Clinical Applications of Prostaglandins and Their Inhibitors

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GIVEN THE POTENTIAL for manipulating the synthesis and activity of one or more prostaglandins, it is important to determine the role of prostaglandins in the pathophysiology and treatment of a number of vascular disorders. The following are a few examples of disorders in which this manipulation may be useful.

Migraine Headaches

One appealing reason for implicating prostaglandins in the pathogenesis of migraine headaches is the ability of one or another of these vasoactive substances to produce constriction or relaxation of cerebral blood vessels, events which are associated, respectively, with the aura and headaches of migraine. Prostaglandins may also be implicated because they reportedly potentiate the effects of bradykinin and other forms of chemically induced pain (perhaps by sensitizing the peripheral pain receptors). Moreover, they are important mediators of the inflammatory response (edema, erythema, tissue damage) and are capable of modulating the release of neurotransmitters from nerve terminals. Unfortunately, only limited data are available to support the existence of these relationships. Available evidence comes from two types of studies: 1) those which examine the effects of prostaglandin administration on cerebral blood flow or on inducing clinical symptoms and signs in man and experimental animals, and 2) studies which examine the ability of prostaglandin inhibitors to alter the frequency and severity of migraine headaches. However, the fact that a particular drug inhibits (or enhances) prostaglandin synthesis and ameliorates (or exacerbates) headache in no sense proves that prostaglandins are involved at some point in the pathway from stimulus to pathological process. What it does suggest though is that prostaglandins are involved at some point in the pathway from stimulus to pathological response.

It has been shown that venous infusion of PGE₁ induces flushing and headache with nausea and vomiting in man. In monkeys PGE₁ increased flow in both the internal and external carotid artery when infused into the common carotid artery. At higher concentrations, however, flow increased sufficiently in the external system to decrease flow in the internal carotid. When inhaled by humans, PGI₂ produced sensations of lightheadedness and "pulsations in the head" which rapidly disappeared 10 to 15 minutes after discontinuing the drug. Severe headache, reported following PGE₁ infusion, was not experienced by these subjects nor by subjects infused with PGI₂ to treat arteriosclerosis obliterans.

Perhaps more compelling were observations that prostaglandin inhibitors were as effective as, or better than ergotamine in decreasing the intensity and shortening the duration of migraine attacks. They also were tolerated better than ergotamine, produced fewer side-effects such as nausea, vomiting, and abdominal pain, and were effective in cases refractory to more traditional pharmacological treatments. Their ability to abort the headache phase of migraine, however, has not been studied or commented upon.

The most striking therapeutic responses have been reported in chronic paroxysmal hemicrania, a disabling unilateral headache syndrome resembling cluster headache except for the absence of headache-free intervals and the preponderance of daytime episodes in women. In nearly every instance treatment with indomethacin or aspirin provided dramatic relief. Prostaglandin inhibitors have also been useful in the treatment of headaches associated with menstrual periods (a time in the fertility cycle which seems to be associated with significantly increased synthesis of prostaglandins). Recent reports also noted the value of cyclooxygenase inhibitors in treating certain cases of ophthalmoplegic migraine or migraine associated with increased platelet aggregability. Some of these platelet abnormalities developed while women were taking oral contraceptives, but others apparently developed de novo. It is interesting to speculate on the possible changes in thromboxane and prostacyclin activity in these subjects. It remains to be proven, however, that there is a quantitative relationship between the severity of occurrence of a headache episode and the platelet disorder. Evidence suggests that there is none; nevertheless, increased platelet aggregability defines an important subgroup of migraine patients. It may also provide a significant link between migraine and the increased incidence of
stroke. Additional data will be needed to clarify this point.

The association of ipsilateral cluster headache, hemicrania, and other head pains which follow carotid endarterectomy or head trauma is interesting in view of the relation between trauma and prostaglandin biosynthesis. The use of corticosteroids to treat some of these vascular headaches may relate to the ability of these drugs to block deacylation of phospholipids and decrease the availability of arachidonic acid. Additional experiments are warranted to clarify the role of prostaglandins in the pathogenesis of migraine headache.

