gustav Carus Dresden and Ernst-Moritz-Arndt University Greifswald, Germany.

Introduction

Idiopathic pulmonary arterial hypertension (IPAH), formerly primary pulmonary hypertension, is a rapidly progressing disease carrying a devastating prognosis. The National Institutes of Health (NIH) Registry on IPAH documented a median survival of 2.8 years after diagnosis without specific therapy [1]. Diagnosis of IPAH is established from a mean pulmonary artery pressure above 25 mmHg at rest or 30 mmHg with exercise and by exclusion of secondary causes of pulmonary hypertension according to the diagnostic criteria reported by Rich et al. and modified according to the World Health Organisation (WHO) proposals of 1998 and 2003 [2–4]. In order to exclude other forms of pulmonary hypertension, our patients underwent scintigraphy (chronic thromboembolic pulmonary hypertension), high-resolution computed tomography (lung disease), serologic testing (HIV infection, connective tissue disease) and comprehensive pulmonary and liver function studies (lung or liver disease).

Long-term treatment with continuous intravenous (IV) epoprostenol, a synthetic analog of prostacyclin, has been shown to improve exercise capacity and survival in patients with IPAH [5]. For IV iloprost, another analog of prostacyclin, comparable clinical efficacy has been demonstrated in smaller studies and the drug is recommended as an alternative IV treatment for this patient group, especially in Europe [6, 7].

In this report, we describe two patients with IPAH in WHO functional classes II and III in whom long-term IV iloprost therapy had to be discontinued because of severe treatment-related complications and who were successfully switched to aerosolized iloprost plus bosentan or to aerosolized iloprost plus bosentan and sildenafil, respectively.

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Patient 1 is a 39-year-old woman. The first symptom of pulmonary hypertension was exertional dyspnea developing during pregnancy in 1997. A healthy child was born in April 1998 following an otherwise normal pregnancy. IPAH was diagnosed in November 1998, with a mean pulmonary arterial pressure (mean PAP) of 53 mmHg, a WHO functional class III and a peak oxygen uptake (peakVO_2) of 9.3 ml/kg/min during exercise testing**.** Anticoagulation therapy with a targeted international normalized ratio (INR) of 2.0–2.5 was started. In March 1999, after confirmation of reimbursement by the insurance company, additional long-term treatment with inhaled iloprost (Ilomedin®, Schering, Berlin, Germany) was initiated at a constant dose of 100 µg nebulized iloprost per day, divided into six single inhalations, as previously described [8]. Iloprost was administered by jet nebulizer (Ilo-Neb®, Nebu Tech, Elsenfeld, Germany) at a concentration of 10 µg/ml. According to an average nebulization rate of 1.7 ml/minute, after 10 minutes a cumulative dose of 17 µg iloprost is nebulized (corresponding to an inhaled dose of 4.3 µg), a dose previously reported as safe and effective for the long-term treatment of pulmonary hypertension [9, 10]. The patient demonstrated no acute vasoreactivity to inhaled iloprost according to the consensus definition of the European Society of Cardiology [11]. After initiating therapy with inhaled iloprost, no improvement in WHO functional class could be achieved. Her initial and follow-up hemodynamic and exercise data are shown in Table 1.

In July 1999, the patient was switched to IV prostanoids because of clinical deterioration with overt signs of right-heart failure. Again, no acute vasoreactivity to epoprostenol (Flolan®, GlaxoWellcome Ltd, Uxbridge, UK) was detected during right-heart catheterization (maximum tolerated dose: 4 ng/kg/min), as shown in Table 1. Following up-titration, the patient was discharged on a dose of 2.5 ng/kg/min IV iloprost. Clinical stabilization was achieved within the first months after switching to IV iloprost, and WHO functional status improved to class II. The dose had to be increased up to 8.5 ng/kg/min during the

Table 1. Patient 1 Initial and follow-up hemodynamics, peak oxygen uptake during exercise testing and functional class

