LEADING ARTICLE

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The Future Potential of Eicosanoids and Their Inhibitors in Paediatric Practice

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Abstract

Eicosanoids may have many potential uses in paediatric practice. Since E-type prostaglandins were first applied to treat ductus-dependent congenital heart diseases in paediatric practice, many eicosanoid-related drugs have been examined for the treatment of pathophysiological conditions in children.

Prostaglandins (PG), thromboxane (TX) and leukotrienes (LT), produced from arachidonic acid in the phospholipids of cell membranes, are considered to be biologically active eicosanoids. Corticosteroids reduce eicosanoid production by impairing phospholipase A_2 activation, while cyclo-oxygenase inhibiting drugs such as the nonsteroidal anti-inflammatory drugs (NSAID) suppress PG and TX production. PGE_1 (alprostadil) and PGE_2 (dinoprostone) therapy has been shown to improve oxygenation in neonates whose pulmonary and systemic blood flow are dependent on a patent ductus arteriosus, while epoprostenol (prostacyclin, PGI_2) and beraprost (beraprost sodium), another PGI_2 analogue, are often effective as acute vasodilators in paediatric pulmonary hypertension.

Synthetic PGE analogues such as misoprostol have gastric antisecretory and cytoprotective effects, and are effective in both prophylaxis and treatment of NSAID-induced gastroduodenal mucosal lesions. Both alprostadil and epoprostenol have been shown to be effective in treating peripheral vascular and skin diseases. Since TX, a platelet aggregator and vasoconstrictor, has been implicated as a potential mediator of asthma, its inhibition by agents such as seratrodast (AA-2414) and ozagrel (OKY-046) has proven effective in the treatment of adult patients with asthma; studies of these agents in paediatric patients is awaited with interest.

Developing the clinical use of eicosanoid-related drugs and assessing the potential use of these drugs requires a 3-phase approach: reducing the complications in the treatment of neonates with ductus-dependent congenital heart diseases and primary pulmonary hypertension requiring PGE_1, PGE_2 and PGI_2 therapy; conducting clinical trials of the synthesis inhibitors and receptor antagonists of TXA_2 and LT that have already been used in the treatment of adult patients with bronchial asthma; and evaluating the efficacy of new modulators of eicosanoid biosynthesis, such as eicosapentaenoic acid and antiallergy drugs, in the treatment of eicosanoid-related diseases in children.

Eicosanoids are autacoids that can be rapidly biosynthesised in almost all tissues of the human body and are important not only in physiological function but also in the pathophysiology of human disease.[1] Prostaglandins (PGs), thromboxanes (TXs) and leukotrienes (LTs), which are produced from arachidonic acid in the phospholipids of cell membranes, are considered to be biologically active eicosanoids.

Physiological and pharmacological studies of eicosanoids have shown marked progress since the chemical structure of primary PGs (PGEs and PGFαs) was determined in the early 1960s. Primary PGs were first applied as a medical treatment in the early 1970s; since then, many clinical studies of synthetic PG analogues have sought to increase their biological and chemical stability and to decrease any adverse reactions resulting from their use.

In paediatric clinical medicine, alprostadil (PGE_1) was first used for the treatment of ductus-dependent congenital heart diseases (CHDs).[2] Since then, the efficacy of drugs related to eicosanoids has been examined in many paediatric diseases. Today, administration of alprostadil and dinoprostone (PGE_2) is essential in the treatment of CHDs that depend on the ductus arteriosus. Primary pulmonary hypertension (PPH) has also responded to administration of epoprostenol (PGI_2), and LT-receptor antagonists have recently been examined for use in the treatment of paediatric bronchial asthma.

