Drug Update

PROSTANOIDS IN THE MANAGEMENT OF LIMB ISCHEMIA

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Prostanoids are prostaglandin analogues which are potent vasodilators and inhibitors of platelet aggregation. This property has been utilized in treatment of limb ischemia where direct arterial surgery or angioplasty is not possible. Prostaglandin E1 (PGE1) was first tried in occlusive arterial disease in 1973 and prostacyclin a few years later. Iloprost, a stable prostacyclin analogue was introduced subsequently. Prostanoids have a short half-life and therefore intravenous or intra-arterial route is required for their administration. This limitation led to development of two orally active compounds, cicaprost and beraprost, and their initial reports are encouraging [1].

Mechanism of action

Prostanoids cause arteriolar and veno-dilatation causing increase in skin temperature and facial flushing. They are also potent inhibitors of platelet aggregation and activation, the effect lasting for 100 minutes or more after the end of infusion. While these two are the most well documented effects, they have other beneficial effects too; they inhibit activation of leukocytes, erythrocyte aggregation is inhibited and deformability increased, mitotic activity and proliferation of smooth muscles of vessel wall is inhibited and they also have a 'cytoprotective effect' whereby the injured cell membrane is prevented from being irreversibly damaged. These actions lead to an increase in supply of oxygen and nutrients as well as their better utilization within the ischemic tissue [2].

Clinical Pharmacology

The majority of prostanoids require intravenous or intra-arterial infusion as they have a very short half-life. Prostacyclin infusion in the dose of 2-5 ng/kg/min causes arteriolar vasodilatation, tachy-

cardia, increase in skin temperature and facial flushing. These cardiovascular effects are short-lived as compared to the effects on platelets which last for almost 2 hours after the end of the infusion. Headache, colicky abdominal pain, ill-defined sense of unease, restlessness, weakness and nausea and vomiting are the reported side-effects but are infrequent. Higher infusion rates of intravenous prostanoids may cause sudden hypotension. Prostanoids are contraindicated where the anti-platelet effect may increase the risk of haemorrhage, e.g. active peptic ulcer, trauma, intracranial haemorrhage. Severe coronary heart disease, congestive heart failure, and arrhythmias are other contraindications, as is pregnancy and lactation.

Clinical use

Iloprost (Ilomedin) in the dose of 2-4 ng/kg/minute intravenously for 6-8 hours every day for 4 weeks has been extensively used in treatment of critical limb ischemia (rest pain in the limb or non-healing ulcers) where direct arterial surgery is not feasible. This presentation is common in late stages of atherosclerotic occlusive arterial disease as well as in thromboangiitis obliterans (Buerger's disease), an occlusive arterial disease involving the small and medium size arteries which is common in India, Japan and Israel. The comparable dose of PGE1 is 40-60 µg per day for 3-4 weeks. A recent meta-analysis of six randomized controlled trials [2] showed that patients treated with iloprost have a significant beneficial effect ($p < 0.05$) in terms of pain relief and healing of ulcers as compared to placebo, naftidofuryl or pentoxifylline. The probability of being alive with both legs (i.e. avoiding an amputation) at six months was also considerably more ($p < 0.05$) with

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iloprost. In general, for critical ischemia the response rates vary between 40-65 per cent. At present it is not possible to predict which of these patients will respond to prostanoid therapy. Prostanoids are also very useful in the treatment of severe secondary Raynouds disease unresponsive to other conventional pharmacotherapy [3]. Initial reports in the management of acute limb ischemia following intra-arterial drug injection are also encouraging [4]. They have also been tried as an adjunct to infragenicular bypass surgery [1] and following microvascular skin-flap reconstruction [5] but their efficacy for these conditions has not been proven by randomized controlled trials.

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