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Iloprost

Old and New Indications

Brinda Banerji, MD, Manish A. Parikh, MD,*† Ruth Minkin, MD,*† William H. Frishman, MD,‡ and Stephen J. Peterson, MD*†*

Abstract: Iloprost is a synthetic long-acting prostacyclin-analog drug used to treat various vascular diseases. The Federal Drug Administration approved the drug in 2004 for pulmonary arterial hypertension, and it has since been shown to be helpful in other vascular conditions such as scleroderma and Raynaud phenomenon. The Federal Drug Administration has now approved the use of iloprost for severe frostbite. This review summarizes the pharmacologic properties of iloprost, its clinical applications, and potential therapeutic benefits in vascular conditions.

Key Words: pulmonary artery hypertension, iloprost, scleroderma, Raynaud phenomenon, chronic limb ischemia, frostbite

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Iloprost mimics the mechanism of action of the eicosanoid prostacyclin and acts as a potent vasodilator. Prostacyclin also inhibits smooth muscle proliferation and platelet aggregation.[1] The first application for iloprost was for pulmonary arterial hypertension (PAH), where the pulmonary arteries are narrowed and thickened, with decreased blood flow to the pulmonary circulation.[2] Prostacyclin is normally made in the human lung, but patients with PAH have a deficiency of pulmonary prostacyclin. For these patients, iloprost is administered via inhalation every 2 hours while awake.[2] Its applications have extended to include autoimmune conditions such as scleroderma and Raynaud phenomenon, limb ischemia, and more recently, severe frostbite.[1,2] Iloprost has vasodilatory and antiaggregation effects, improving symptoms and outcomes in these challenging diseases.[3,4] The Federal Drug Administration (FDA) approval of iloprost for use in severe frostbite represents a step toward an effective treatment for this potentially serious and debilitating condition.[5] This review covers the pharmacological properties and the clinical utility of iloprost in vascular diseases.

MECHANISM OF ACTION

Prostacyclin is a member of the eicosanoid family of prostaglandins, which are lipid mediators derived from arachidonic acid, which inhibit platelet aggregation, reduce capillary permeability, activate fibrinolysis, and serve as potent vasodilators. Iloprost is a long-acting analog of prostacyclin, made synthetically, which acts on prostacyclin receptors that are present on the membranes of vascular smooth muscle cells.[2] When Iloprost binds to its receptor, it increases the intracellular levels of cyclic adenosine monophosphate, causing vasodilation. Iloprost, in turn, causes a reduction in pulmonary vascular resistance that accompanies vasodilation in treating PAH. Therefore, the result is increased exercise tolerance, a decrease in symptoms, and prevention of further disease deterioration.[1,2] These vasodilatory effects improve blood flow through smaller vessels, enhancing tissue perfusion and reducing ischemic injury in conditions such as scleroderma and Raynaud phenomenon.[4] Iloprost further increases the intracellular concentration of cyclic adenosine monophosphate by inhibiting its degradation and, therefore, inhibits the proliferation of smooth muscle by reducing the activity of fibroblasts, which can soften the skin-thickening process and frequency of digital ulcers.[3,4] In the case of frostbite, iloprost improves tissue damage due to improved microcirculation in the affected areas to prevent necrosis and amputation.[5] Iloprost inhibits platelet aggregation and prevents microvascular thrombosis.[5] In these situations, iloprost is given intravenously in a monitored setting and can be given centrally or peripherally. It should be started at a rate of 0.5 ng/kg/min and increased by 0.5 ng/kg/min to a maximum dose of 2 ng/kg/min; the dose is escalated until the patient has significant side effects, the most common being headache and facial flushing.[6,7] Iloprost is given for 6 hours a day for an average of 7 days. Patients with a higher body mass index have more adverse reactions to iloprost.[8]