**Prostaglandins, Stroke, and Thromboembolic Disease**

In the first part of this review, the vasoactive nature of most prostaglandins was discussed. PGI₂, PGE₂, and PGD₂, the major prostaglandins in brain, can relax brain blood vessels when added in relatively small amounts in vitro (PGE₂α and TXA₂ are potent vasoconstrictors). As noted above, large and small cerebral vessels form the same prostaglandins as blood vessels from other organs. Therefore, it is not surprising that drug treatments which affect prostaglandin synthesis may also modify cerebral blood flow and reactivity. However, experimental results with prostaglandin inhibitors are conflicting and difficult to interpret. In one animal study administration of large indomethacin doses reduced resting cerebral blood flow, increased vascular resistance, and attenuated the vasodilator response to carbon dioxide inhalation. In another, indomethacin in somewhat lower doses did not affect basal flow rates or carbon dioxide responsiveness but did blunt the vasodilating response to topical arachidonic acid application. Some of these indomethacin effects have not been observed in other reported experiments. One study showed that indomethacin blocked the hyperemic response induced by occlusion of both carotid arteries in the cat.

Many of these seemingly contradictory results may be due to one or another opposing biological activities of prostaglandins, and the resultant pharmacological response in each case would then depend on the route of administration, the potency and duration of drug action, the particular prostaglandins involved, and the chosen vascular bed. These possibilities may be further modified by indomethacin's ability to block prostaglandin synthesis in parenchymal cells such as neurons and glia, an action which potentially could alter blood flow and vascular reactivity. New drugs need to be developed which can act on selected populations of cells and at specific sites in the biosynthesis of or receptor activation by the various prostaglandins.

Reductions in cerebral blood flow after stroke and trauma may also cause alterations in brain fatty acid metabolism, further modifying blood vessel tone and reactivity. After three minutes of ischemia, brain levels of free arachidonic acid were found to increase dramatically. During this period prostaglandin levels did not change (prostaglandin synthesis is oxygen dependent). After reperfusion by releasing the carotid ligatures, brain levels of all prostaglandins showed marked increases. These increases may be important in the pathogenesis of the no-reflow phenomenon. Intravenous infusion of indomethacin before the induction of ischemia eliminated areas of diminished flow after restoring the circulation. The ability to limit no-reflow was also observed after combined treatment with indomethacin and PGI₂. On the basis of these and other observations, it has been suggested that a constituent of blood (and brain), perhaps TXA₂, contributes to the no-reflow phenomenon. Changes in levels of prostaglandins and their metabolites were also reported in both hemispheres of gerbil brains after unilateral carotid ligation and after brain trauma.

There are few studies of arachidonic acid metabolism in humans after strokes. Stroke and trauma may be accompanied by significant alterations in cerebrospinal fluid levels of the various prostaglandins according to recent reports. In one preliminary study infusion of aspirin did not appear to alter cerebral blood flow. Use of prostaglandin synthesis inhibitors, such as aspirin or other nonspecific anti-inflammatory agents, in the prophylaxis and management of cerebrovascular disorders has been the topic of several excellent reports and will not be discussed here. It is important to emphasize, however, that one important rationale for using aspirin and related anti-inflammatory agents is their ability to inhibit the aggregation of platelets and thereby reduce the tendency for thromboembolic phenomena in vessels supplying the brain and heart.

**Prostaglandins and Vasospasm Complicating Subarachnoid Hemorrhage**

Prostaglandins and related compounds (especially TXA₂, PGE₂α, and endoperoxides) have been implicated in the pathogenesis of vasospasm following subarachnoid hemorrhage. Evidence to support such a relationship derives mostly from observations in experimental models. Thus, the intracisternal administration of prostaglandins and their metabolites (among other compounds) produced vasospasm in large meningeal blood vessels. Pretreatment with long-acting nonspecific anti-inflammatory agents (presumably to inhibit the cyclooxygenase enzyme) reduced the incidence of spasm and blocked its behavioral consequences.

One hypothesis relates the development of spasm to defective synthesis of PGI₂ by cerebral blood vessels. According to this formulation the absence of such a potent dilator potentiates the constricting effects of one or more of the many vasoactive constituents present.
ent in CSF following subarachnoid hemorrhage. In one study PGF_{2\alpha} administration reversed the spasm of baboon intracranial arteries induced by CSF from such an affected patient.\textsuperscript{23} Studies in humans indicate that levels of prostaglandins or their metabolites are elevated in cerebrospinal fluid.

