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Subcutaneous to Intravenous Prostacyclin Analogue Transition in Pulmonary Hypertension

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Abstract

Introduction—Prostacyclin analogues are FDA-approved therapies for the treatment of Pulmonary Arterial Hypertension (PAH) and can be administered by inhalational, intravenous (IV) or subcutaneous (SQ) routes. Since there is limited data to guide the transition between SQ to IV prostacyclin analogues we describe our experience.

Methods—We performed a retrospective review of PH patients diagnosed by right heart catheterization who underwent transition from SQ to IV prostacyclin analogues.

Results—We included 7 patients with PAH and 2 with chronic thromboembolic pulmonary hypertension in this retrospective study. Median (IQR: interquartile range) age was 54 (39–63) years and 67 % were women. Reasons for the SQ to IV switch were site pain (n=6, 67%), major surgery (n=2, 22%) and septic shock (n=1, 11%). SQ treprostinil was converted to IV treprostinil (n=5, 56%) or IV epoprostenol (n=4, 44%). When SQ treprostinil was converted to IV treprostinil, the initial mean (range) dose decreased from 84.9 36.5–167) to 70.8 (24–114) ng/kg/min. When SQ treprostinil was converted to IV epoprostenol, the dose decreased from 24.5 (17.5–30) to 13.3 (9–20) ng/kg/min. The patient transitioned from SQ to IV treprostinil in the context of septic shock died a month after the hospitalization. No deteriorations were observed in the remaining patients during the first year.

Conclusion—Under careful monitoring, SQ treprostinil was transitioned to IV treprostinil or epoprostenol without complications. Dosing down-adjustment was needed in some patients switched from SQ to IV prostacyclin analogues.

Keywords

Treprostinil; Epoprostenol; Subcutaneous; Intravenous; Pulmonary Hypertension

Introduction

Pulmonary arterial hypertension (PAH) is a condition characterized by an increase in the mean pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) that

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might result in right heart failure and death[1,2]. For patients with severe forms of PAH, continuous parenteral administration of prostacyclin-analogues remain the treatment of choice[3]. Current FDA approved parenteral prostacyclin analogues therapies include epoprostenol and treprostinil.

Treprostinil is a prostacyclin analogue with a terminal half-life of 4.5 hours that can be delivered subcutaneously (SQ) or intravenously (IV), whereas epoprostenol has a half-life of < 6 minutes and can only be administered by the IV route[4–6]. Continuous subcutaneous treprostinil infusion received FDA approval for the treatment of PAH after demonstrating an increase in exercise capacity compared to placebo[7]. Long-term studies in PAH patients using SQ treprostinil also showed improvements in symptoms, exercise capacity and hemodynamics[8–10]. Furthermore, an open-label uncontrolled study suggested that treprostinil improves exercise capacity, hemodynamics as well as survival in subjects with severe inoperable chronic thromboembolic pulmonary hypertension (CTEPH)[11]. Overall, the main advantage of SQ treprostinil is that it obviates the need of central venous catheters that can be associated with line infections, thrombosis and paradoxical emboli[8].

Subcutaneous treprostinil might not be adequate in certain patients due to reasons such as pain and erythema at the site of SQ infusion[7,10–12], progression of the disease[10] and the need to have a more consistent route of delivery during prolonged surgeries[10,13] or shock states. To circumvent these limitations patients are on occasions transitioned from SQ treprostinil to IV treprostinil or epoprostenol; however there are no published investigations to guide these conversions. Thus, we retrospectively studied PAH and CTEPH patients who underwent transition from SQ to IV prostacyclin analogues. We particularly focused on the reason for the switch, titration strategy, medication dosage and adverse effects before and after the switch.

Methods

Between November 2000 and September 2012 a total of 45 pulmonary hypertension (PH) patients diagnosed by right heart catheterization were treated at Cleveland Clinic with SQ treprostinil for 104 patient-year. During this period, nine patients were switched from SQ to IV treprostinil or from SQ treprostinil to IV epoprostenol. We identified these patients using information prospectively collected in our Pulmonary Vascular Registry and upon reviewing the charts of PH patients treated with prostacyclin analogue therapy. The study was approved by the Institutional Review Board at Cleveland Clinic (protocol approval number: 13–321). Informed consent was waived.

Patients were admitted to the medical intensive care unit and pulmonary hemodynamics were obtained before, during and after the transition. We carefully reviewed the medical records to identify the cause of PH, reason for changing the SQ route of administration, dose of SQ treprostinil and whether patients were taking other PAH-specific medications. We also recorded New York Heart Association (NYHA) functional class, prostacyclin analogues side effects, six-minute walk test results (total distance walked and percentage of predicted[14]), platelet count, echocardiographic and hemodynamic parameters, hospitalizations and survival status at baseline and for up to a year after the transition. In

addition, we documented the prostacyclin analogue dose during the first year after the transition and whether patients needed to start or increase other PAH-specific medications.