1. Biosynthesis and Inhibition of Eicosanoids

The eicosanoids constitute a group of lipid mediators derived from 20-carbon fatty acids. The most predominant and important fatty-acid precursor is arachidonic acid, a membrane phospholipid that has been esterified in the 2-position. The release of arachidonic acid from membrane phospholipids is stimulated by a variety of biochemical and mechanical stimuli through activation of phospholipase A_2 (PLA_2).[3] The small pool of free arachidonic acid is subsequently metabolised either through the cyclo-oxygenase pathway to PGs and TXs[4] or through the lipoxygenase pathway to LTs;[5] this mechanism is called the arachidonic acid cascade (fig. 1). Inhibition of enzyme activity for the biosynthesis of eicosanoids helps to regulate this cascade. Many such inhibitors have been used in the treatment of eicosanoid-related diseases, including inflammatory and allergic diseases. Corticosteroids have been shown to reduce eicosanoid production by impairing the activation of PLA_2, which is regarded as the rate-limiting enzyme for eicosanoid biosynthesis.[6] Cyclo-oxygenase–inhibiting agents, such as the nonsteroidal anti-inflammatory drugs (NSAIDs), suppress the production of PGs and TXs.[7] Recently, TXA_2 synthetase and lipoxygenase inhibitors, and the TXA_2- and LT-receptor antagonists, have been examined for the treatment of bronchial asthma.[8]

2. Clinical Uses of Prostaglandin Agents in Paediatric Practice

2.1 Patent Ductus Arteriosus–Dependent Congenital Heart Diseases

Alprostadil and dinoprostone therapy has been established for the preoperative management of neonates with ductus-dependent CHDs.[9] In early clinical studies, infusions of either alprostadil or dinoprostone were consistently effective in improving the oxygenation of neonates whose pulmonary and systemic blood flow were both dependent on the patency of the ductus arteriosus.[10,11] These compounds have also been used as treatment when there is a complete transposition of the great arteries causing poor interatrial mixing, either before or after balloon atrial septostomy.[11] Recent studies have examined ways to use them for prolonged periods, focusing on complications as well as efficacy.[12,13]

There are distinct advantages in using an oral rather than an intravenous PG preparation. Oral preparations have proven to be particularly suitable for long term use and have enabled most infants so treated to grow satisfactorily. Infants are initially treated with oral dinoprostone for 1 to 4 weeks, and are then evaluated on an individual basis to deter-

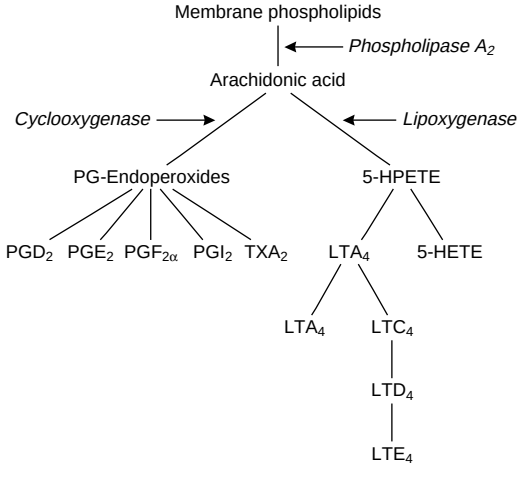

Fig. 1. Biosynthetic pathways of eicosanoid metabolism: arachidonic acid cascade. **HETE** = hydroxy-eicosatetraenoic acid; **HPETE** = hydroperoxy-eicosatetraenoic acid; **LT** = leukotriene; **PG** = prostaglandin; **TX** = thromboxane.

mine whether to proceed with surgery or continue a longer course of treatment to encourage further growth.[14]

Kramer et al.[12] recently evaluated low-dose alprostadil infusion treatment of neonates with ductus-dependent CHDs. They demonstrated that alprostadil can be effectively administered in doses lower than the recommended 0.05 to 0.1 mg/kg/min. In particular, avoiding high initial doses and providing low maintenance doses allowed long term treatment without serious complications.

Recently, lipo-alprostadil (lipid microspheres containing PGE_1) has been used clinically.[15] Its action is the same as free PGE_1, but it is more resistant than the latter to enzymatic inactivation in the body and causes less adverse effects.[13] Although lipo-PGE_1 is now exclusively used for the treatment of neonates with ductus arteriosus-dependent CHDs in Japan, worldwide studies of its efficacy and complications are still required.