Date mo/yr	Medication	PAP (mean) mmHg	CI l/min/m^2	PVR dyn s cm^{-5}	RAP mmHg	SvO2 %	VO_2peak ml/kg/min	FC
11/98	0	80/38 (53)	1.37	1707	10	56	9.3	III
	after inhal of ilo	79/33 (48)	1.55	1383	8	62		
07/99	0	94/47 (64)	1.12	2663	14	43	6.6	IV
	PGI_2 (4 ng/kg/min)	94/49 (60)	1.36	2048	10	52		
09/00	IV ilo (6.5 ng/kg/min)	64/29 (44)	1.55	1374	1	61	12.4	III
08/03	IV ilo (8.0 ng/kg/min)	92/25 (56)	2.17	1015	0	69	18.4	II
02/04	bos + IV ilo (8.5 ng/kg/min)	64/22 (38)	2.79	608	0	75	24.9	II
	bos + no IV ilo	78/25 (44)	2.10	945	0	69		
02/05	after nocturnal treatment on-hold of bos + inhal of ilo	59/23 (36)	2.10	706	6	66	24.7	II

PAP pulmonary artery pressure; *CI* cardiac index; *PVR* pulmonary vascular pressure; *RAP* right atrial pressure; *SvO_2* mixed venous oxygen saturation; *VO_2peak* peak oxygen uptake during exercise testing with a cycle ergometer; *FC* World Health Organisation functional class; *mo* months; *yr* years; *inhal* inhalation; *ilo* iloprost; *PGI_2* epoprostenol; *bos* bosentan.

Table 2. Patient 2 Initial and follow-up hemodynamics, 6-minute walk distance and functional class

Date mo/yr	Medication mmHg	PAP (mean)	CI l/min/m^2	PVR dyn s cm^{-5}	RAP mmHg	SvO2 %	6 MWD m	FC
01/01	0 after inhal. of ilo.	73/35 (48) 65/28 (40)	1.5 2.4	1264 635	12 9	54 65	210	III
05/01	before 1. morning dose of inhal ilo	85/45 (58)	1.2	1920	19	45	145	IV
11/01	IV ilo (1.5 ng/kg/min)	65/32 (43)	1.7	1159	7	53	210	III
05/03	IV ilo (2.5 ng/kg/min)	74/31 (45)	1.9	1067	7	54	220	III
02/05	14 mo after switch from IV ilo + bos to bos + inhal ilo + sildenafil (after nocturnal treatment on-hold)	84/28 (49)	1.7	1200	8	54	240	III

PAP pulmonary artery pressure; *CI* cardiac index; *PVR* pulmonary vascular pressure; *RAP* right atrial pressure; *SvO_2* mixed venous oxygen saturation; *6 MWD* 6-minute walk distance; *FC* World Health Organisation functional class; *mo* months; *yr* years; *inhal* inhalation; *ilo* iloprost; *PGI_2* epoprostenol; *bos* bosentan.

following years, in accordance with her clinical status. With this approach, exercise and hemodynamic parameters stabilized (a minimal cardiac index (CI) of 1.6 l/min/m^2 was recorded). Because of three severe recurrent catheter-line infections, finally leading to a breast abscess in January 2004, removal of the Hickman catheter and surgical drainage of the abscess became necessary. Iloprost (8.5 ng/kg/min) was temporarily administered via a peripheral vein and oral bosentan was added at 62.5 mg twice a day (Tracleer®, Actelion, Alschwill, Switzerland). Four weeks later (February 2004) the bosentan dose was increased to 125 mg twice a day and right-heart catheterization was performed, which revealed only moderate pulmonary hypertension with a mean PAP of 38 mmHg and a CI of 2.8 l/min/m^2 (see Table 1). In this situation the dose of IV iloprost was gradually decreased over eight hours and then terminated, resulting in a decrease of CI to 2.1 l/min/m^2 and a slight increase of mean PAP to 44 mmHg. After terminating IV therapy with iloprost, oral treatment with bosentan (125 mg twice daily) was continued and combined with aerosolized iloprost six times daily. At that time iloprost (Ventavis®) had been approved in Europe for inhalation in patients with IPAH in WHO functional class III. Six ampoules of Ventavis® (20 µg each) per day were administered by ultrasonic nebulizer (Venta-Neb®, Nebu Tech, Elsenfeld, Germany), corresponding to an inhaled dose of 5 µg per inhalation. One year later (February 2005), follow-up right-heart catheterization (more than 8 hours following the last iloprost inhalation and prior to the morning dose of bosentan) revealed a slightly decreased CI and increased pulmonary vascular pressure (PVR) at rest, when compared with the values found one year earlier with IV iloprost. The WHO functional class and peakVO_2 remained unchanged after switching therapy from IV iloprost (plus bosentan for four weeks) to inhaled iloprost plus bosentan.

