Antiplatelet effects of prostacyclin analogues: Which one to choose in case of thrombosis or bleeding?

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Abstract
Prostacyclin and analogues are successfully used in the treatment of pulmonary arterial hypertension (PAH) due to their vasodilatory effect on pulmonary arteries. Besides vasodilatory effect, prostacyclin analogues inhibit platelets, but their antiplatelet effect is not thoroughly established. The antiplatelet effect of prostacyclin analogues may be beneficial in case of increased risk of thromboembolic events, or undesirable in case of increased risk of bleeding. Since prostacyclin and analogues differ regarding their potency and form of administration, they might also inhibit platelets to a different extent. This review summarizes the recent evidence on the antiplatelet effects of prostacyclin and analogue in the treatment of PAH, this is important to consider when choosing the optimal treatment regimen in tailoring to an individual patients’ needs. (Cardiol J 2021; 28, 6: 954–961)

Key words: prostacyclin analogues, pulmonary arterial hypertension, platelets, antiplatelet effect, thrombosis, bleeding

Introduction
Since 1935 when prostaglandin was isolated for the first time [1], many scientists have focused on a thorough study of arachidonic acid transformation products and their various biological functions. One of the major prostaglandins is prostacyclin (PGI2), which was discovered by John R. Vane in 1976 [2]. Endogenous PGI2 binds to prostacyclin receptor (IP) on pulmonary vessels smooth muscle cells and platelets. Activated IP receptor induces production of cyclic adenosine monophosphate (cAMP), which activates protein kinase A (PKA) and results in smooth muscle relaxation, inhibition of platelet aggregation and reduction of cell proliferation [3]. Synthetic PGI2 analogues have a similar effect on cells as does natural PGI2. Nowadays, PGI2 and its analogues are being used due to their vasodilating, antithrombotic and anti-proliferative effects [4]. The main indication for PGI2 and analogues is advanced pulmonary arterial hypertension (PAH) and peripheral vascular disorders [5]. Treprostinil, iloprost and beraprost are the most frequently used prostacyclin analogues [4]. Selexiopag is a non-prostanoid IP receptor agonist and a promising new alternative for classic PGI2 analogues [6].

As PGI2 analogues vary depending on the way of administration, pharmacokinetics, binding and affinity for IP receptors, they may also inhibit platelets to a different extent [5]. These differences result in various side effects and complications associated with the of PGI2 analogues and implicate the need to tailor the treatment according to a patient’s individual needs. Because the intensity of antiplatelet effect of PGI2 analogues have not been clarified, choosing the best therapeutic option for individual patients at high risk, or with...
a history of thrombosis or bleeding remains challenging. This review (i) describes the role of PGI₂ in hemostasis, (ii) summarizes the recent evidence on the antiplatelet effect of PGI₂ analogues in the treatment of PAH, and (iii) provides recommendations regarding the choice of the optimal PGI₂ analogue in case of thrombosis or bleeding.

Role of prostacyclin in hemostasis

PGI₂ plays a prominent role in hemostasis, both due to its effect on vascular endothelium, smooth muscle cells and platelets. When a blood vessel wall is damaged, collagen and von Willebrand factor (vWF) are exposed enabling platelets adherence to the subendothelium and granule content release [7]. Thromboxane A2 (TxA2) and adenosine diphosphate (ADP) released from, or produced by activated platelets contribute to platelet aggregation, which temporarily repairs vascular injury. ADP also induces the conformation change of glycoprotein (GP) IIb/IIIa type receptor, allowing binding of fibrinogen to GP IIb/IIIa and cross-linking of the adjacent platelets. The released calcium ions (Ca²⁺) bind to phospholipids that are exposed on the surface of activated platelets and provide a co-factor for the assembly of coagulation factors, facilitating thrombus formation [8]. The processes of primary hemostasis are counteracted by PGI₂, which is a thromboxane receptor antagonist. The main task of PGI₂ is to limit the coagulation to the small area where it is needed, and to sustain patency of the blood vessel [9].