2.2 Primary Pulmonary Hypertension

PPH is an intractable disease with a poor prognosis, and mortality is especially high for patients younger than 2 years. Infusion of epoprostenol is often effective as an acute vasodilator in paediatric PPH.[16] Therapy with this drug, however, has 2 major drawbacks, namely bradycardia and systemic hypotension.[17]

Takigiku et al.[18] recently showed that infusion of a new vasodilator, lipo-PGI_2, produced a marked reduction in pulmonary blood pressure and resistance in an infant with PPH, without systemic hypotension. Lipo-PGI_2, a PGI_2 analogue incorporated in lipid microspheres, is resistant to enzymatic inactivation. Moreover, lipid microspheres accumulate in the injured portions of vessels. Lipo-PGI_2 therapy may become a useful treatment in infants with PPH by targeting the site of pulmonary vascular damage.

The authors also demonstrated the efficacy of orally-administered beraprost (beraprost sodium), a PGI_2 analogue, in the treatment of an infant with PPH, after successful treatment with an intravenous infusion of PG preparations.[18] Changing to beraprost resulted in no increase in pulmonary or decrease in systemic blood pressures. Oral preparations of PGI_2 may facilitate its long term use.

Inhalation of epoprostenol reverses pulmonary vasoconstriction in hypoxic dogs to a similar degree to that achieved by nitric oxide.[19] Aerosolised PGI_2 has been shown to reduce both pulmonary blood pressure and the resistance associated with improved matching of ventilation and perfusion in patients with adult respiratory distress syndrome.[20] Recently, aerosolised PGI_2 therapy has been applied in infants with pulmonary hypertension and has demonstrated selective pulmonary vasodilation.[21]

2.3 Gastroduodenal Mucosal Lesions

Synthetic PGE analogues such as misoprostol and enprostil have gastric antisecretory and cytoprotective effects. In adults they are effective in both prophylaxis and treatment of gastroduodenal injury induced by NSAIDs, which inhibit cyclooxygenase activity and reduce gastric mucosal PGs.[22]

Studies in children of the efficacy and adverse effects of PGE analogues are few. One report

showed that misoprostol, a synthetic PGE_1 analogue, can lead to clinical improvement in children with juvenile rheumatoid arthritis who present with NSAID-related symptoms.[23] Recently, Gazarian et al.[24] also demonstrated that misoprostol was effective in the treatment of gastrointestinal tract symptoms in children receiving NSAIDs, and resulted in a significant increase in haemoglobin levels.

Corticosteroids are known to impair the increase of endogenous gastric mucosal PGE_2 by inhibiting PLA_2 activity in children.[25] Therefore, synthetic PGE analogues can be expected to be effective for the prophylaxis and treatment of corticosteroid- as well as NSAID-induced gastroduodenal damage in children.

2.4 Peripheral Vascular and Skin Diseases

PGE_1 has been shown to be involved in peripheral vasodilation and antiplatelet mechanisms. Intravenous administration of alprostadil is effective in peripheral vascular diseases.[26] Lipo-PGE_1 is also used for the treatment of peripheral circulatory disorders in connective tissue diseases, such as systemic lupus erythematosus and progressive systemic sclerosis.[27]

Tsutsui et al.[28] reported the successful treatment of one child and 3 adults with livedo vasculitis using beraprost. They proposed that beraprost is not only an effective antiplatelet therapy but also normalises thrombomodulin expression on the endothelial cells in livedo vasculitis. Oral administration of PGI_2 analogues may permit long term therapy.

Recent studies have demonstrated the clinical effectiveness of ointments containing alprostadil for the treatment of skin diseases, including chronic skin ulcers and burn wounds.[29,30] The application of alprostadil ointment in combination with skin-graft surgery improved functional and aesthetic results in patients with deep dermal burns by minimising the area of the donor site.[30] This would be especially useful for children with extensive burns, because of the shortage of available tissue as donor-site material for skin grafting.[30]

3. Clinical Uses of Cyclo-Oxygenase–Inhibiting Agents

Many drugs that inhibit cyclo-oxygenase, namely NSAIDs, are widely used in paediatric practice as anti-inflammatory agents, as anticoagulants, and for closing patent ductus arteriosus in premature babies through decreased production of PGs and TXs. Unfortunately, the adverse effects of the inhibition of PG production include gastroduodenal mucosal injury and renal dysfunction.

