



Use of Continuous Infusion Epoprostenol in a Patient with Secondary Raynaud's Phenomenon

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Abstract

Purpose: To describe a unique prostacyclin dosing regimen utilized to treat a case of secondary Raynaud's phenomenon and summarize the existing literature on parenteral prostacyclin use for Raynaud's phenomenon in adult patients.

Summary: A 54-year-old female was admitted for initiation of continuous intravenous infusion epoprostenol to treat secondary Raynaud's phenomenon which failed to respond to nifedipine and sildenafil. The infusion was titrated to a target dose of 9 ng/kg/min for 5 days. Upon completion of treatment, improvements in the patient's pain, range of motion, and digital perfusion were observed. Sustained improvements were noted seven weeks later. Parenteral prostacyclins may therefore be considered for Raynaud's phenomenon which fails to respond to conventional therapies. Epoprostenol has previously been used to treat Raynaud's phenomenon mainly in the form of intermittent, intravenous infusions. There are logistical concerns associated with the use of a continuous infusion prostacyclin which should be addressed before this therapy is chosen.

Conclusion: This case highlights a successful outcome in a patient with secondary Raynaud's phenomenon treated with a 5-day continuous infusion of epoprostenol. It is reasonable to consider this treatment regimen in patients with secondary Raynaud's phenomenon in whom other treatments have failed.

Keywords: Secondary Raynaud's Phenomenon; Epoprostenol; Prostacyclin; Prostanoid; Prostaglandin.

Introduction

Raynaud's phenomenon is an exaggerated vascular response to cold temperature or emotional stress. This phenomenon is due to abnormal vasoconstriction of digital arteries and cutaneous arterioles due to a local defect in normal vascular responses. As a result, patients experience clearly defined color changes of the skin of the digits. Raynaud's phenomenon may also manifest as a complication of connective-tissue disease

such as scleroderma, which is referred to as secondary Raynaud's phenomenon [1]. First-line pharmacological therapy includes dihydropyridine calcium channel blockers such as nifedipine or amlodipine. Phosphodiesterase-5 inhibitors, endothelin receptor antagonists, and topical nitrates may also be included for patients intolerant of calcium channel blockers [2]. Parenteral prostanoid therapy is reserved for patients

with threatened or established digital ischemia who failed to respond to aforementioned therapy. This involves administration of a prostaglandin (preferably a prostacyclin analogue) such as iloprost, treprostinil, or epoprostenol. This case report focuses on parenteral prostanoid therapy utilized for secondary Raynaud's phenomenon refractory to conventional therapies.

Methods

PubMed searches were performed using the search terms Raynaud's phenomenon, prostacyclin, iloprost, treprostinil, and epoprostenol in the English literature. Patient data contained in this case report was extracted directly from the electronic health record.

Case Report

A 54-year-old Caucasian female with a past medical history significant for systemic sclerosis complicated by Raynaud's phenomenon, iron deficiency anemia, major depressive disorder, and osteoporosis was transferred from a general medicine floor to the medical intensive care unit for initiation of epoprostenol therapy to treat Raynaud's phenomenon, which was accompanied by pain and necrosis of her digits bilaterally. Prior to admission, the patient was treated with oral sildenafil and nifedipine but failed to improve clinically as evidenced by persistent pain in her digits from ongoing ischemia. On admission, the patient's physical exam was notable for necrosis of the second and fifth digits of her right hand, the third digit of her left hand, as well as the third digit of her left foot. The patient was also noted to have increasing dyspnea on exertion which was attributed to worsening anemia and treated with intravenous iron.

On day two of the patient's admission, an epoprostenol continuous infusion was initiated via a peripheral IV line at a dose of 1 nanogram per kilogram per min (ng/kg/min) [dosing weight=38.7 kilograms]. The dose of epoprostenol was to be increased by 1 ng/kg/min every 30 min until dose-limiting side effects occurred up to a maximum dose of 9 ng/kg/min for a minimum of five days. This dosing regimen was selected based on the findings of previous literature, in which epoprostenol doses up to 10 ng/kg/min have been administered to patients with Raynaud's phenomenon but appear to be unnecessary given that significant therapeutic benefits have been associated with lower doses of the drug (**Table 1**). Therefore, a lower target dose was chosen to decrease the potential for epoprostenol-related adverse effects.

The patient tolerated the epoprostenol infusion until a dose of 6 ng/kg/min was reached. At this point, she began to experience mild headache and jaw pain. Additionally, the patient was experiencing intermittent episodes of hypotension which prevented the scheduled titration of the medication. Resumption of the titration schedule occurred upon resolution of the adverse effects until a dose of 8 ng/kg/min was reached, at which the patient's headache became substantially worse, she developed new-onset emesis, and she once again became hypotensive (76/54 mm Hg). These side effects delayed achievement of the goal administration rate of 9 ng/kg/min by an additional 36.5 hs. Once reached, the epoprostenol infusion continued to run at 9 ng/kg/min for the remainder of the 5-day treatment course (**Figure 1**).

