THE NORTHERN HOSPITAL

ILOPROST

Introduction

Iloprost is a synthetic analogue of the prostaglandin derivative **PGI_2** (known **more** specifically as **prostacyclin**).

Two formulations are available, Iloprost for inhalation (trade name in Australia, **Ventavis)** and iloprost for IV infusion (trade name in Australia, **Ilomedin**).

Prostacyclins:

1. Inhibit platelet aggregation

2. Vasodilate blood vessels of the pulmonary arterial and systemic arterial vascular beds

Indications for iloprost include:

1. Pulmonary hypertension, (via inhalation)

2. Raynaud's phenomenon (via IV infusion).

3. Buerger's disease (via IV infusion).

4. PVD (via IV infusion).

History

Prostaglandins were first isolated from seminal fluid in 1935 by the Swedish physiologist **Ulf von Euler** and independently by **M.W. Goldblatt**. The name itself, derives from the prostate gland, which von Euler mistakenly believed they were derived. They were in fact derived from the seminal vesicles. Later it was shown that PGs are can be found in virtually every tissue in the body.

E. J. Corey was the first to synthesize PGs (prostaglandin F2α and prostaglandin E2) in 1969, which won him the Japan Prize in 1989.

In 1971, a U.K. research team, headed by **Professor John Vane**, demonstrated that aspirin-like drugs could inhibit the synthesis of prostaglandins.

Vane and a team from the Wellcome Foundation, also identified a lipid mediator they called "PG-X" which inhibited platelet aggregation, and was 30 times more potent than

any other then known anti-aggregatory agent PG-X, would later become known as **prostacyclin.**

The biochemists **Sune K. Bergström, Bengt I. Samuelsson** and **John R. Vane** were jointly awarded the 1982 Nobel Prize in Physiology or Medicine for their research on prostaglandins.

Chemistry

The **prostanoids** are part of a family of biologically active lipids derived from the action of cyclooxygenases or prostaglandin synthases upon the twenty-carbon essential fatty acids or eicosanoids.

Prostanoids can be further subdivided into three main groups:

1. Prostaglandins:

And two prostaglandin derivatives:

2. Prostacyclins:

   These are powerful locally acting:

   - Vasodilators

   And

   - Inhibitors of platelet aggregation

   Through their role in vasodilation, prostacyclins are involved in inflammation.

   They are synthesized in the walls of blood vessels and serve the physiological function of preventing needless clot formation, as well as helping to regulate the contraction of smooth muscle tissue.

3. Thromboxanes:

   Conversely, thromboxanes (produced by platelet cells) are:

   - Vasoconstrictors

   And

   - Facilitate platelet aggregation.

   Their name comes from their role in clot formation (thrombosis).

Classification

Prostacyclin (PGI_2) analogues include:

1. **Iloprost**
2. Epoprostenol
3. Treprostinil

Preparations

Nasal spray:

- Nebules of 2 mL as 10 mcg/mL - i.e 20 mcg per ampoule.

Solution for infusion:

Iloprost trometamol as:

- Ampoule of 1 mL (i.e. 100 μg)
- Ampoule of 0.5 ml aqueous solution contains 67 microgram (or 0.067 mg) iloprost trometamol, which is equivalent to 50 microgram (or 50 microgram) of iloprost

Mechanism of Action

Iloprost:

1. Inhibits platelet aggregation
2. Vasodilates blood vessels of the pulmonary arterial and systemic arterial vascular beds

Pharmacodynamics

The pulmonary vasodilatory effect of inhaled iloprost is of **short duration** (1 - 2 hours).[2]

As iloprost has a relatively short half-life -pronged daily infusions are required, over a period of days, weeks, or even months to produce significant clinical results.

In situations of Raynaud's phenomenon, several weeks of improvement is expected with 4-5 days treatment, justifying intermittent treatment periods during a problem period such as winter months.