The first reported cyclo-oxygenase, COX-1, is constitutively expressed in most tissues at fairly constant levels. Recently, a second cyclo-oxygenase, COX-2, was discovered,[31] which is normally undetectable in many tissues, but can be expressed at high levels in macrophages and other cell types after stimulation with inflammatory mediators.[32]

As such, COX-2–selective inhibitors are gaining significant attention in clinical situations as they are likely to have fewer adverse effects than the traditional nonselective COX inhibitors.[33] COX-2–selective inhibitors are likely to prove to be potent and well tolerated anti-inflammatory agents in the paediatric field.

4. Clinical Uses of Synthetic Inhibitors and Receptor Antagonists of TXA_2

TXA_2, a platelet aggregator and vasoconstrictor, has been implicated as a potential mediator of asthma. It induces potent contraction of airway smooth muscles and airway hypersensitivity.[34] Seratrodast, a TXA_2-receptor antagonist, and ozagrel, a specific inhibitor of TXA_2 synthesis, have proven to be beneficial for the treatment of adult patients with bronchial asthma in Japanese studies.[35,36]

TXA_2, as well as many arachidonic acid cyclo-oxygenase metabolites, such as PGD_2, $PGF_{2\alpha}$, PGH_2 and others, stimulate TXA_2/PGH_2 receptors, and can play a pathophysiological role in asthma.[37] Seratrodast competitively antagonises the TP receptor and has been shown to reduce bronchial hyper-responsiveness to methacholine in pa-

tients with asthma.[38] Ozagrel has also been shown to ameliorate symptoms of exercise-induced asthma in adults.[39] In children, however, no clinical trial has been reported to date. It may also be worthwhile to examine the efficacy of those drugs in the treatment of paediatric bronchial asthma.

5. Clinical Uses of Synthetic Inhibitors and Receptor Antagonists of LTs

Cysteinyl leukotrienes (LTC_4, LTD_4 and LTE_4), which are released from inflammatory cells such as mast cells and eosinophils, appear to mediate many of the pathophysiological processes associated with bronchial asthma, including mucus production, decreased mucociliary clearance, vascular permeability change, and smooth muscle contraction.[40]

A wide range of LT-receptor antagonists and LT-synthesis inhibitors have been identified, characterised and tested in clinical trials for the treatment of asthma.[8] Since the identification of the initial group of active compounds, attempts have been made to modify their structure so as to increase their potency, bioavailability and selectivity, and thus minimise their adverse effects.

In clinical trials in adults, the effects of oral LTD_4-receptor antagonism [zafirlukast (ICI-204,219)] and oral 5-lipoxygenase inhibition (zileuton) on pulmonary function and clinical symptoms have been demonstrated.[41,42] Reiss et al.[43] have recently shown that montelukast, a new oral LTD_4-receptor antagonist, provides benefits in the treatment of adult patients with chronic asthma; these benefits occur irrespective of the presence of concomitant inhaled corticosteroids.

To date, no studies have evaluated LT-receptor antagonists and LT-synthesis inhibitors in the treatment of children with bronchial asthma. Results from trials in adults, however, suggest that these drugs should also be considered for children. Pranlukast, an oral cysteinyl LT-receptor antagonist, is well tolerated and effective in the treatment of adult patients with asthma,[44] and is being used for children with asthma in Japanese studies. Sampson et al.[45] showed a persistent increase in plasma LTB_4 and urinary LTE_4, metabolites of cysteinyl LTs, after acute asthma in children, and suggested that 5-lipoxygenase inhibition, which inhibits both LTB_4 and cysteinyl LTs, should be considered for the treatment of bronchial asthma.

6. Complications of Eicosanoid-Related Drugs

In ductus-dependent CHDs, apnoea and cardiovascular complications, including hypotension, are more common during infusion of alprostadil than during low dose treatment with oral dinoprostone, but diarrhoea and elevated temperatures are much less common.[9] Such complications as cortical hyperostosis and gastric-outlet obstruction have been described after long term treatment with alprostadil infusions.[46,47] These changes in bone and gastric mucosa can persist for months after alprostadil has been discontinued.