As no established protocols were available, different methods were used for transitioning SQ treprostinil to IV treprostinil or epoprostenol. Clinical symptoms and hemodynamics were used to guide the transition. Up-titration of IV treprostinil was stopped either when achieving the SQ dose or when patients developed adverse effects. Meanwhile, up-titration of IV epoprostenol was stopped at a predetermined level (usually lower than the SQ treprostinil dose) or when side effects developed.

Statistical analysis

Data are presented as number of patients (percentages) or median (IQR: interquartile range) when appropriate. McNemar and paired samples Wilcoxon tests were used for comparison of categorical and continuous paired data, respectively. All *p* values reported are two-tailed. A p value of < 0.05 was considered significant. The statistical analyses were performed using the statistical package IBM SPSS, version 20 (IBM; Armonk, New York).

Results

Baseline Characteristics

We included 9 patients with a median age of 54 (39–63) years. Six (67%) of them were women. PH etiologies were idiopathic PAH in 4 patients (44%), connective tissue associated PH in 2 (22%), portopulmonary hypertension in 1 (11%) and CTEPH in 2 (22%). Of the patients with CTEPH one had pulmonary thromboendarterectomy while receiving prostacyclin analogues and the other was not a candidate for surgery because of the distal thromboemboli location.

The median (IQR) NYHA functional class was 3 (2–3.5). Six (67%) patients were on other PH-specific medications at the time of transition (phosphodiestearase inhibitors: 6 (67%) and endothelin receptor antagonists: 3 (33%)). Platelets were 190,000 (98,000–267,000)/μL. Patients walked 326 (250–501) meters (53 (39–61) % of predicted[14]) during the six-minute walk test. Echocardiography obtained 25 (12–52) days before the transition revealed that right ventricular dysfunction was either moderate or severe in 7 patients (78%) with an estimated right ventricular systolic pressure of 87 (79–112) mm Hg. Patients were on SQ treprostinil for 367 (64–1442) days before the transition. During the six months before transition, the SQ dose of treprostinil was stable in six patients, while it was slowly uptitrated in the remaining three. Side effects of SQ treprostinil immediately before transition included flushing (n=4, 44%) diarrhea (n=4, 44%), jaw pain (n=3, 33%) and nausea (n=1, 11%).

Reason for the transition

Patients were transitioned due to pain at the site of administration (n=6, 67%), prolonged surgery (n=2, 22%) and septic shock (n=1, 11%). Five subjects were transitioned from SQ to IV treprostinil (all after 2006) due to pain at the site of delivery (n=2), need for prolonged

surgery (n=2) and septic shock (n=1). Four individuals were switched from SQ to IV treprostinil (all before 2006) due to pain at the site of administration.

Titration protocol

Subcutaneous treprostinil was converted to IV treprostinil (n=5, 56%) or IV epoprostenol (n=4, 44%). A variety of protocols were used as shown in table 1 and 2. The median (IQR) duration of the transition process was 42 (23–56) hours. There were no failed attempts in switching to intravenous prostacyclin.

When patients were transitioned from SQ to IV treprostinil, the mean (range) dose decreased from 84.9 (36.5–167) to 70.8 (range: 24–114) ng/kg/min. Meanwhile, when patients were switched to IV epoprostenol the mean (range) prostacyclin analogue dose decreased from 24.5 (17.5–30) to 13.3 (9–20) ng/kg/min.

Follow-up after transition

NYHA functional class, platelets, right ventricular function and estimates of right ventricular systolic pressure by echocardiography were similar (n=6 as one patient died and the other two were converted back to the SQ route, table 3). During the first year after conversion, two hospitalizations were documented due to Hickman line infection. No other PH-specific medications were added during this time period. After the transition, uptitration of IV epoprostenol continued in all four patients over the course of a year (9 to 14 ng/kg/min, 13 to 14 ng/kg/min, 20 to 24 ng/kg/min and 11 to 26 ng/kg/min).

The patient that was converted from SQ to IV treprostinil due to septic shock died 29 days after the discharge to a tertiary care hospital closer to her home. We consider that her death was not related to the change in the route of administration of treprostinil, but to her advanced refractory PH and the fact that she was not a candidate for transplantation due to neuromuscular weakness related to critical illness. One patient was weaned off of treprostinil six days after undergoing surgery for CTEPH. Another patient was transitioned back to SQ treprostinil a day after her total mastectomy. The conversion back to SQ treprostinil was performed by simply discontinuing the IV and starting SQ treprostinil. Up-titration of IV treprostinil continued in the other 2 patients. In fact, over a course of a year, the IV treprostinil dose increased from 24 to 63 ng/kg/min in one patient and from 114 to 153 ng/kg/min in the other.