In an **acute ischemic crisis**, a **rapid reversal** of symptoms usually occurs. [5]

Pharmacokinetics

Absorption:

- Iloprost is administered via inhalation for pulmonary hypertension.

  It is administered by IV infusion for arterial occlusive disease.

Distribution

- Following intravenous infusion, the apparent steady-state volume of distribution is 0.6 to 0.8 L/kg in healthy subjects. No studies have been performed following inhalation.

- Total plasma protein binding of iloprost is concentration independent in the range of 30 - 3000 picogram/mL and amounts to approximately 60 %, of which 75 % of this is due to albumin binding.

- Human placental transfer is unknown. [4]

- Whether there is excretion into breast milk is unknown. [4]

Metabolism and excretion:

- Iloprost is extensively metabolized principally via beta-oxidation of the carboxyl side chain.

  No unchanged substance is eliminated.

  The main metabolite is tetranor iloprost, which is found in the urine in free and conjugated form in 4 diastereoisomers.

  Tetranor iloprost is pharmacologically inactive.

  In vitro studies suggest that metabolism of iloprost in the lungs is similar after intravenous administration or inhalation.

- Half-life is around 20 - 30 minutes.

Indications

Indications for iloprost include:

1. Pulmonary hypertension:

   - Treatment of moderate or severe primary and secondary pulmonary hypertension

Us with caution in COPD and asthma (may worsen bronchospasm).

2. Raynaud's phenomenon:

   - Treatment of patients with severe disabling Raynaud's phenomenon unresponsive to other therapies.

     In patients who receive optimal vasodilator therapy with first-line agents but who either have severe symptoms that have a markedly adverse effect upon quality of life or have digital ulcers or macrovascular events associated with Raynaud phenomenon that threaten digital loss, intravenous (IV) infusions of a prostaglandin should be commenced. [5]

3. Buerger's disease:

   - Treatment of advanced thromboangiitis obliterans (Buerger's disease) with critical limb ischaemia in cases where revascularization is not indicated.

4. PVD:

   - Treatment of patients with severe peripheral arterial occlusive disease (PAOD), including arteriosclerosis and diabetic angiopathy, particularly those at risk of amputation and in whom surgery or angioplasty is not possible.

     Surgery however should not be delayed in patients requiring urgent amputation (e.g. in infected gangrene).

Contra-indications/precautions

These include:

1. Hypersensitivity to iloprost

2. Iloprost nebuliser solution should not come into contact with skin and eyes

3. Caution in conditions where the effects on platelets might increase the risk of haemorrhage:

   - e.g. active peptic ulcers, trauma, intracranial haemorrhage.

4. Significant cardiac disease:

   Including:

   - Severe coronary artery disease or unstable angina

- Myocardial infarction within the last six months
- Decompensated cardiac failure if not under close medical supervision.
- Severe arrhythmias
- Suspected pulmonary congestion
- Cerebrovascular events (e.g. transient ischaemic attack, stroke) within the last 3 months.
- Acute or chronic congestive heart failure (NYHA II-IV)
- Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension.

5. Pulmonary hypertension due to venous occlusive disease.

6. Drug interactions:

   - Iloprost may increase the antihypertensive effect of other vasodilating and antihypertensive agents, such as β-receptor blockers, calcium antagonists, vasodilators and ACE inhibitors.
   - Because iloprost inhibits platelet function, its use with anticoagulants (such as heparin coumarin-type anticoagulants), or other inhibitors of platelet aggregation (such as acetylsalicylic acid, non-steroidal anti-inflammatory medicines, phosphodiesterase inhibitors and nitro vasodilators e.g. molsidomine) may increase the risk of bleeding.

     If this occurs, iloprost administration should be stopped.

7. Hepatic impairment, (in particular those with cirrhosis):

   - Dose reduction may be required.

8. Renal impairment, (in particular those on dialysis):

   - Dose reduction may be required.

9. Paediatric use.

   - The experience in children and adolescents (patients below 18 years of age) is limited.

     The manufactures therefore do not recommended use in this population.