Following platelet-rich thrombus formation, further steps include activation of plasma coagulation factors and formation of crosslinked fibrin by two pathways: extrinsic and intrinsic. The extrinsic pathway is activated by the tissue factor (TF) exposed by vessel injury and released from platelets, which is necessary for activation of factor VII. The complex consisting of Ca²⁺, TF and factor VII can then activate factor X, which starts the common pathway [10]. In the intrinsic pathway, factor XII is activated by contact with the damaged vascular surface, high molecular weight kininogen and kallikrein. This complex initiates the cascade of activation of factor XI and IX. The next step is the activation of factor X, which starts the common pathway. Finally, factors Xa, Va and Ca²⁺ form a complex that converts prothrombin to thrombin, which then converts fibrinogen to fibrin to form a fibrin polymer. After that, plasma transglutaminase (factor XIII) stabilises the clot. Although PGI₂ is not directly involved in clot formation, appropriate platelet aggregation is a prerequisite for clotting. Hence, PGI₂ may affect secondary hemostasis and clot formation as well.

Prostacyclin receptors

Prostacyclin receptors (IP) are seven-transmembrane G protein-coupled receptors, exposed on vascular smooth muscle cells and platelets [11]. The main characteristics of the IP receptors are summarized in Table 1. There are four types of IP receptors on platelets: IP, DP, TP and EP₃. The IP and DP receptors have anti-aggregatory effects, whereas the TP, EP₃ have pro-aggregatory effects [12].

Figure 1 shows the function of IP and DP receptors. The IP receptor works in two ways. First, it activates Gs protein, associated with adenylyl cyclase (AC) to produce cAMP [13], resulting in phosphorylation of the vasodilator-stimulated phosphoprotein (VASP) by protein kinase A. VASP suppresses the activation of the membrane GP IIb/IIIa, thus preventing platelet aggregation [14]. Second, IP activates Gq protein [15]. Activation of Gq protein stimulates phospholipase C to synthesize second messengers which increases the intracellular Ca²⁺ concentration. Increases Ca²⁺ reduces the amount of cAMP, which might facilitate platelet aggregation [16]. However, the Gq-mediated effect of PGI₂ is less significant, so that the net effect of PGI₂ binding to IP receptor is anti-aggregatory. The DP receptor activates Gs protein only, therefore raising the intracellular cAMP concentration and potentiating platelet inhibition.

Table 1. Receptors for prostacycline and its analogues on platelets.

| Receptor | G-protein coupled | Effect of activation | Agonist |
|----------|------------------|---------------------|---------|
| DP [25, 49] | Gs              | cAMP↑               | epoprostenol, iloprost, treprostinil |
| IP [23, 24, 25, 48] | Gs > Gq       | cAMP↑               | epoprostenol, iloprost, treprostinil, beraprost, selexipag |
| TP [22] | Gq > Gs = Gi   | cAMP↓↓              | iloprost |
| EP₃ [23, 24] | Gs > Gq = Gs   | cAMP↑               | epoprostenol, iloprost, beraprost |

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| TP [22] | Gq > Gs = Gi   | cAMP↓↓              | iloprost |
| EP₃ [23, 24] | Gs > Gq = Gs   | cAMP↑               | epoprostenol, iloprost, beraprost |

cAMP — cyclic adenosine monophosphate
TP receptor affects the activity of three G proteins: Gq protein strongly, and both Gi and Gs in a less significant way. Since the effect of TP on Gi and Gs are contradictory, the net effect of this receptor is executed via Gq protein, resulting in reduced cAMP concentration and a pro-aggregatory effect [17, 18]. However, the TP receptor can also form heterodimers with the TP receptor [19]. The IP-TP heterodimer function is similar to the IP receptor (anti-aggregatory), since the TP compound is overpowered. The EP3 receptor activates the same G proteins as TP receptor, but most significantly the Gi protein, resulting in reduced cAMP and platelet aggregation [20].