Patient 2 is a 55-year-old woman who was diagnosed with IPAH in January 2001 after presenting with a history of two syncopes and progressive exertional dyspnea for one year. She was in WHO functional class III with a six-minute walk distance (6 MWD) of 210 m. Right-heart catheterization revealed a mean PAP of 48 mm Hg, a right atrial pressure (RAP) of 12 mm Hg, a PVR of 1264 dyn s cm^{-5} and a CI of 1.5 l/min/m^2 (see Table 2). After inhalation of nebulized iloprost (17 µg), mean PAP decreased to 40 mmHg and PVR to 635 dyn s cm^{-5}, while CI increased to 2.4 l/min/m^2 (see Table 2). Anticoagulation treatment and inhalation of iloprost was initiated, as described above. Four months later (May 2001) the patient was admitted with clinical and hemodynamic signs of right-heart failure (see Table 2). Continuous IV iloprost therapy was started while inhaled iloprost was tapered and discontinued within three days. The IV iloprost dose at discharge was 1.5 ng/kg/min. In August and November of 2001, the patient was seen in our outpatient clinic without clinical signs of right-heart failure. She was in WHO functional class III, her 6 MWD were 230 m and 210 m, respectively, and cardiopulmonary exercise testing revealed a peakVO_2 of 12.0 ml/kg/min. Thereafter, the dose of iloprost was increased to 1.9 ng/kg/min, and to 2.5 ng/kg/min six months later. In summer 2003, the patient was listed for double-lung transplantation and oral bosentan was added because she remained in WHO functional class III with a 6 MWD of about 200–220 m. Before adding bosentan, right-heart catheterization (May 2003) showed a CI of 1.9 l/min/m^2, a RAP of 7 mm Hg, a mean PAP of 45 mm Hg, and a PVR of 1067 dyn s cm^{-5}.

Between March and November 2003, three severe episodes of central-line-related infections occurred, necessitating repeated placements of new catheters. In December 2003 dislocation of the central line with subcutaneous perivascular fluid accumulation was diagnosed and the central line was finally removed. Iloprost was temporarily administered through a peripheral vein. At this time, the patient was in WHO functional status class III with a 6 MWD of 270 m and a peakVO_2 of 14.8 ml/kg/min. Inhalation of iloprost was re-initiated and IV iloprost was slowly reduced over the next five days in a stepwise fashion (0.5 ng/kg/min per day) on a pulmonary ward without pulmonary catheter monitoring. In addition to the preexisting therapy of inhaled iloprost and oral bosentan, oral sildenafil (Viagra®, Pfizer, Kent, UK) was started at a dose of 50 mg three times a day. Right-heart catheterization (after nocturnal treatment withdrawal) 14 months after switching medication to this triple-therapy (February 2005) revealed a CI of 1.8 l/min/m^2, a RAP of 8 mm Hg, a mean PAP of 49 mmHg

and a PVR of 1200 dyn s cm^{-5}. At that time the patient was still in WHO functional class III with a 6 MWD of 240 m and a peakVO_2 of 14.3 ml/kg. She remained on the waiting list for lung transplantation.

Discussion

This is the first report describing two IPAH patients without functional deterioration following transition from long-term treatment with continuous IV iloprost to a combination of inhaled iloprost plus oral bosentan and to inhaled iloprost, bosentan plus sildenafil, respectively. The duration of iloprost therapy prior to the switch was 4.5 and 2.5 years, respectively. These two patients maintained an unchanged WHO functional status (classes II and III) for 12 and 14 months after withdrawal of IV iloprost therapy, respectively. Before and after transfer from IV iloprost to non-invasive combination treatment, peak VO_2 in patient 1 and peak VO_2 and 6 MWD in patient 2 remained almost unchanged.