Pregnancy

There is limited information available following the use of iloprost during pregnancy. No congenital malformations or adverse effects have been noted in infants exposed to the medicine in early pregnancy.. Iloprost is unlikely to pose clinically significant effects on the fetus due to the short half-life of the medicine.

If iloprost is used during pregnancy, monitor fetal development and maintain maternal safety and wellbeing via a multidisciplinary team approach. As iloprost may inhibit platelet aggregation, also monitor for bleeding, particularly during delivery and the postpartum period. [4]

Breast feeding

There have been no reports following the use iloprost during breastfeeding. Due to the short half-life and poor bioavailability of the medicine, iloprost is unlikely to pose harmful effects to the breastfed infant. If iloprost is the treatment of choice, observe the breastfed infant for possible side effects, such as vomiting, flushing and irritability. [4]

Adverse Effects

1. Pain at the infusion site.
    - A cutaneous vasodilation may give rise to a streaky erythema above the infusion vein.
2. On contact with the skin, iloprost may provoke long-lasting but painless erythema.
3. Hyperhidrosis
4. Headache
5. Flushing (due to vasodilation)
6. GIT upset:
    - Nausea, vomiting and diarrhoea.
7. Hypotension/ syncope/ orthostatic hypotension.
    - Do not begin treatment if systolic BP < 85 mm Hg.
8. Bleeding events:
    - As an antiplatelet agent, bleeding may be aggravated in high risk situations, such as active peptic ulcers, trauma, intracranial haemorrhage.

9. Dyspnea/ chest tightness/ bronchospasm.

- Iloprost inhalation can induce bronchospasm, especially in patients with bronchial hyper-reactivity

Dosing

Nebulizer for Pulmonary Hypertension: [1]

Iloprost 2.5 micrograms by nebulizer 6 - 9 times a day.

Can be increased to 5 micrograms 6 - 9 times a day if necessary and if tolerated.

Iloprost nebuliser solution should not come into contact with skin and eyes

During nebilization sessions a facial mask must be avoided and only a **mouthpiece** should be used.

IV Infusion for Occlusive Arterial Disease:

See local hospital protocols for exact details of infusions.

In general terms:

Iloprost is administered after dilution as an intravenous infusion over **6 hours daily** via a peripheral vein or a central venous catheter.

The duration of treatment is up to **4 weeks.**

Shorter treatment periods (**3 - 5 days**) are often sufficient in **Raynaud's phenomenon** to achieve improvement over several weeks.

Continuous infusion over several days is **not** recommended. This is because of the possible development of **tachyphylaxis** of platelet effects and the possibility of rebound platelet hyperaggregability at the end of treatment, although no clinical complications associated with these phenomena have been reported.

The dose is adjusted according to individual tolerability within the range of:

- **0.5 to 2.0 ng/ kg /min.**

During the first 2 - 3 days, the individually tolerated dose is established.

