

Cutaneous Reaction to Continuously Inhaled Iloprost

Keywords: Pulmonary Vascular Resistance/Hypertension; Intensive Care; Nitric Oxide; Pediatric; Congenital Heart Disease; Norwood Procedure

Abstract

Pulmonary arterial hypertension is characterized by an increase in pulmonary vascular resistance. It may occur in diverse clinical settings, such as congenital heart disease, chronic lung disease, connective tissue disease, or could be idiopathic. Pulmonary arterial hypertension may cause significant morbidity and mortality. Iloprost is a stable prostacyclin analog with vasodilatory properties. To overcome its systemic side effects, the inhaled route has been used to obtain pulmonary selectivity. We herein report an unusual case of a cutaneous reaction to continuous inhaled iloprost. To our knowledge, there are scarce case reports on cutaneous side-effects of inhaled iloprost in the pediatric population. The objective of this clinical case report is to highlight this unusual reaction to avoid incorrect diagnoses and treatments.

Introduction

Inhaled iloprost is a prostacyclin analog utilized as a specific pulmonary vasodilator in the treatment of pulmonary arterial hypertension. Most reported adverse effects are due to its pulmonary and systemic vasodilatory effect. In rare cases it can cause cutaneous adverse effects.

Clinical Summary

A 2-year-old male with Trisomy 21, double outlet right ventricle, unbalanced atrioventricular canal defect, aortic stenosis, and hypoplastic aortic arch (single ventricle physiology), status post Norwood and bidirectional Glenn procedure, was admitted due to respiratory distress in the setting of an RSV infection. In a previous cardiac catheterization, borderline high Glenn pressures with a mean of 15-16 mmHg were noted. He was treated with non-invasive ventilation, oxygen supplementation with FiO₂ up to 100%, and nitric oxide at 40 ppm. His oxygen saturation with supplemental oxygen and nitric oxide ranged between 70-80%, expected with his single ventricle physiology. Due to failure to improve, two weeks after admission, he underwent cardiac catheterization in which his left pulmonary artery was stented and a venovenous collateral was occluded.

Twenty-two days into his hospital course, he deteriorated with oxygen saturation dropping to 40-50%. Pulmonary vasodilator therapy was further escalated by adding inhaled iloprost. To accomplish this, 20 µg of iloprost was diluted in 20 mL of normal saline to create a 1 µg/mL solution, which was delivered via a non-invasive ventilation using a RAM cannula at a rate equivalent to 1 µg/h. Over a period of 48 hours, the rate was gradually increased to 2 µg/h with a goal of 4 µg/h. When a rate of 2 µg/h was reached, an erythematous blanching rash was noted around his nose. The rash was not raised, pruritic, or did not cause the patient any discomfort. Several emollient creams were attempted, including Vaseline and Aquaphor balm, without any improvement. Due to concern that it could be a fungal rash, nystatin



Ramirez ML^{1*}, Plescher B², Santana-Acosta D² and Khan DM³

¹Pediatric Residency Program, Nicklaus Children's Hospital, Miami, USA

²Division of Pediatric Critical Care, Nicklaus Children's Hospital, Miami, USA

³Division of Cardiology, Nicklaus Children's Hospital, Miami, USA

*Address for Correspondence

Ramirez ML, Pediatric Residency Program, Nicklaus Children's Hospital 3100 SW 62nd Ave Miami, USA. E-mail Id: Monica. ramirezmendizabal@nicklaushealth.org

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cream was used, and intravenous fluconazole was given. Again, no improvement was noted. As the rate increased to 3 µg/h and later to 4 µg/h, the rash spread around his nose to include his perioral region (Figure 1). In one instance, the patient removed his RAM cannula, exposing his neck to the nebulized iloprost and the rash was noticed transiently on his neck in the exposed area. Because of this, it was assumed that the rash could be secondary to the vasodilatory effects of the iloprost. Over the following days, as the iloprost was weaned and discontinued, the rash appeared to have a dose-dependent reaction. The rash gradually self-resolved within 12 hours of discontinuing the medication and significant improvement was seen within 24 hours (Figure 2).

Discussion

Pulmonary vasoconstriction is a mechanism that is intrinsic to the pulmonary vasculature. Smooth muscle of the pulmonary arteries contain voltage-gated potassium and calcium channels sensitive to low oxygen states. The vasoconstriction reflex is a contraction of vascular smooth muscle in response to low regional partial pressure of oxygen. It can help redirect blood flow away from poorly ventilated parts of the lungs. Elevated resistance in the pulmonary circulation after chronic hypoxia may lead to pulmonary hypertension. Pulmonary arterial hypertension is characterized by a gradual increase in pulmonary vascular resistance and can lead to progressive right ventricular failure and death.[1] Nonetheless, increased awareness of the disease



Figure 1: Erythematous, blanching rash noted on day 4 of inhaled Iloprost.