In the final analysis, it may be difficult to distinguish which of the many constituents, either alone or in combination, produces vasospasm after subarachnoid hemorrhage. Nevertheless, there are sufficient reasons to determine the usefulness of PGF_{2\alpha} and prostaglandin inhibitors in the treatment of vasospasm complicating subarachnoid hemorrhage.

Promising Uses for the Prostaglandins
In Disorders of Blood Vessels

Exogenously administered prostacyclin is now being tried in man and experimental animals to limit some clotting abnormalities induced by platelets interacting with artificial surfaces. For example, recent reports comment on the utility of administering PGF_{2\alpha} during extracorporeal circulation.\textsuperscript{30,31} Indeed, PGF_{2\alpha} infusion limited the degree of thromboxanea and microembolization complicating hemodialysis, charcoal hemoperfusion, cardiopulmonary bypass, and extracorporeal membrane oxygenation. It significantly reduced the need for adding an anticoagulant like heparin and thereby minimized risks of serious bleeding and osteoporosis. Theoretically, PGF_{2\alpha} should also reduce the frequency of clotting complications associated with implanting synthetic heart valves or blood vessels. It should also be useful in endarterectomies, at least until the luminal surfaces have become re-endothelialized.

Infusions of PGF_{2\alpha} (like PGE_{1}) appear to promote healing and reduce the pain of ischemic leg ulcers associated with severe peripheral vascular disease.\textsuperscript{32} PGF_{2\alpha} also reportedly improves muscle blood flow for at least six weeks after a single infusion. The drug may act by limiting platelet aggregation and deposition. It is also possible that PGF_{2\alpha}, like PGE_{1}, prevents release of degradative enzymes such as lysosomal proteases and phospholipases, acts as an anti-inflammatory agent in these tissues, directly promotes epidermal growth, and/or relaxes vascular smooth muscle. Additional experiments are needed to clarify the mechanism of action of PGF_{2\alpha} in this disorder.

Impaired PGF_{2\alpha} production has been reported in human and experimental models of atherosclerosis. Vessels with fatty streaking, fibrous intimal thickening, or complicated lesions exhibited a 25 to 40% reduction in their ability to form prostacyclin in vitro.\textsuperscript{32} Reduced PGF_{2\alpha} activity has also been found in atheromatous plaques removed from the carotid artery during endarterectomy. This finding may partly explain the increased incidence of thromboembolic complications in patients with arteriosclerotic blood vessels. Reduced prostacyclin formation has also been demonstrated in blood vessels from diabetic patients. Deficient PGF_{2\alpha} formation may account for the increased platelet adhesiveness reported in diabetic patients. Platelets from these subjects appear more susceptible to the aggregating effects of arachidonic acid and exhibit a greater capacity to form prostaglandins than matched controls.\textsuperscript{33}

These bits of evidence support the notion that diabetes and atherosclerosis are accompanied by an imbalance between TXA_{2} and PGI_{2}, the net effect of which is to favor aggregation and deposition of platelets on the surface of endothelial cells. Such an imbalance may contribute to the pathogenesis of thrombosis in these patients. One approach to treating patients with one or both of these diseases, then, would be to restore a more normal balance between the two derivatives of arachidonic acids. If this postulate is true, then PGF_{2\alpha} (or stable PGF_{2\alpha} analogues) or TXA_{2} inhibitors should be of value.

PGF_{2\alpha} may also be useful in managing transient ischemic attacks and treating strokes in evolution. Similarly, it could be used to limit progression of unstable or crescento angina and help prevent coronary occlusion in high-risk populations. Indeed, in one study PGF_{2\alpha} prevented or rapidly reversed blockage of a partially obstructed coronary blood vessel in the dog.\textsuperscript{34}

