



Metered dose inhaler delivery of treprostinil for the treatment of pulmonary hypertension

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ABSTRACT

Background: The stable prostanoid analogue treprostinil is approved as continuous infusion for treatment of pulmonary arterial hypertension. Unique drug characteristics may render this prostanoid feasible for inhalation therapy with a metered dose inhaler.

Methods and results: Randomised open label investigation of acute haemodynamic effects, safety and tolerability of inhaled treprostinil delivered in seconds by a metered dose inhaler (MDI-TRE). Inhaled nitric oxide (NO) and MDI-TRE were applied once during right heart catheter investigation to 39 consecutive patients with pre-capillary pulmonary hypertension. Doses of 30 µg, 45 µg and 60 µg MDI-TRE were investigated in separate groups of patients. Haemodynamics and blood gases were measured for 2 h following treprostinil application. Acute haemodynamic responses to NO and MDI-TRE were comparable. MDI-TRE significantly improved haemodynamics compared to placebo inhalation. MDI-TRE induced effects were comparable to a historical control group that inhaled treprostinil from an ultrasonic nebuliser. The 120 min area under the curve for PVR changes due to placebo, 30 µg, 45 µg or 60 µg MDI-TRE was 1114 ± 998 , -870 ± 940 , -2450 ± 2070 and -2000 ± 900 min%. Reduction of systemic vascular resistance and pressure were not clinically relevant. No significant side effects were observed. No impact on ventilation/perfusion matching by treprostinil was demonstrated in 5 patients with pre-existing gas exchange limitations by use of the multiple inert gas elimination technique.

Conclusions: The application of inhaled treprostinil with a metered dose inhaler is feasible and well tolerated. It induced a sustained pulmonary selective vasodilatation.

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1. Introduction

Pulmonary arterial hypertension may be treated with prostacyclin or its stable analogues iloprost and treprostinil [1–4]. Prostacyclin, due to its short half life, may only be administered as continuous intravenous infusion. Iloprost treatment provided clinical efficacy by intravenous [3] and inhaled application [5]. Treprostinil has a significantly extended half life [6]. It is approved for i.v. as well as s.c. infusion, the latter avoiding septic events associated with indwelling intravenous catheters. The subcutaneous application however often leads to infusion site pain. We therefore sought for an alternative application route for treprostinil

and already demonstrated that the inhalation of treprostinil is safe, well tolerated and evokes acute pulmonary selective vasodilatation without relevant systemic side effects [7]. Continuous treatment with inhaled treprostinil administered four times daily was noted to be effective and without relevant side effects in small open label non-randomized trials [8,9]. A clinical phase IIb trial investigating inhaled treprostinil adjunct to sildenafil or bosentan treatment in PAH has just been completed.

In preceding studies we found that quite high doses of inhaled treprostinil could be safely deposited in the lung in as little as a single breath [8]. This suggested for the first time the possibility to deliver a potent vasodilator for pulmonary hypertension treatment with a metered dose inhaler.

In this open label study of acute vasodilator challenge during right heart catheter investigation we addressed the safety, tolerability and pulmonary vasodilator potency of inhaled treprostinil

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applied in seconds by a metered dose inhaler (MDI-TRE) and compared it to inhaled nitric oxide, which is the standard medication to test pulmonary vasoreaction. We provide evidence for a long lasting acute effect of MDI-TRE on pulmonary haemodynamics in the absence of systemic side effects and gas exchange deteriorations.

2. Methods and patients

The protocol was approved by the institutional review board of the University of Giessen. Written informed consent was obtained before enrolment.

A total number of 39 consecutive patients with moderate to severe pre-capillary pulmonary hypertension were enrolled in an open label, placebo controlled trial. Randomisation to the treatment groups that received either 30 µg, 45 µg or 60 µg treprostinil, which were completed one after the other, relied on the random schedule of patients for routine diagnostic right heart catheter procedures. Patient characteristics were: f/m = 25/14, age 59 ± 2.3 years, mean pulmonary artery pressure (PAP) 45 ± 1.8 mmHg, pulmonary vascular resistance (PVR) 734 ± 52 dynes $\cdot$ s $\cdot$ cm $^{-5}$, pulmonary capillary wedge pressure (PCWP) 8.6 ± 0.5 mmHg, central venous pressure (CVP) 6.4 ± 0.7 mmHg, cardiac output (CO) 4.5 ± 0.2 l/min, central venous oxygen saturation (SvO $_2$) 62.3 ± 1.2 mmHg (mean $\pm$ SEM). Disease aetiologies were idiopathic pulmonary arterial hypertension (iPAH; $n = 13$), PAH of other causes ($n = 10$) and non-operable chronic thromboembolic pulmonary hypertension (CTEPH; $n = 16$). The patient characteristics of the separate groups are shown in Table 1.