Due to the fact that the IP receptors have both anti- and pro-aggregatory modes of action, the net clinical effect (thrombosis and bleeding) of PGI2 and analogues are difficult to predict. Recently, there has been a search for a substance, which would specifically bind to the IP receptor, resulting in the introduction of selexipag [21]. Selexipag has a much higher affinity to platelet-inhibiting receptors (IP and DP), and none to platelet-activating receptors (TP and EP3). However, whether this specificity is associated with a higher bleeding tendency remains to be investigated.

Differences in pharmacodynamics and pharmacokinetics of prostacyclin and analogues

PGI2 and analogues are available in parenteral and oral form. Different routes of administration result in differing pharmacokinetics of each drug. PGI2 and analogues are primarily metabolized by cytochromes P450 in the liver, especially by CYP2C8. Selexipag is the only PGI2 analogue which has an active metabolite. Short half-life of PGI2 and analogues often requires continuous infusions by external or implantable intravenous infusion pumps. Epoprostenol, iloprost and beraprost bind both to the antiaggregatory IP and DP receptors and to the pro-aggregatory EP3 [22–24]. Iloprost also binds to the pro-aggregatory TP receptor [22]. Treprostinil binds only to the anti-aggregatory IP and DP receptors [25]. Selexipag is a specific IP receptor agonist [24]. Consequently, the route of administration, metabolism of PGI2 and analogues and their binding profile may define their side effects, including thrombosis and bleeding. The comparison of pharmacokinetics, pharmacodynamics and side effects of the most commonly used drugs PGI2 analogue are thoroughly summarized in Table 2.

![Figure 1. Effects of activation of IP and DP for prostacyclin receptors on platelets; abbreviations — see text.](image_url)

Table 2. Comparison of pharmacokinetics, side effects, contraindications of the most commonly used drugs which target the prostacyclin pathway.

| Drug1 | Route of administration | Pharmacokinetics | Side effects related to the route of administration | Side effects not related to the route of administration |
|-------|-------------------------|------------------|----------------------------------------------------|-----------------------------------------------------|
| Epoprostenol [50, 51] | i.v. infusion (Flolan®, Veletri®) | Bioavailability: 100%  
Metabolism:  
Spontaneous degradation in blood  
Enzymatic degradation in the liver  
Elimination:  
Mainly urine (84%)  
T½ < 6 min | Bleeding  
Infection  
(catheter-related)  
Malfunction of the infusion pump  
Pain  
Sepsis  
Thromboembolic event | Anorexia  
Diarrhoea  
Dizziness  
Flushing  
Headache  
Hypotension  
Jaw pain  
Musculoskeletal pain  
Nausea  
Vomiting  
Tachycardia  
Vasodilation |
Table 2 (cont.). Comparison of pharmacokinetics, side effects, contraindications of the most commonly used drugs which target the prostacyclin pathway.