Discussion

The data presented show that transition from SQ treprostinil to IV treprostinil or epoprostenol can be done safely under careful supervision, independently of the protocol used. We did not observe any significant variation in clinical, functional or echocardiographic measurements before and after the transition.

Subcutaneous treprostinil is completely absorbed with a 100% bioavailability[15]. The elimination half-life for healthy volunteers receiving a prolonged SQ infusion is between 2.9 to 4.6 hours[6,16]. In PAH patients that received a steady dose of SQ treprostinil there was a linear proportionality between dose and plasma concentration over a range of 10 to 125

ng/kg/min[17]. Despite its proven efficacy, SQ treprostinil may need to be converted to an IV prostacyclin analogue due to uncontrollable infusion site pain or the need to assure a stable systemic delivery in special conditions such as prolonged surgeries or shock, where there may be reduced local tissue perfusion.

Before the year 2006 and when indicated, SQ treprostinil was converted to IV epoprostenol. At that point in time, the change in the prostacyclin analogue was based on the limited data supporting the efficacy of treprostinil given IV. As expected, the dose of intravenous epoprostenol was lower than that of SQ treprostinil because of the protocol used and the fact that epoprostenol has a higher equimolar potency than treprostinil[18].

Previous investigations suggested that it is safe to switch IV epoprostenol to SQ treprostinil (switching ratio between 1:0.75 and 1:2) by slowly reducing epoprostenol while progressively increasing treprostinil[5,18–21]. Similarly, Sitbon et al. safely transitioned clinically stable PAH patients from IV epoprostenol to IV treprostinil by a direct switch (“rapid switch protocol”) in a 1:1 ratio. The investigators then adjusted the treprostinil dose in the outpatient setting over a 12-week period, achieving a two-fold increase compared to the baseline epoprostenol dose (individual dose range between 1.5 – 3 fold)[5]. More recently, Minai et al. rapidly switched PH patients from IV epoprosterenol to IV treprostinil by terminating the epoprostenol infusion and initiating treprostinil at a dose 20% higher. This initial dose of treprostinil was then uptitrated through an 8-week period based on clinical factors (8-week ratio 1:1.8)[19].

After the year 2006, patients were converted from SQ to IV treprostinil once data on safety and efficacy on IV treprostinil became available[4]. We found that the IV dose of treprostinil was to some degree lower than the SQ one, even when we tried to achieve the same dosage. This was because two patients had flushing and diarrhea when trying to achieve the expected IV dose; hence the final IV dose was decreased by 66 and 68% of the SQ dose, respectively. It is difficult to explain this reduction in treprostinil dosage. An open-label cross-over investigation in healthy volunteers using a relatively low dose of treprostinil (10 ng/kg/min) demonstrated that SQ and IV treprostinil were bioequivalent per steady-state pharmacokinetic analysis[6]. In patients with PAH, McLaughlin et al. compared the acute effects of 10 ng/kg/min of SQ and IV treprostinil and showed that both delivery routes produced similar short-term (75 minutes for the IV and 150 minutes for the SQ routes) decreases in PVR[12]. Using pharmacokinetic data, the authors found that the apparent biological half-life was longer for SQ than IV treprostinil (55–117 minutes versus 26 to 42 minutes)[12]. It is possible that although the two routes of administration are bioequivalent overall, there may be patients who do not exactly fall in the regression line, especially when receiving higher doses than the ones described in the pharmacokinetics studies. Furthermore, the longer apparent biological half-life of the SQ route could have temporarily increased the parenteral levels and explained a lower initial IV treprostinil dose. In fact, over a course of a year, the IV treprostinil dose increased in the two patients that continued treatment through this route.

Little information is known on how to transition patients from SQ to IV prostacyclin analogue formulations. Reisbig et al. successfully converted a patient from SQ treprostinil to

IV epoprostenol and proposed a staggered protocol for the transition with the goal of minimizing adverse effects[22]. The authors proposed a decrease in treprostinil of 5 ng/kg/min (this dose may vary), and a similar increase in epoprostenol every 4 hours while monitoring for signs / symptoms related to under-dosage or excessive pharmacologic effects. If these signs / symptoms manifest, then the dose of epoprostenol is increased or decreased by 2 ng/kg/min, respectively. While this algorithm has a sound pharmacokinetic base since it reflects the markedly different half-life of these two prostacyclin analogs, it was tested in one patient and more importantly it lasted approximately 60 hours[22].

