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 the specific locus of the 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 vomit-
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 are 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. PG12, PGE1, and PGD2, the major prostaglandins in brain, can relax brain blood vessels when added in relatively small amounts in vitro (PGF2α 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, PGE1, 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 cyclo-oxygenase 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 pres-
ent in CSF following subarachnoid hemorrhage. In one study PGI₄ administration reversed the spasm of baboon intracranial arteries induced by CSF from such an affected patient. 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 PGI₄ 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 PGI₄ during extracorporeal circulation. Indeed, PGI₄ infusion limited the degree of thrombocytopenia 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, PGI₄ 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 PGI₄ (like PGE₂) appear to promote healing and reduce the pain of ischemic leg ulcers associated with severe peripheral vascular disease. PGI₄ 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 PGI₄, like PGE₂, 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 PGI₄ in this disorder.

Impaired PGI₄ 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. Reduced PGI₄ 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 PGI₄ 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.

These bits of evidence support the notion that diabetes and atherosclerosis are accompanied by an imbalance between TXA₂ and PGI₄, 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 PGI₄ (or stable PGI₄ analogues) or TXA₂ inhibitors should be of value.

PGI₄ 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 crescendo angina and help prevent coronary occlusion in high-risk populations. Indeed, in one study PGI₄ prevented or rapidly reversed blockage of a partially obstructed coronary blood vessel in the dog.

A distinct advantage of PGI₄ over other forms of therapy is its relatively low toxic-therapeutic ratio. 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). PGI₄ infusion was tolerated better than infusion of PGE₂. 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 PGI₄ 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 PGI₄, 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 PGI₄, 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 TxAg synthesis that are nontoxic to humans. This remains an active area of research inves-
igation.

The hemolytic uremic syndrome and thrombotic thrombocytopenic purpura (TTP) are two related dis-
orders 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 PGII biosynthesis. Serum levels of 6-keto PGF\(_\alpha\) 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) re-
quired for stimulating endogenous synthesis of PGII. Presumably, treatment with either PGII or inhibitors of thromboxane synthetase should also improve this condition (PGII infusion did not increase the platelet count in one small series of patients with TTP).

One interesting and useful application of prostaglan-
dins and their synthetic inhibitors is to manage patent ductus arteriosus and various forms of congeni-
tal 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, PGII, and PGE\(_2\), 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 30% 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 PGE\(_2\) or PGII 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 PGE\(_2\) or PGII significantly improve pressure in the descending aorta and reduce the gradient between the pulmonary artery and descend-
ing 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 pro-
cedures. Longer-acting agents may prove useful for maintaining the patency of arteriovenous shunts.

Acknowledgment

Some of the work described in this report was supported by grant #25368 from the NHLBI. Dr. Moskowitz is an Established Investigator of the American Heart Association. Dr. Coughlin is supported by the Insurance Medical Scientist Scholarship Fund.

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Clinical applications of prostaglandins and their inhibitors.
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doi: 10.1161/01.STR.12.6.882

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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