| Drug         | Route of administration | Pharmacokinetics | Side effects related to the route of administration | Side effects not related to the route of administration |
|--------------|-------------------------|------------------|------------------------------------------------------|------------------------------------------------------|
| Treprostinil | s.c. infusion \(^2\)   | Bioavailability: 100%  
\(\text{Metabolism: Degradation in the liver (primarily CYP2C8)}\)  
\(\text{Elimination: Mainly urine (79%) T½ 2–4 h}\) | Abcess  
Bleeding/bruising  
Infection (infusion pump-related)  
Malfunction of the infusion pump  
Pain  
Other site reactions (erythema, induration, rash) | Bleeding  
Diarrhoea  
Dizziness  
Headache  
Hypotension  
Jaw pain  
Nausea  
Edema  
Vomiting  
Tachycardia  
Vasodilatation |
|              | i.v. infusion \(^3\)   | Bioavailability: 100%  
\(\text{Metabolism: Degradation in the liver (primarily CYP2C8)}\)  
\(\text{Elimination: Mainly urine (79%) T½ 2–4 h}\) | Abcess  
Bleeding/bruising  
Infection (catheter-related)  
Malfunction of the infusion pump  
Pain  
Sepsis  
Thrombophlebitis  
Other site reactions (swelling, paraesthesia’s, erythema, induration, rash) | Diarrhoea  
Dizziness  
Flushing  
Headache  
Nausea  
Sepsis  
Vasodilatation |
| Inhalation   | Inhalation \(^1\)   | Bioavailability: 64–72%  
\(\text{Metabolism: Degradation in the liver (primarily CYP2C8)}\)  
\(\text{Elimination: Mainly urine (70%) T½ 3–4 h}\) | Cough  
Epistaxis  
Hemoptysis  
Nasal discomfort  
throat irritation  
Throat pain  
Wheezing | Diarrhoea  
Dizziness  
Flushing  
Headache  
Nausea  
Sepsis  
Tachycardia  
Vasodilatation |
| p.o.         | (Orenitram\(^*\))   | Bioavailability: 17%  
\(\text{Metabolism: Degradation in the liver (primarily CYP2C8)}\)  
\(\text{Elimination: Mainly urine (70%) T½ 1–1.5 h}\) | Abdominal discomfort  
Diarrhoea  
Nausea  
Vomiting | Diarrhoea  
Dizziness  
Flushing  
Headache  
Jaw pain  
Hypokalemia |
| Iloprost     | Inhalation \(^1\)   | Bioavailability: 63%  
\(\text{Metabolism: Oxidation in the liver}\)  
\(\text{Elimination: Mainly urine (68%) T½ 20–30 min}\) | Cough  
Epistaxis  
Hemoptysis  
Nasal discomfort  
throat irritation  
Throat pain | Diarrhoea  
Dizziness  
Flushing  
Headache  
Hypotension  
Insomnia  
Jaw pain  
Nausea  
Vomiting  
Tachycardia  
Vasodilatation |
| Beraprost    | p.o. \(^1\)   | Bioavailability: 50–70%  
\(\text{Metabolism: Degradation in the liver}\)  
\(\text{Elimination: Mainly faeces (75%) T½ 30–40 min}\) | Diarrhoea  
Nausea | Diarrhoea  
Flushing  
Headache  
Increased bilirubin, lactate dehydrogenase, triglycerides |
| Selexipag    | p.o. \(^1\)   | Bioavailability: 49%  
\(\text{Metabolism: Hydrolysis in the liver and intestine (primarily CYP2C8)}\)  
\(\text{Elimination: Mainly faeces (93%) T½ 3–4 h}\) | Diarrhoea  
Decreased appetite  
Nausea  
Vomiting | Anaemia  
Arthralgia  
Headache  
Hyperthyroidism  
Flushing  
Myalgia  
Rash |

\(^1\) Contraindications to the use of any of the PGI\(_2\) analogues: heart failure with reduced left ventricular ejection fraction, severe hepatic impairment (Child Pugh class C), concomitant use of strong inhibitors of CYP2C8 (e.g. gemfibrozil), hypersensitivity to the drug; \(^2\) The preferred administration route of treprostinil; \(^*\) External or implantable intravenous infusion pump
Thrombosis and bleeding during prostacyclin and analogues therapy

Epoprostenol

Epoprostenol not only inhibits platelet reactivity, but also decreases platelet count [26]. It was reported that epoprostenol induces thrombocytopenia in 35–65% of patients [27, 28]. Hence, bleeding complications may occur during treatment with epoprostenol. For example, among 31 patients with idiopathic PAH (iPAH), who were treated both with epoprostenol and anticoagulants, 11 bleeding episodes occurred (35%), 9 of which were alveolar hemorrhages [29]. However, the concomitant anticoagulation may have biased the results. In a prospective, randomized, multicenter, open-label clinical trial which compared the efficacy of the continuous intravenous infusion of epoprostenol on top of conventional therapy versus conventional therapy alone in 81 patients with severe iPAH (New York Heart Association [NYHA] class III or IV), 4 out of 41 patients treated with epoprostenol (9.8%) experienced bleeding at the catheter site, and 1 experienced a thrombotic event (paradoxic embolism) [30]. However, the rate of bleeding and thrombotic events in the control group were not reported [30]. Herrero et al. [31] described 3 cases of severe PAH in pregnancy, treated with epoprostenol and complicated with thrombocytopenia, caesarean section wound hematoma and postpartum hemorrhage. Louis et al. [32] described 3 cases of nontraumatic subdural hematomas during treatment with PGI₂ and analogues (1 with epoprostenol, 1 with iloprost and 1 with treprostinil). However, all episodes occurred in patients with low platelet count, and all patients received concomitant anticoagulation, making it impossible to determine the real cause of bleeding events. Altogether, it seems that epoprostenol may increase the risk of bleeding. However, since the hitherto studies were prone to confounding factors such concomitant anticoagulation, lack of control group and small sample size, more research is needed to draw firm conclusions.