On the final day of epoprostenol therapy the patient reported decreased pain in her digits as well as increased range of motion. She had visual improvements in her digits which were noted to be pink, warm, and well-perfused. The patient was monitored for a total of 18 hs following completion of the infusion and subsequently discharged home from the medical intensive care unit. She followed up with her outpatient rheumatologist seven weeks after discharge who noted sustained improvements in the perfusion of the digits on her right hand and left foot.

Discussion

Prostacyclin is a form of prostaglandin which causes systemic vasodilation and prevents platelet aggregation via amplification of cyclic adenosine monophosphate (cAMP) levels in the vascular bed and platelets, respectively. Through interaction with G-protein coupled receptors, prostacyclin stimulates adenylate cyclase leading to increased cAMP production [3]. Given their potential therapeutic benefit, prostacyclins have been developed and utilized for the treatment of several vasoconstrictive disorders.

Parenteral prostacyclins have been used in the treatment of severe Raynaud's phenomenon which fails to respond to conventional forms of therapy. Iloprost has been the most commonly used prostacyclin (**Table 1**). However, iloprost is commercially available in the U.S. only as an inhalation which failed to improve the frequency or severity of attacks in a previous study [4]. Epoprostenol and treprostinil offer the benefit of parenteral administration and have been associated with clinical improvement in symptoms associated with Raynaud's phenomenon [5-10].

There is considerable variability in the parenteral prostacyclin regimens used in secondary Raynaud's phenomenon patients to date (Table 1). Despite these differences, IV prostacyclins are most commonly administered as a series of intermittent IV infusions for this indication. In this patient, epoprostenol was administered as a continuous IV infusion. Upon outpatient follow-up seven weeks later, much of the patient's clinical improvements were noted to have persisted. Sustained improvements associated with epoprostenol use in Raynaud's phenomenon have been reported previously [7]. Conversely, other studies have suggested that the benefits obtained from parenteral prostacyclins may diminish over time [9,11,12]. The sustainability of the benefits derived from epoprostenol therapy is therefore unclear and may serve as a potential area for future study. Overall, it may be reasonable to

consider repeating this course of epoprostenol in the future if the patient's symptoms recur.

The potential benefits of parenteral prostacyclin therapy should be weighed against its shortcomings. Administration of prostacyclins often requires treatment in an inpatient setting, potentially even an intensive care unit for close monitoring and appropriately trained nursing personnel. A continuous IV infusion poses additional concerns and will continually occupy a site of IV access. Furthermore, epoprostenol has a short half-life (6 min), meaning that even brief interruptions have the potential to compromise treatment. Formulations of epoprostenol also lack stability and need to be replaced every 24 h.

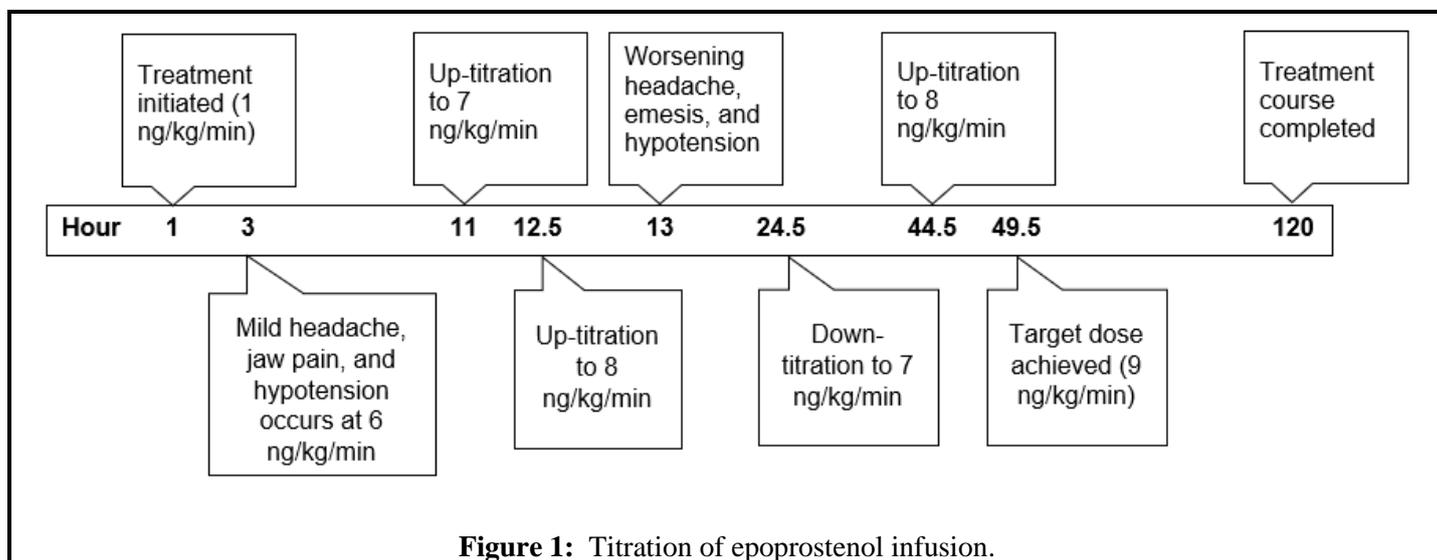


Figure 1: Titration of epoprostenol infusion.