CLINICAL APPLICATIONS

Pulmonary Hypertension

PAH is one of the 5 types of pulmonary hypertension in which the small pulmonary arteries narrow and thicken, reducing blood flow to the lungs.[1,2,9] The increase in pulmonary vascular resistance and mean arterial pressures can cause severe respiratory distress and may progress to right ventricular dysfunction and failure, with the possibility of early demise. Iloprost is very well tolerated for PAH, and patients have shown improvement in their 6-minute walk tests and exercise capacity.[1,2,9] While patients have improved clinically, it is not clear that this population's mortality has changed. Iloprost is an ideal agent for this disease management; the goal is to prevent the increased vascular resistance that occurs in the pulmonary artery, potentially culminating in right heart strain and right heart failure. The drug is inhaled and exerts selective local vasodilation in the pulmonary vasculature. Inhalational administration allows tiny amounts to enter the systemic circulation, minimizing the possibility of systemic adverse events. Iloprost has a quick onset of action with maximal effect at 6 weeks. PAH patients are treated with inhaled treatments 4–6 times per day. Iloprost is chemically more stable than prostacyclin, which has a very short half-life.[9] The half-life of iloprost is 20–30 minutes. It should never be used more than every 2

From the *Department of Medicine, New York Presbyterian Brooklyn Methodist Hospital, Brooklyn, NY; †Weill Department of Medicine, Weill Cornell Medicine, New York, NY; and ‡Department of Medicine, New York Medical College, Valhalla, NY.

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Correspondence: Stephen J. Peterson, MD, Department of Medicine, Weill Cornell Medicine, 506 6th street, Brooklyn, NY 11215. E-mail: stp9039@nyp.org.

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hours.[10] This is sometimes supplemented with oral medications for maximal effect. Clinical studies have established that iloprost significantly improves exercise capacity, delays clinical worsening, and improves functional class in PAH patients.[1,2] Furthermore, iloprost decreases platelet aggregation, reducing the risk of in situ thrombosis, which can be a significant complication in PAH. In PAH, iloprost was well tolerated; hence, it is an excellent therapeutic option in the long-term management of patients with this incurable disease.[9] Iloprost proved to be a very useful addition to the armamentarium against PAH, improving quality of life and presenting as a potent alternative to more invasive therapy.

Scleroderma

In autoimmune diseases, such as scleroderma, there is widespread organ involvement dominated by an inflammatory process that causes excessive fibrosis of blood vessels. Iloprost improves the microcirculation in patients with scleroderma, allowing digital ulcers to improve.[3] Iloprost has vasodilatory and antiaggregation properties, which improve blood flow to the affected extremity and reduce thrombosis and clinical symptoms.[3] Clinical trials have demonstrated that iloprost improves microcirculation, allowing for the reduction of the frequency and severity of digital ulcers, and promotes the healing of existing ulcers.[11] Iloprost may play a further antifibrotic role through the reduction of fibroblast activity responsible for skin, vascular, and visceral changes and deposition of collagen in the skin and other tissues.[4] In patients who have scleroderma, iloprost represents an important adjuvant therapy because this form of medication may alleviate symptoms and allow an improvement in the quality of life. Iloprost has been successfully used in the treatment of scleroderma, as it is a potent vasodilator, and is now considered the first-line treatment of the digital vasculopathy caused by scleroderma; it may even slow disease progression, but that remains to be proven.[3,4] Raynaud phenomenon occurs very early during scleroderma and may precede diagnosis by up to 2 years. Iloprost has been shown to have beneficial effects on microcirculation because it is vasodilatory and has antiplatelet activity.[11] Iloprost has been most useful in patients with chronic critical leg ischemia that is caused by Buerger disease and atherosclerosis. It has also been useful to decrease the size of a myocardial infarct after ischemia-reperfusion injury.[12,13]

Raynaud Phenomenon

In Raynaud phenomenon, the smaller arteries of the skin constrict vigorously in response to cold, severely reducing blood flow. This results in pain, skin discoloration, ulceration, and, in extreme conditions, tissue damage due to ischemia. Iloprost is a very efficient treatment option for such patients. It induces vasodilation that increases blood flow, alleviating the ischemic symptoms of Raynaud phenomenon.[4] Clinical studies have demonstrated that iloprost significantly reduces the vasospastic attacks of Raynaud phenomenon in frequency, duration, and severity.[14] In addition, iloprost promotes the healing of ischemic ulcers and can prevent the development of new ulcers.[11] Intravenous administration of iloprost has shown sustained improvement in microvascular function in patients with Raynaud phenomenon.[15]