Humbert et al. demonstrated a trend towards improved hemodynamics and clinical parameters following the addition of oral bosentan to IV epoprostenol [12]. Similarly, in our first patient CI reached a maximum with the highest dose of IV iloprost four weeks after adding bosentan (Table 1, February 2004). The second patient increased her 6 MWD from 220 m (May 2003) to 270 m (December 2003) following the addition of oral bosentan (June 2003) to a constant dose of IV iloprost.

Hemodynamic studies were performed not earlier than three weeks following catheter removal, in order to avoid any interference with infection-related changes.

Patient 1 performed cardiopulmonary exercise testing using a cycle ergometer instead of six-minute walks. In this patient, CI fell by about 30% after stopping long-term therapy with IV iloprost, an effect that lasted for the next 12 months. This persistent decrease in CI was accompanied by an increase in pulmonary capillary wedge pressure of about 5 mmHg and right atrial pressure of 6 mmHg. Consequently, calculated pulmonary vascular resistance only rose by approximately 100 dyn s cm^{-5} from 608 to 706 dyn s cm^{-5} between February 2004 and February 2005. Despite this decreased CI at rest, patient 1 was in WHO functional class II. During exercise testing she was able to reach about 75% of her predicted peakVO_2 values (Table 1). Likewise, peak systolic blood pressure during exercise was well preserved at 160 mmHg. In the publication of Wensel et al. peak oxygen uptake (≤ 10.4ml/kg/min) and peak systolic arterial blood pressure (≤ 120 mmHg), but not hemodynamic parameters at rest, were independent predictors of survival in IPAH patients [13].

Patients with IPAH remaining in WHO functional classes III or IV despite therapy with epoprostenol have a worse survival than patients who improve to WHO functional classes I or II [14, 15]. For this reason our second patient remained listed for lung transplantation.

Epoprostenol has been successfully used in patients with IPAH and other forms of PAH [15, 16]. The evidence for the efficacy of epoprostenol is much stronger than that for IV iloprost, although few studies have compared these substances [6, 11, 17]. However, according to these limited data, clinical efficacy of iloprost seems to be comparable to that of epoprostenol in the treatment of IPAH. Iloprost has the advantage of having a longer half-life than epoprostenol, making iloprost potentially safer than epoprostenol in the case of accidental interruption of the infusion [18]. Furthermore, the saline solution of iloprost is reasonably stable at room temperature for five days and can be refrigerated for 33 days, avoiding the need to cool the infusion pump [19]. In addition, iloprost is less expensive than epoprostenol in Germany [19]. However, in Germany neither IV iloprost nor IV epoprostenol is approved for the therapy of IPAH. We preferred IV iloprost because of its longer half-life, easier handling and lower costs.

Initially, therapy was started with inhaled iloprost in both patients. This therapy was chosen because of the reported improvements of symptoms and exercise capacity in patients with IPAH and WHO functional class III and in some patients with life-threatening pulmonary hypertension and progressive right-heart failure [20, 21]. Secondly, we tried to avoid the considerable risks of IV therapy, including hypertensive crisis following interruption of therapy and catheter infection. Successful switch from inhaled iloprost to oral bosentan has been previously described in a stable patient with portopulmonary hypertension and WHO functional class II [22]. In our patients a switch from inhaled to IV iloprost became necessary because of clinical deterioration. Recompensation could be achieved with IV iloprost administration. In the study of Hoeper et al., only 50% of patients with IPAH showed a benefit after switching therapy from inhalation to IV administration of iloprost [23].

Successful withdrawal of long-term epoprostenol therapy for pulmonary arterial hypertension has recently been described in three patients with IPAH who had a mean PAP of < 25 mmHg and a CI of ≥ 2.5 l/min/m^2 while on epoprostenol [24]. The three patients were switched to nifedipin, to bosentan plus diltiazem plus sildeanfil, or to bosentan plus nifedipin, respectively, while down-titration of epoprostenol was performed. In contrast to the normalized PAP in those patients, our patients presented with significantly elevated pressures in the pulmonary arteries at the time of switch to oral and inhaled therapy. Furthermore, as acute vasoreactivity to inhaled iloprost could not be demonstrated in our patients, calcium channel blockers were not considered as alternative therapeutic options.