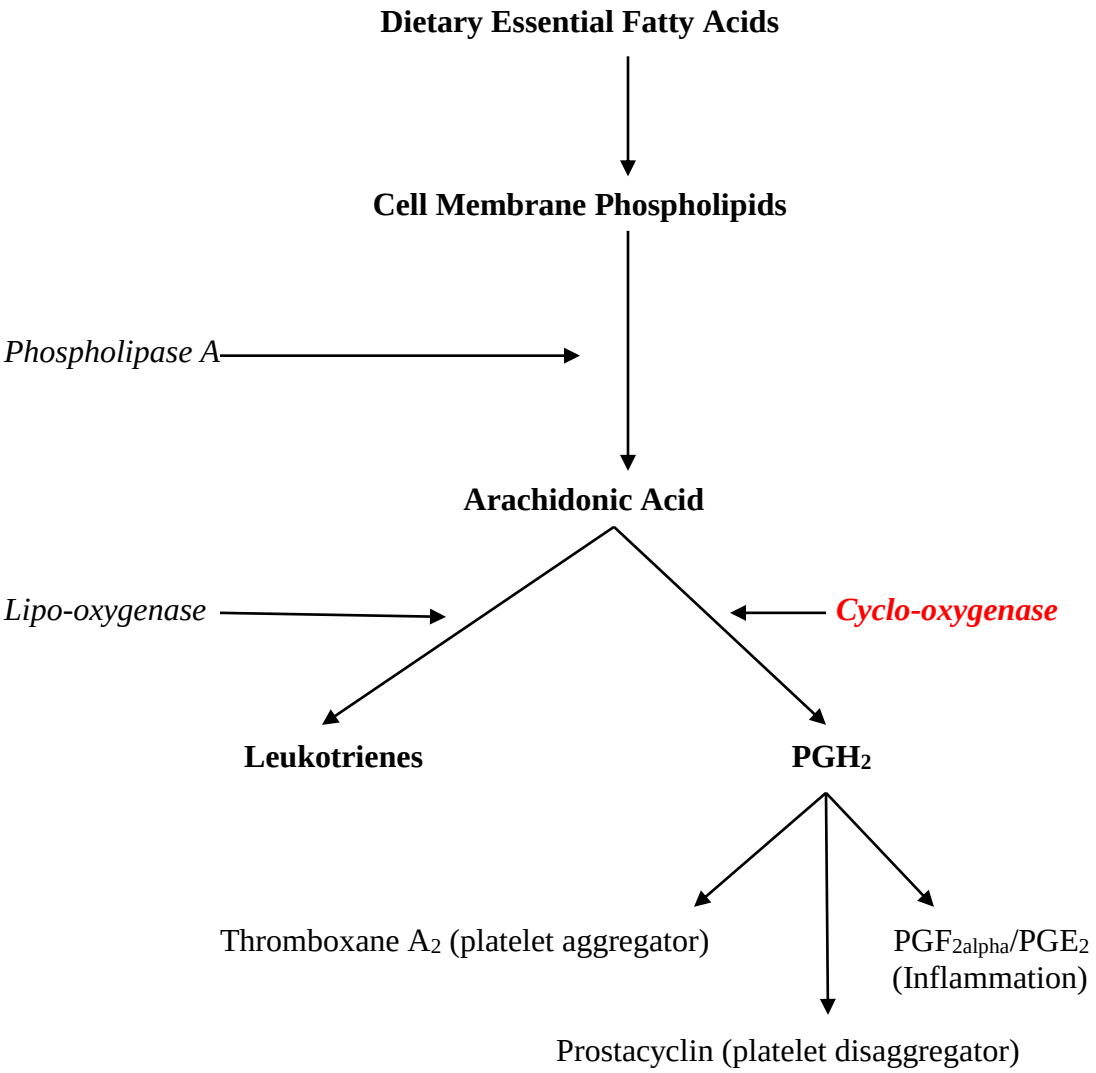
For this purpose, treatment should be started at an infusion rate to deliver 0.5 ng/kg/min. For 30 minutes.

The dose should then be increased at intervals of about 30 minutes in steps of 0.5 ng/kg/min. up to 2.0 ng/kg/min.

The exact infusion rate should be calculated on the basis of body weight to effect an infusion within the range of 0.5 - 2.0 ng/kg/min.

Appendix 1

NSAID Action



Platelet aggregation will depend on the ratio:

Prostacyclin
Thromboxane A_2

Aspirin irreversibly inhibits cyclo-oxygenase.

Other NSAIDS reversibly inhibit cyclo-oxygenase

References

1. eTG - March 2016

2. Iloprost - Nebulizer Solution in MIMs Website, 1 September 2016.

3. Ilomedin Product Information Sheet, Bayer New Zealand Limited, 19 March 2012.

4. Iloprost in RWH Pregnancy & Breastfeeding Guidelines, February 2015.

5. Iloprost in Up to Date Website, Accessed August 2016.

Dr J. Hayes
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