Baseline values were determined 20 min after placement of the catheter (7F Swan Ganz Catheter, Edwards Life Sciences, Irwin, CA, USA). Heart rate, pulmonary and systemic blood pressures and cardiac output were measured and blood gases were taken during each pharmacological intervention at defined time points. Cardiac output (CO) was measured with the thermodilution method by bolus-injection of 10 ml cooled sterile saline solution. At least three CO measurements were done at each time point and averaged. Following initial baseline recordings, we applied 20 ppm inhaled nitric oxide (NO) for a duration of 5 min to every patient previous to the treprostinil inhalation as a comparative agent. After NO was stopped and PAP and CI had returned back to baseline, patients of the three separate dose groups received a single dose of either 30 µg ($n = 12$), 45 µg ($n = 9$) or 60 µg ($n = 20$) metered dose inhaler-treprostinil sodium (MDI-TRE). Dose escalations in single patients were not performed, each patient received only a single dose and the effect was recorded for 120 min. Treprostinil was applied with the Respimat[®] metered dose inhaler (Boehringer, Ingelheim, Germany). Physical aerosol characteristics of the MDI devices were controlled by laser diffractometry as previously reported [10]. The mass median aerodynamic diameter (MMAD) of treprostinil-aerosol was 4–5 µm, which was suitable for alveolar deposition. Treprostinil-aerosol volume delivered by one puff from the MDI was 15 µl. The MDI was either filled with a concentration of

1000 µg/ml treprostinil sodium (15 µg TRE per puff) or with 2000 µg/ml (30 µg TRE per puff). The different doses in this study were applied as 2 puffs of 1000 µg/ml (30 µg), 3 puffs of 1000 µg/ml (45 µg) or 2 puffs of 2000 µg/ml (60 µg). Haemodynamics and gas exchange parameters were recorded for 120 min after MDI-TRE inhalation. The Respimat[®] device was chosen for this study because the implemented “soft mist” technology seemed to be well suited for the peripheral lung deposition of highly active drugs like prostanoids as it generates a rather slow stream of aerosol instead of a sharp pulse that may result in higher oral and pharyngeal deposition.

The impact of MDI-TRE on ventilation–perfusion matching was measured in five patients (30 µg TRE, $n = 2$; 45 µg TRE, $n = 1$; 60 µg TRE, $n = 2$) with pre-existing gas exchange limitations by use of the multiple inert gas elimination technique (MIGET) as it was previously described [11,12].

3. Statistical analysis

Mean values, standard deviation, standard error of the mean or 95% confidence intervals were calculated. Statistical analysis of areas under the curve was done by use of a paired *t* test. For analysis of repeated measurements over time comparing placebo and MDI-TRE or MDI-TRE and ultrasonic nebulisation one way ANOVA for repeated measurements with Bonferroni post test was performed. Statistical analysis was done with the Graph Pad Prism 5 software.

4. Results

4.1. Safety and tolerability

The inhalation of treprostinil sodium from a metered dose inhaler was well tolerated, only mild and transient cough for a maximum of 1 min was reported by some patients. No systemic side effects like headache, flush, nausea or dizziness were observed.

4.2. Acute haemodynamic changes due to MDI-TRE

Doses of 30 µg, 45 µg and 60 µg MDI-TRE reduced PVR from 575 ± 104 dynes to 494 ± 109 dynes, from 964 ± 184 dynes to 720 ± 229 dynes and from 667 ± 149 dynes to 530 ± 132 dynes, respectively (mean $\pm$ 95% confidence interval). Mean pulmonary artery pressure was reduced by 30 µg, 45 µg or 60 µg MDI-TRE from 40.1 ± 4.9 mmHg to 33.3 ± 4.4 mmHg, from 50.4 ± 6.2 mmHg to 38.1 ± 8.4 mmHg and from 39 ± 4.8 mmHg to 32.2 ± 4.9 mmHg, respectively. Pulmonary vasodilatation surpassed the observation time of 120 min in the 45 µg and 60 µg groups. The lower dose of 30 µg TRE induced a somewhat shorter effect on pulmonary vascular resistance; however, the maximal drop in PVR was comparable, arguing for a prolonged effect of higher dose depositions. In contrast, placebo inhalation did not induce pulmonary vasodilatation but lead to a slight increase in PVR over the time of the right heart catheter investigation (Fig. 1). Because the

Table 1

Patient characteristics of the investigated groups. Treprostinil was administered by a metered dose inhaler device (MDI-TRE) or in a historical group by an ultrasonic device (US-TRE). PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; SaO $_2$ = arterial oxygen saturation; SvO $_2$ = central venous oxygen saturation. Data are mean $\pm$ standard error of the mean.

	Placebo ($n = 4$)	MDI-TRE 30 µg ($n = 11$)	MDI-TRE 45 µg ($n = 8$)	MDI-TRE 60 µg ($n = 20$)	US-TRE 32 µg ($n = 6$)	US-TRE 48 µg ($n = 6$)	US-TRE 64 µg ($n = 3$)
Age [years]	61 ± 8	54 ± 4.2	54 ± 6.5	65.5 ± 3.1	56.8 ± 3.7	51.2 ± 2.4	57.3 ± 9.1
PAP [mmHg]	49.5 ± 10.1	46.5 ± 3.0	53 ± 3.0	39.7 ± 2.0	44.2 ± 2.2	55.5 ± 3.1	45.3 ± 5.2
PVR [dynes]	896 ± 163	608 ± 57.7	1029 ± 119	663 ± 81	856 ± 78	939 ± 69	769 ± 267
CO [l/min]	4.46 ± 0.9	5.3 ± 0.5	4.0 ± 0.4	4.4 ± 0.3	3.8 ± 0.2	3.9 ± 0.2	4.5 ± 1.1
SAP [mmHg]	98 ± 8.1	88.5 ± 3.1	80.5 ± 3.6	86.1 ± 2.0	96.3 ± 2.5	91.2 ± 5.1	99 ± 3.2
SaO $_2$ [%]	85.3 ± 4.5	90.0 ± 1.2	89.5 ± 1.2	90.6 ± 0.5	92.8 ± 1	92 ± 1.2	94.2 ± 1.3
SvO $_2$ [%]	57.5 ± 3.9	65.5 ± 1.7	59.0 ± 3.8	62.5 ± 1.6	63.6 ± 1.1	62 ± 3.6	66.3 ± 1.5

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