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Clin Chest Med 28 (2007) 127–142

CLINICS
IN CHEST
MEDICINE

Prostanoid Therapy for Pulmonary Arterial Hypertension

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Prostaglandins were first described by von Euler in 1933 and prostaglandin I_2 (PGI_2, prostacyclin, epoprostenol), a product of endothelial cells in all vascular tissues, was first discovered in 1976. The potential clinical roles of epoprostenol in the acute [1] and chronic [2] treatment of pulmonary arterial hypertension (PAH) were initially described in case series in the early 1980s. Epoprostenol was approved for the chronic treatment of idiopathic PAH by the U.S. Food and Drug Administration (FDA) in 1996 after a randomized, controlled trial showed improved short-term survival [3]. The availability of this agent dramatically changed the approach to treatment and prognosis for patients who have PAH. Since this time, the indications for the use of epoprostenol have expanded and structural modifications have led to the development of additional longer acting molecular analogs for clinical use (Table 1) [4]. Epoprostenol and its structural analogs are collectively termed *prostanoids*. Prostanoid agents currently being used or evaluated for treatment of PAH include epoprostenol, treprostinil, iloprost, and beraprost. Epoprostenol, treprostinil, and iloprost are currently available in the United States. The structures of these molecules are shown in Fig. 1 [5]. Ongoing areas of investigation include alternative routes of prostanoid administration and the use of prostanoids in treating other classes of pulmonary hypertension (PH).

Epoprostenol and the arachidonic acid pathway

Epoprostenol is a member of the eicosanoid family. Eicosanoids are the 20 carbon essential fatty acids derived from arachidonic acid. This family of biologically active mediators includes the prostacyclins, thromboxanes, and leukotrienes. Eicosanoids are critical mediators of smooth muscle contraction, vasodilation and constriction, vascular permeability, platelet aggregation, and lymphocyte chemotaxis and proliferation. Metabolism of phospholipids by phospholipase A2 yields arachidonic acid. Leukotrienes are produced by metabolism of arachidonic acid through the 5-lipoxygenase pathway. Prostaglandins and thromboxanes are produced by metabolism of arachidonic acid through the cyclooxygenase pathway (Fig. 2).

Epoprostenol and pulmonary arterial hypertension pathogenesis

Vasoconstriction, cellular proliferation, and thrombosis lead to the development and progression of PAH. Pulmonary vascular endothelial cell products involved in the regulation of these processes include epoprostenol, nitric oxide, endothelin, serotonin, and thromboxane [6–8]. Since it was discovered, epoprostenol has been known to be a potent vasodilatory, cytoprotective, and antithrombotic agent. Epoprostenol inhibits platelet aggregation and thrombus formation

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0272-5231/07/$ - see front matter
doi:10.1016/j.ccm.2006.11.008

Table 1
Prostanoid agent routes of administration and half-life

Prostanoid agent	Routes of administration for PAH treatment	Half-life in circulation
Epoprostenol	Intravenous[a]	6 min [44]
Treprostinil	Subcutaneous	240 min [47]
	Intravenous	
	Inhaled[a]	
	Oral[a]	
Iloprost	Inhaled	20–30 min [62]
	Intravenous[a]	
Beraprost	Oral[b]	60 min [4]

[a] Route of administration not approved in the United States.
[b] Agent not approved for PAH treatment in the United States.

and also promotes dispersion of preexisting platelet aggregates [9–11]. The cytoprotective effect of epoprostenol has been shown in animal models of tissue injury, including prevention of gastric ulcer formation, reduction in myocardial infarct size, and prevention of endotoxin-mediated lung injury [12–15]. The evaluation of epoprostenol in the treatment of PAH has shown several additional properties. The observation that the chronic response to treatment significantly exceeded the acute vasodilatory response suggested that epoprostenol might also be a mediator of

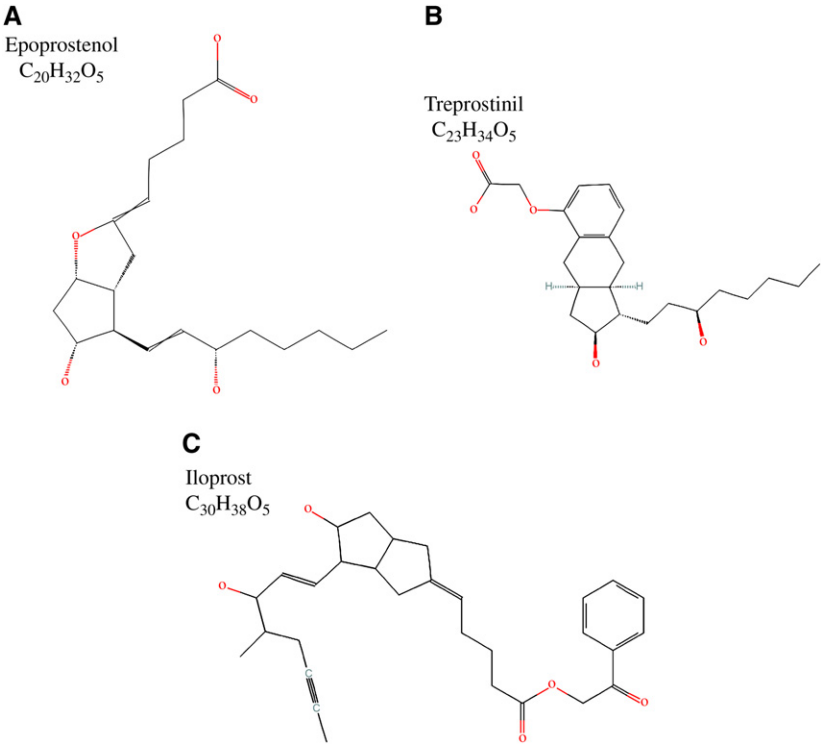

Fig. 1. Molecular structures of epoprostenol (*A*), treprostinil (*B*), and iloprost (*C*). (*From* Wishart DS, Knox C, Guo AC, et al. Drugbank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res 2006; 34(Database issue):D668–72; with permission.)