Treprostinil

In a prospective study including 860 patients with PAH treated with subcutaneous treprostinil with or without warfarin, the incidence of bleeding was 35% (206/590) in patients on combined therapy, and 42% (112/270) in patients only receiving treprostinil (13 severe, 29 moderate and 70 mild bleeding episodes) [33, 34]. Similarly, in a double-blind, placebo-controlled, multicenter trial comprising 470 patients with PAH, either idiopathic or associated with connective tissue disease or congenital heart disease, 34% patients experienced infusion site bleeding or bruising with treprostinil (79/233), and as much as 44% with a placebo (102/236) during 12 weeks of treatment [35]. The incidence of gastrointestinal (GI) bleeding was only 0.01% (3/233) on treprostinil, and 2 out of 3 patients who experienced GI bleeding had increased international normalized ratio (INR; 3.1 and 4.0). In another study, the estimated incidence of GI bleeding with subcutaneous administration of treprostinil was 1.3% [36]. However, in a case series of 5 infants with PAH associated with chronic lung disease and treated with subcutaneous treprostinil, there were no bleeding or bruising episodes [37]. Altogether, although the treatment with subcutaneous treprostinil seems to be associated with relatively high rate of small and local bleeding, this rate was comparable to the placebo, which implies an effect of the infusion system, but not the drug itself. Recently, a double-blind, phase 3, randomised controlled trial was conducted, where 105 patients with chronic thromboembolic pulmonary hypertension, classified as non-operable, or with persistent or recurrent pulmonary hypertension after pulmonary endarterectomy, on chronic anticoagulation were divided into high-dose (~30 ng/kg/min, n = 53) and low-dose (~3 ng/kg/min, n = 52) of subcutaneously administered treprostinil. There were no severe bleeding adverse events in the low dose group and single episodes of hemoptysis and hematoma in the high-dose group. Noteworthy, 3 (5.8%) episodes of epistaxis were observed in the low-dose group, and only 1 (1.9%) episode in the high-dose group, implying that the bleeding on subcutaneous treprostinil is not dose-related [38].

Besides subcutaneous infusion, which is the preferred administration route of treprostinil, it may also be administered intravenously. In a retrospective, multi-center study involving 12 patients with PAH treated with subcutaneous infusion of treprostinil, with intolerable pain at the infusion site, an intravenous infusion pump was implanted. During the postoperative period, 4 (33%) patients experienced a small hematoma in the implantation site that required a single evacuation by puncture. In 1 patient, puncturing of the pump area was required 3 times due to a recurrence of the hematoma. However, this patient had concomitant coagulopathy due to splenomegaly associated with liver cirrhosis resulting in thrombocytopenia [39]. However, intravenous infusion might increase the bleeding risk, although no head-to-head compari-
sons between the routes of treprostinil administration are available.

The efficacy and safety of inhaled treprostinil was evaluated in 9 patients with pulmonary hypertension and concomitant chronic obstructive pulmonary disease [40]. After 16 weeks of treatment, none of the patients experienced a clinically significant bleeding episode, and 1 patient reported blood in sputum [40]. Hence, it seems that treprostinil administered in inhalation may be safer than administered subcutaneously or intravenously, but the heterogeneity and small sample size of the study groups require caution when interpreting the results.