Frostbite

Frostbite is a cold injury that occurs upon exposure to prolonged low temperatures, where the skin and tissues freeze. This happens to distal extremities such as fingers, toes, ears, and the nose. The initial symptoms are numbness and redness of the skin, but they can progress and become pale or bluish. The complications from frostbite include necrosis of the tissues, infection, and nerve damage and can sometimes result in an amputation of the affected digit or limb. If frostbite is not promptly treated it may result in chronic injury, with chronic pain and cold sensitivity, and tissue loss.[5] Recently, iloprost has been shown to be effective in treating frostbite with its recent FDA approval, preventing platelets from adhering to the endothelium after injury, thus creating a delicate balance between tissue prostacyclin and thromboxane A2, a lipid also from the eicosanoid family that plays a role in blood clotting, inflammation, and tissue injury.[16] Iloprost inhibits the vasoconstriction induced by thromboxane and increases the formation of tissue plasminogen activator. This reduces oxidative stress from free radicals.[17] Iloprost is known to have a considerable vasodilatory effect and antithrombotic action, resulting in an improvement of blood flow to affected regions and limiting the resultant microvascular thrombosis secondary to frostbite. The increased microcirculation due to iloprost decreases the severity of tissue injury and thus prevents ischemia and promotes tissue and limb salvage. Clinical trials have demonstrated that administering intravenous iloprost within a short time following an injury significantly reduces the need for surgical amputation and improves overall outcomes for patients with frostbite.[5,18] These findings subsequently led to FDA approval of iloprost for severe frostbite, underlining its importance as a therapeutic option.[19] Recent literature evaluated the efficacy of iloprost in relation to frostbite. Due to its established pharmacological properties, it offers a crucial intervention for a condition with limited therapeutic options. A review by Gauthier et al[16] emphasizes that iloprost efficiently enhances the microvascular flow, thus limiting tissue necrosis and reducing the chances of amputation. This was a small open-label trial involving only 47 patients. The design was 3 different treatment arms: (1) iloprost alone, (2) buflomedil (another vasoactive drug that is used to medically treat the circulation), and (3) the third group treated with iloprost and tissue plasminogen activator. None of the iloprost group (21%) needed an amputation. This is further supported by Poole and Gauthier,[17] who reported positive results from northern Canada with iloprost in treating severe frostbite, indicating its use in saving digits that would otherwise have a very high risk of amputation. This is further confirmed by the systematic review by Regli et al,[20] where it was found that iloprost significantly improves tissue salvage among frostbite patients, especially if combined with other interventions like hyperbaric oxygen therapy. As early as 2021, Magnan et al[21] were even speculating about a synergistic effect of iloprost and hyperbaric oxygen therapy on improving digit salvage rates. The FDA license of iloprost as the first medication expressly indicated for treating severe frostbite represents a giant leap forward in managing the condition and raising the standard of care.[22,23] Furthermore, observational results by Crooks et al[24] reflect that intravenous iloprost reduces incidences of digital amputation, hence making this drug of paramount importance in the therapeutic options available for frostbite management. These studies demonstrate the myriad applications of iloprost and its substantial impact on frostbite management. Recent approval for use in frostbite further extends indications for this medication. It provides a valuable option in reducing the impact of severe frostbite in patients injured due to extreme cold.

CONCLUSIONS

The therapeutic use of iloprost has shown promising results in vascular diseases: PAH, scleroderma, Raynaud phenomenon, chronic limb ischemia, and more recently frostbite. This medication has demonstrated considerable positive effects for both vasodilation and antiplatelet aggregation. It also increases fibrinolytic activity. The recent FDA approval of iloprost for the treatment of frostbite further confirms its safe use. It is the first drug to be approved for the treatment of severe frostbite after clinical evidence showed that iloprost could improve blood supply, reduce tissue injury, and decrease the need for surgical amputation. It offers a new standard of care for this devastating medical condition. Headache, flushing,

and discomfort of the jaw are some of the common side effects from the administration of this drug, but these side effects are easily managed. The clinician will have to balance the side effects with the potential vascular benefits offered. Iloprost has become an effective therapy for vascular diseases and severe frostbite, and knowledge about its myriad effects continues to evolve. This advance opens the potential for expanded clinical use and has already shown a reduction in amputation for cases of severe frostbite. Further studies will help determine other vascular uses of iloprost. In the meantime, the vasodilation, the inhibition of platelet aggregation, and increased fibrinolytic activity make it the ideal drug to reverse the severe vasoconstriction and thrombosis that are hallmarks of severe frostbite.

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