Recently, low dose alprostadil treatment and lipo-PGE_1 therapy, which require less alprostadil, have been employed to inhibit the complications of alprostadil;[12,13] indeed, these treatments did reduce complications. Hypotension is the most significant adverse effect of epoprostenol infusion in the treatment of PPH, although it is a rare complication if the drug has been prepared for oral administration.[18] The effects of lipo-PGI_2 and aerosolised PGI_2 on inhibiting such a complication have also been examined,[18,21] and the results showed inhibition of hypotension. Oral administration of misoprostol, a PGE_1 analogue, can cause diarrhoea as an adverse effect, but this is not common.[24]

Reversible adverse effects, such as gastrointestinal symptoms, liver dysfunction and exanthema, have been observed as complications of LT synthesis inhibitors and receptor antagonists in adult patients.[8] It is not clear whether these complications are unique to a particular chemical entity or are due to inhibition of LT actions, inhibition of their synthesis, or both. Children with bronchial asthma need to be studied to determine whether complications arising from using LT synthesis inhibitors and

receptor antagonists correlate with duration of treatment.

7. New Modulators of Eicosanoid Biosynthesis

7.1 Eicosapentaenoic Acid

Eicosanoids derived from arachidonic acid exhibit pathophysiological actions such as inflammation, allergy, platelet agglutination and vasoconstriction.[1] In contrast, eicosanoids derived from eicosapentaenoic acid (EPA), an n-3 polyunsaturated fatty acid (PUFA), show little such action, and compete with the actions of the arachidonic acid–derived eicosanoids by exhibiting anti-inflammatory and antiallergic actions.

In recent years, EPA has become the focus of many studies and is now finding clinical use in the treatment of various pathological conditions, such as inflammation and allergy in adult patients.[48,49] In Japan, EPA has proved to be beneficial for the treatment of peripheral vascular diseases and hyperlipidaemia in adults. Although there are very few studies of the effects of EPA and other n-3 PUFAs in the paediatric clinical field,[50,51] these compounds may be used to treat inflammatory and allergic diseases in children as a supportive therapy in the near future.

7.2 Antiallergic Drugs

Some antiallergic drugs inhibit the release of chemical mediators, including eicosanoids, from mast cells and other inflammatory cells, and block their effects on target organs.

Eliakim et al.[52] have recently shown that orally administered ketotifen, an antiallergic drug, effectively prevents mucosal damage in experimental colitis by significantly reducing the mucosal generation of eicosanoids. They have also shown that ketotifen inhibits the accumulation of colonic eicosanoids in patients with active ulcerative colitis.[53]

Since antiallergic drugs are relatively well tolerated, a long trial may show them to be effective in preventing relapsing, chronic inflammatory and allergic diseases in paediatric patients.

8. Conclusions

Although it can be difficult to apply to children, especially neonates, newly developed drugs produced for adult patients can sometimes be more efficacious in treating paediatric patients than they are in adults. Alprostadil and dinoprostone are prime examples of drugs that were developed for adults, and are now considered to be essential in the treatment of neonates with ductus-dependent CHDs and PPH. Studies focused on ways to inhibit adverse reactions and to increase the efficacy and tolerability of PG may permit their long term use.

COX-2–selective inhibitors may prove to be potent and well tolerated anti-inflammatory agents in children. Oral cysteinyl LT-receptor antagonists (e.g. pranlukast and others in its class) are some of the most promising drugs for the prophylaxis and treatment of paediatric bronchial asthma. Other paediatric diseases, including neonatal respiratory distress syndrome, chronic lung diseases and inflammatory bowel diseases, whose pathophysiologies may be associated with overproduction of TXA_2 and LTs, will also be addressed during the clinical trials of more potent and specific synthetic inhibitors and receptor antagonists of TXA_2 and LTs.

Realising the potential of eicosanoids in paediatric practice will depend on further evaluations of the pathophysiology related to eicosanoid biosynthesis, and the clinical efficacy and complications of eicosanoid-related drugs in paediatric diseases.

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