This study has limitations including a) retrospective and single-center investigation, and b) lack of a standard protocol to convert patients from SQ to IV prostacyclin analogues; however this factor is also a strength, since it allowed to evaluate different protocols and show no appreciable benefit of any of them. Despite these limitations our data showed that transition from SQ to IV prostacyclin analogues can be done safely under adequate supervision independently of the protocol used.

Conclusion

Under close monitoring, the transition from SQ treprostinil to IV treprostinil or IV epoprostenol can be done safely and without any significant adverse effect to the patient. The protocol used for titration had no impact in the transition outcome. The dose of IV prostacyclin analogues may initially be lower, especially when converting SQ treprostinil to IV epoprostenol.

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Abbreviations

CTEPH	chronic thromboembolic pulmonary hypertension
IV	intravenous
PAH	pulmonary arterial hypertension
PH	pulmonary hypertension
PVR	pulmonary vascular resistance
RV	right ventricle
RVSP	right ventricular systolic pressure
SQ	subcutaneous

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Table 1

Transition from SQ to IV treprostinil:

Patient number	**1**		**2**		**3**		**4**		**5**	
Route of administration	**SQ**	**IV**	**SQ**	**IV**	**SQ**	**IV**	**SQ**	**IV**	**SQ**	**IV**
Initial Dose (ng/kg/min)	36.5	-	73	-	87	-	167	-	61	-
Dose at Discharge (ng/kg/min)	-	24	-	73	-	87	-	114	-	56
Titration protocol	SQ dose was decreased and IV increased by 1/3 the SQ dose.		SQ dose was decreased and IV increased 1 hour later by 1/2 the SQ dose		SQ dose was decreased and IV increased 1 hour later by 1/2 the SQ dose		SQ dose was decreased and IV increased by 1/4 the SQ dose		SQ dose was discontinued and IV dose initiated	
Number of intervals	3		2		2		4		1	
Time between the interval (hours) [*]	3–4		2		1–2		2		-	
Time for fine titration after the initial switch (hours) [#]	37.5		7		42		19		-	
Total duration of titration (hours) [¶]	44.5		11		45		43.5		-	

[*] Approximate time between the intervals.

[#] Fine titration that occurred after the initial switch based on side effects and target dose.

[¶] May exceed the time between intervals and time for fine titration.

Table 2

Transition from SQ treprostinil to IV epoprostenol:

Patient number	**6**		**7**		**8**		**9**	
Route of administration	**SQ**	**IV**	**SQ**	**IV**	**SQ**	**IV**	**SQ**	**IV**
Initial Dose (ng/kg/min)	17.5	-	23	-	27.5	-	30	-
Dose at Discharge (ng/kg/min)	-	9	-	13	-	20	-	11
Titration protocol	IV dose was titrated up after stopping the SQ treprostinil.		IV dose was titrated up while the SQ dose was decreased.		IV dose was titrated up every 1–2 hr. SQ dose was down-titrated every 2–6 hr		IV dose was up-titrated every 1 hour. SQ treatment was discontinued when dose of epoprostenol reached 6 ng/kg/min	
Units of change per interval	Epoprostenol was increased by 1 ng/kg/min		Epoprostenol was increased by 1 ng/kg/min and treprostinil decreased by 2 ng/kg/min		Epoprostenol was increased by 1–2 ng/kg/min and treprostinil reduced by 2.5–10 ng/kg/min		Epoprostenol was increased by 2 ng/kg/min	
Number of intervals	7		13		8		4	
Time between the interval (hours) *	1		0.5–1.5		0.5–2		0.5–1.5	
Time for fine titration after the initial switch (hours) #	0		0		48		16	
Total duration of titration (hours) ¶	21.5		30		72		20	

*Approximate time between the intervals.

#Fine titration that occurred after the initial switch based on side effects and target dose.

¶May exceed the time between intervals and time for fine titration.

Table 3

Comparison of variables, before and after switching the route of administration of the prostacyclin analogue.

Variables	Before transition Median (IQR) or n (%)	After 1 year Median (IQR) or n (%)
n ¶	6	6
NYHA	3 (2.3–3.5)	2.5 (2–3)
Platelets (units/uL)	222,000 (135,000–286,000)	199 (101,000–301,000)
Six-minute walk distance (m)	373 (306–563)	486 (397–515)
RVSP (mmHg) *	89 (84–120)	92 (58–110)
RV dysfunction *		
-Normal / Mild	1 (17)	1 (17)
-Moderate / Severe	5 (83)	5 (83)

* by echocardiography.

¶ Data on six patients (one patient died and the other two were converted back to the SQ route).

Abbreviations: IQR: interquartile range, NYHA: New York Heart Association, RV: right ventricular, RVSP: right ventricular systolic pressure.