A distinct advantage of PGF_{2\alpha} over other forms of therapy is its relatively low toxic-therapeutic ratio.\textsuperscript{33} It can be administered to man or experimental animals in small doses sufficient to produce measurable effects on platelet function but with relatively few side-effects (including tachycardia, flushing, mild headache, and, in some instances, restlessness, mild drowsiness, hypotension, and abdominal cramping). PGF_{2\alpha} infusion was tolerated better than infusion of PGE_{1}. However, in animal toxicological studies severe hypothermia developed as a complication of extreme peripheral vasodilation. This side-effect has not been reported with therapeutic doses in man. If other side-effects of PGF_{2\alpha} did occur, they were all short lived and rapidly reversible. Most importantly, there were no dangerous abnormalities of clotting or vessel integrity accompanying its use. Severe hypotension can of course produce cardiovascular complications; these have been observed with PGF_{2\alpha}, as well as with other hypotensive agents. (Neuropathological changes were not observed at the light microscopic level, and the EEG reportedly remained unchanged during treatment.) Tachycardia and lowered blood pressure can limit the usefulness of PGF_{2\alpha}, particularly in patients with evolving disorders of coronary and cerebral blood flow. Therefore, it may be necessary to develop prostaglandin-like compounds which disaggregate platelets but do not affect smooth muscle, and vice versa. Of course, hypotension may not always be considered an unwanted side-effect since prostacyclin may one day be administered to treat malignant hypertension.

Another approach to treatment of disorders characterized by enhanced platelet aggregation is to administer drugs which are selective inhibitors of thromboxane synthesis. As mentioned above, this inhibitory action was one reason aspirin was chosen for clinical trials in the prophylaxis and treatment of myocardial infarction. There is a great need for selec-
tive inhibitors of TxA2 synthesis that are nontoxic to humans. This remains an active area of research investigation.

The hemolytic uremic syndrome and thrombotic thrombocytopenic purpura (TTP) are two related disorders characterized by deposition of platelet thrombi in the microcirculation of the kidneys and sometimes the brain. These thrombi appear to develop as a result of increased aggregation of platelets, perhaps due to defective PGI2 biosynthesis. Serum levels of 6-keto PGF1α were reportedly lower than control values in one series of patients with TTP. Administration of normal plasma markedly improved this clinical condition and was thought to supply a missing factor(s) required for stimulating endogenous synthesis of PGI2. Presumably, treatment with either PGI2 or inhibitors of thromboxane synthetase should also improve this condition (PGI2 infusion did not increase the platelet count in one small series of patients with TTP).

One interesting and useful application of prostaglandins and their synthetic inhibitors is to manage patent ductus arteriosus and various forms of congenital heart disease. Blood normally flows through the ductus from the pulmonary artery to the descending aorta in utero, thereby bypassing the lungs; locally synthesized prostaglandins, PGI2, and PGF2α, reportedly participate in maintaining the patency of this duct. At birth the ductus undergoes constriction and permanent closure via oxygen-dependent mechanisms. In premature infants the duct often does not close at birth, and significant shunting occurs from the pulmonic to systemic circulation, particularly in infants with the respiratory distress syndrome. When shunting appears to compromise further respiratory function, the ductus can be closed by infusing indomethacin. Approximately 50% of infants so treated respond with closure; the remaining show some improvement and close spontaneously at a later time or require surgical ligation. When patency of the ductus persists because of ductal muscle hypoplasia or other structural defects, administration of indomethacin is not effective. In some instances the patency of the ductus may be essential for the flow of systemic blood to the pulmonary circulation (e.g., in tricuspid, aortic, and pulmonary atresia). The infusion of PGE2 or PGI2 reverses the constriction and improves the flow of blood through the pulmonary circulation until definitive surgery can be performed under more stable conditions.

Another use for the dilating prostaglandins is in managing congenital disorders of the aorta, such as aortic atresia or coarctation, where closure of the ductus would severely compromise blood flow to the systemic circulation. Under these circumstances infusions of PGE2 or PGI2 significantly improve pressure in the descending aorta and reduce the gradient between the pulmonary artery and descending aorta.

Prostaglandin infusion may also become a useful adjunct for maintaining the patency of recently anastomosed blood vessels (e.g., superficial temporal artery to the middle cerebral artery or after anastomosis of other vessels in the heart or large tributaries of the aorta). It has already been used successfully for dilating blood vessels to improve the diagnostic quality of various angiographic procedures. Longer-acting agents may prove useful for maintaining the patency of arteriovenous shunts.

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