In another report, mono-therapy with aerosolized iloprost failed to replace long-term IV epoprostenol administration in three patients with severe pulmonary hypertension who were classified as WHO class II while on treatment with continuous epoprostenol infusion (10–16 ng/kg/min) [25]. Two of these patients had IPAH and one of them showed a positive response to inhaled iloprost (mean PAP decreased from 87 to 44 mmHg, PVR from 1717 to 486 dyn s sec^{-5} and cardiac output increased from 3.7 to 6.3 l/min). Comparable acute hemodynamic effects of inhaled iloprost were demonstrated in the second patient with IPAH. Nevertheless, because of acute right-heart failure, weaning from long-term treatment with IV epoprostenol could not be completed successfully in either patient, even with repeated inhalations of aerosolized iloprost. The short duration of the hemodynamic effect of inhaled iloprost was assumed to be responsible for the

weaning failure. Therefore, mono-therapy with aerosolized iloprost was not considered as an alternative therapeutic strategy to IV epoprostenol by these authors.

In another report, 9 out of 23 stable adult patients with PAH in WHO functional classes II or III who were receiving long-term epoprostenol were successfully switched to oral bosentan [26]. Most of these patients were females (19 of 23 patients), and IPAH was the predominant diagnosis (12 of 23 patients). The group who failed transition to oral bosentan had a higher proportion of male patients, a higher PAP and showed a trend towards a longer duration and higher doses of pre-existing epoprostenol therapy. Two patients with excellent functional capacity subsequently had to stop bosentan because of liver function abnormalities. No liver function abnormalities due to bosentan were seen in our patients. Overall, only 40% of the stable adult patients with PAH described in that paper underwent successful transition from IV epoprostenol therapy to mono-therapy with bosentan.

In seven out of eight IPAH children treated with IV epoprostenol for more than a year, concomitant use of bosentan allowed for a reduction of epoprostenol dose without deterioration of clinical and hemodynamic parameters. In three children with normal or near-normal pulmonary artery pressures on epoprostenol, the addition of bosentan allowed discontinuation of epoprostenol and stabilization of hemodynamics for up to a year [27].

Hoeper et al. demonstrated that combinations of bosentan, sildenafil and inhaled iloprost in conjunction with a goal-oriented treatment strategy provide acceptable long-term results in patients with severe pulmonary arterial hypertension. This approach even reduced the need for IV prostaglandin treatment and lung transplantation. They also reported on two patients whose treatment was changed from IV iloprost to a combination of bosentan and sildenafil and who remained stable throughout the observation period. One patient was in WHO functional class III with 6 MWD remaining between 350 m and 400 m before and after transfer from IV iloprost to bosentan/sildenafil (follow-up 24 months after switching). The other patient was in WHO functional class I–II with 6 MWD > 500 m prior to transfer to bosentan/sildenafil treatment and the clinical situation remained excellent and unchanged throughout the observation period of 13 months [28].

Analyses of cost effectiveness for various therapies are of increasing importance for health professionals. Therapy of PAH is very expensive. The daily cost of IV iloprost treatment in our first patient ranged between € 1235 and € 1417 in 2003. The daily cost of two bosentan tablets was € 115 and for six ampoules of iloprost (each 20 µg, Ventavis®) was € 198 in 2004. Thus, the expenses were much lower with non-invasive combination therapy than with IV iloprost. Whether stable patients with residual pulmonary hypertension despite IV prostanoid treatment can be safely and effectively switched to an alternative non-invasive combination therapy should be tested in clinical trials.

Conclusion

This report documents that two patients with IPAH were safely weaned from long-term IV iloprost therapy to a combination of inhaled iloprost and oral bosentan or to inhaled iloprost, bosentan and sildenafil, respectively.

Conflict of interest

M. Halank, C. Opitz, G. Hoeffken and R. Ewert received speaker‘s honoraria from Actelion (Allschwill, Switzerland), the manufacturer of bosentan, and from Schering (Berlin, Germany), the manufacturer of iloprost. The present manuscript was not funded by Actelion, Schering or any other third party.

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