Iloprost

Intravenous iloprost was investigated in a prospective study in 30 patients with systemic sclerosis, leading to only 1 bleeding episode (intracranial hemorrhage) during 3 years follow-up. The same patient had previously suffered a central retinal vein thrombosis [41]. Intravenous iloprost was also evaluated in a randomized, placebo-controlled study in 300 patients as adjuvant to surgery for acute ischemia of lower limbs, with similar incidences of bleeding in patients treated with iloprost and placebo at 3 month follow-up [42]. Inhaled iloprost, in turn, was used to treat PAH due to preterm rupture of foetal membranes in 4 extremely low-birthweight neonates (23–25 weeks gestation, 448–645 gram weight) under spontaneous breathing, supported by nasal continuous positive airway pressure. There was no prolonged bleeding incident noted in any of the patients [43]. Altogether, it seems that both intravenous and inhaled iloprost may be safe, but there is too little data to draw firm conclusions.

Beraprost

In a prospective clinical trial comprising 308 patients with acute ischemic stroke, patients were divided into an experimental group (n = 154) treated with beraprost (40 µg, twice daily) and a control group (n = 154) treated with acetylsalicylic acid only (100 mg, once daily). Both treatment regimens were administered orally and continued for 6 months after hospital discharge. At 6 months, the coagulation parameters (activated partial thromboplastin time, prothrombin time, INR and fibrinogen) and bleeding rates were comparable between the groups [44]. Similarly, in a prospective clinical study including 55 patients with end-stage renal disease on hemodialysis, beraprost (n = 23, 120 µg per day) did not increase the rate of bleeding, compared to the standard therapy (n = 32) [45]. Altogether, the preliminary data implicate that treatment with beraprost does not increase the rate of bleeding, but this conclusion needs to be confirmed in future studies.

Selexipag

The GRIPHON (PGI2 Receptor Agonist In Pulmonary Arterial Hypertension) study took place in 181 centres and was the biggest clinical trial in patients with PAH. In this double-blind, randomized, placebo-controlled study, the efficacy and safety of selexipag was investigated in 1156 patients in different stadiums of PAH [21]. Selexipag did not increase the rate of bleeding, including gastrointestinal hemorrhage [46], and did not have a substantial effect on platelet aggregation [47]. Based on this study, selexipag seems to be a safe treatment regimen in PAH.

Discussion

PGI2 and analogues are widely used in treatment of PAH, but their antiplatelet effect and related bleeding complications are still insufficiently investigated. Experimental data suggests that the IP and DP receptors have antiaggregatory effects, whereas the TP and EP3 have pro-aggregatory effects by modulating the intracellular concentration of cAMP [23–25, 48, 49]. Consequently, drugs which bind to the IP and DP receptors only (treprostinil, selexipag) are expected to have higher antiplatelet activity than those which bind to IP, DP and EP3 receptors (epoprostenol, beraprost) and to all receptors (iloprost). However, data from clinical studies do not always comply with experimental insights. For example, it seems that epoprostenol and treprostinil may increase bleeding risk, especially if treprostinil is administered subcutaneously or intravenously [33–35, 39]. In addition, a randomized controlled trial on 105 patients treated with treprostinil administered subcutaneously showed that the frequency of bleeding complications was not dose-related [38]. On the contrary, no increased bleeding tendency was seen with iloprost, beraprost and selexipag. Hence, one could consider avoiding epoprostenol and treprostinil, and rather choose iloprost, beraprost or selexipag in patients with increased bleeding risk, or with a history of bleeding. However, since the hitherto studies were prone to confounding factors such as concomitant anticoagulation, lack of control group, small sample size and heterogeneity, the previous
results should be interpreted with caution, and more evidence is needed to draw firm conclusions. Especially, large-scale, randomized clinical studies to compare different PGI₂ analogues head-to-head are urgently needed to determine the optimal treatment regimen in patients with increased risk of thrombosis or bleeding, tailored to an individual patients’ needs.

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