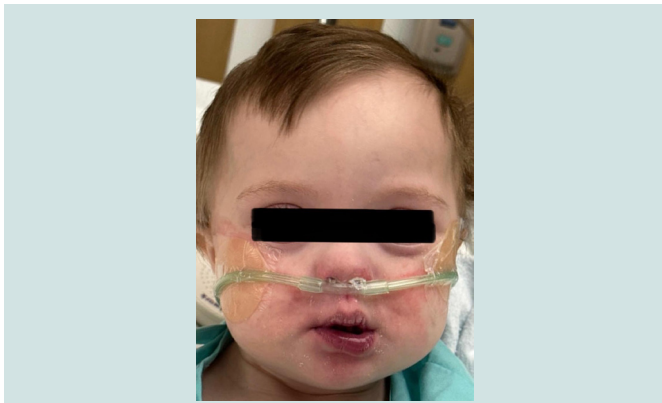


Figure 2: The patient's face 24 hours after discontinuation of inhaled Iloprost.

and vasodilator therapy have improved patients' survival and quality of life. Pulmonary vasodilator treatment includes supplemental oxygen, nitric oxide, endothelin receptor antagonist (bosentan and ambrisentan), phosphodiesterase inhibitor (sildenafil), prostacyclin analogues (epoprostenol, treprostinil, and iloprost), and guanylate cyclase stimulators, to name a few. Although there is a beneficial effect on the right ventricular afterload, utilizing vasodilators may cause concomitant systemic vasodilation, ultimately aggravating the patient's condition. Chronic treatment with vasodilatory therapy administered via intravenous or subcutaneous routes may be limited by problems such as line infections, thrombosis, or site pain. Administering vasodilator therapy via inhalation agents can help target the lungs directly and prevent systemic vasodilation [2].

Inhaled iloprost is a prostacyclin analog that is selective for pulmonary vasculature with an elimination half-life of 20–30 minutes. Pharmacodynamic effects may be observed up to 30-90 minutes following a single inhaled dose. Prostacyclin is a potent short-acting vasodilatory and platelet aggregation inhibitor produced by the vascular endothelium. It can help decrease pulmonary vascular resistance and increase cardiac output and systemic oxygen delivery. Several reports have been published concerning inhaled iloprost in acute pulmonary hypertensive crisis in children with pulmonary arterial hypertension related to congenital cardiac disease. [3,4] Olscheski et al. [5] reported that the local vasodilatory effect of inhaled iloprost outlasts the disappearance of this agent from the systemic circulation, this supported the hypothesis that drug deposition was preferentially pulmonary as compared to systemic. An explanation may be that some percentage of iloprost may be retained in the perivascular lung tissue after nebulization. It may possess a longer half-life than systemic iloprost as it is exposed to the catabolic capacity of the liver.

Although inhaled iloprost therapy is currently approved for treating pulmonary arterial hypertension in adults, little is known about the potential side effects of inhaled iloprost in the pediatric population. A study showed that a notable side effect of inhaled iloprost was bronchoconstriction, potentially limiting its use. Nonetheless, this side effect could be prevented with inhaled steroids before starting treatment. The most common side effects reported were headache,

cough, and dizziness, which generally improved within several days of initiation. [6] Feito Rodriguez et al. [7] reported a case in which direct application of iloprost to the skin resulted in a sudden linear erythematous facial rash that spontaneously resolved. It was noted that on contact with the skin, iloprost invoked long-lasting but painless erythema due to local vasodilatation. Additionally, a study reported a cutaneous reaction to inhaled Treprostinil, a prostacyclin analog. The mask-like erythematous reaction was believed to be a vasodilatory effect secondary to Treprostinil. As our case, the erythema gradually self-resolved over 48 hours after discontinuation of therapy [8].

Conclusion

Owing to our patient's physiology and symptoms, we used continuous inhaled iloprost therapy to improve ventilation-perfusion mismatch. Our case depicts an unusual complication of inhaled iloprost that may serve as a useful reference to other clinicians caring for patients with pulmonary arterial hypertension and can help prevent interruption of treatment due to the alarming appearance of cutaneous adverse effects.

Disclosures and Freedom of Investigation

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Author's Statement

Consent for publication was granted by the patient's mother prior to submission.

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