Table 1: Use of parenteral prostacyclins for Raynaud's phenomenon in adult patients.

Reference	N	Prostacyclin	Target Dose	Duration of Infusion	Dosing Interval	Length of Therapy	Comparator	Endpoints
Belch JJ et al [5]	5	Epoprostenol	10 ng/kg/min	5 h	Weekly	3 weeks	N/A	Healing of ischemic ulcers; Hand temperature
Dowd PM et al [6]	25	Epoprostenol	10 ng/kg/min	Continuous	Continuous	3 days	N/A	Frequency of Raynaud attacks; Severity of Raynaud attacks; Change of temperature,

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								cold tolerance, and stiffness of hands
Belch JJ et al [7]	14	Epoprostenol	7.5 ng/kg/min	5 h	Weekly	3 weeks	Placebo	Frequency of Raynaud attacks ^a ; Duration of Raynaud attacks ^a ; Hand temperature ^a
Bellucci S et al [8]	8	Epoprostenol	7.5 ng/kg/min	5 h	Weekly	3 weeks	N/A	Capillary appearance; Capillary function; Prostacyclin metabolism
Kingma K et al [9]	12	Epoprostenol	8 ng/kg/min	5 h	Weekly	3 weeks	Placebo	Forearm blood flow ^a ; Forearm vascular resistance ^a ; Fingertip skin temperature ^a ; Laser Doppler-estimated finger skin blood flux ^a ; Transcutaneous oxygen tension ^a
Engel G et al [10]	1	Treprostinil	15 ng/kg/min	Continuous	Continuous	16 weeks	N/A	Healing of lesions
Fitscha P et al [11]	13	Epoprostenol	5 ng/kg/min	6 h	Daily	10 days	N/A	Frequency of Raynaud attacks; Severity of Raynaud attacks; Skin temperature
McHugh NJ et al [13]	29	Iloprost	2 ng/kg/min	6 h	Daily	3 days	Placebo	Frequency of Raynaud attacks ^a

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								Severity of Raynaud attacks ^a
Yardumian DA et al [14]	12	Iloprost	3 ng/kg/min	5 h	Daily	3 days	Placebo	Frequency of Raynaud attacks ^a ; Digital blood flow ^a
Rademaker M et al [15]	23	Iloprost	2 ng/kg/min	8 h	Daily	3 days	Nifedipine	Frequency of Raynaud attacks; Duration of Raynaud attacks; Severity of Raynaud attacks; Number of digital lesions ^a ; Digital blood flow ^a
Torley HI et al [16]	55	Iloprost	2 ng/kg/min	6 h	Daily	3 days	Low-dose iloprost (0.5 ng/kg/min)	Frequency of Raynaud attacks; Duration of Raynaud attacks; Severity of Raynaud attacks; Healing of ulcers
Wigley FM et al [17]	35	Iloprost	2 ng/kg/min	6 h	Daily	5 days	Placebo	Frequency of Raynaud attacks; Duration of Raynaud attacks; Severity of Raynaud attacks; Healing of cutaneous lesions ^a
Wigley FM et al [18]	131	Iloprost	2 ng/kg/min	6 h	Daily	5 days	Placebo	Frequency of Raynaud attacks ^a ; Raynaud severity score ^a ; Physician assessment

								of Raynaud severity ^a
Zachariae H et al [19]	12	Iloprost	2 ng/kg/min	6 h	Daily	8-13 days	N/A	Treatment of imminent gangrene; Healing of ischemic ulcers
Scorza R et al [20]	46	Iloprost	2 ng/kg/min	8 h	Daily	5 days	Nifedipine	Modified Rodnan skin score ^a ; Raynaud Phenomenon severity score ^a
Milio G et al [21]	60	Iloprost	2 ng/kg/min	6 h	Daily	10 days	Variably-dosed iloprost	Frequency of Raynaud attacks ^a ; Duration of Raynaud attacks ^a

^aStatistically significant difference favouring prostacyclin therapy

Conclusion

Epoprostenol is a systemic vasodilator and inhibits the aggregation of platelets in the vasculature. This case demonstrates a successful outcome in a patient with secondary Raynaud's phenomenon treated with a 5-day continuous infusion of epoprostenol titrated to a target dose of 9 ng/kg/min. Therefore, it is reasonable for healthcare providers to consider this regimen as a treatment modality for secondary Raynaud's phenomenon refractory to conventional therapies.

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Conflict of Interest

The authors have no actual or potential conflicts of interest to report.

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