Platelet and Antiplatelet Agents in Strokes

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STrokes caused by thromboembolic occlusive events may involve the platelet in several ways: (1) production of platelet-fibrin thrombi, (2) containment of bleeding into the area of ischemia, and (3) participation in atheromatous formation. One accepted pathogenesis for small recurrent strokes (transient ischemic attacks or TIAs) is recurrent embolization of platelet-fibrin thrombi or atheromatous material from extracranial atheroma. Therefore, drugs which inhibit platelet participation in thrombus or atheromatous formation might help prevent strokes, provided that bleeding distal to an occlusion is minimal, that hemostasis can be achieved by alternative mechanisms, and that antiplatelet agents (APAs) selectively allow platelets to promote hemostasis while impairing other platelet activities. Full understanding of the use of these drugs in patients with cerebrovascular accidents requires knowledge about the role of platelets in hemostasis, thrombosis, and atherogenesis; the relationships of specific biochemical events in the platelet-to-platelet function; and empirical observations about the use of so-called APAs.

Role of Platelets in Hemostasis and Thrombosis

Diseases mediated by arterial thrombosis are the leading causes of death and disability in man. The bulk of an arterial thrombus is a fibrin latticework enmeshing leukocytes and red cells. However, the obligate bridge between the bulk of the thrombus and the altered endothelium or nonbiological surface is the platelet. It is very unusual for components of the blood to initiate thrombosis unless the surface over which the blood flows is biochemically or physically altered and/or flow patterns are abnormal. Hence, platelet participation in strokes is a reactive process. Platelets respond to a variety of stimuli by changing shape, adhering to abnormal surfaces or to each other, and secreting a variety of materials in the "release reaction." When the platelet is sufficiently stimulated, there is an explosive movement of intracellular granules to the center of the platelet followed by degranulation and secretion of the granules into an intricate canalicular system that is in direct continuity with the plasma. Adenosine diphosphate (ADP), epinephrine, and collagen cause the platelet to release a number of constituents, including nonmetabolizable adenosine triphosphate (ATP) and ADP, serotonin, calcium, and platelet factor 4. Thrombin is a stronger agonist which can release additional constituents such as fibrinogen and lysosomal hydrolytic enzymes. Other materials may be secreted from the cytoplasm independent of the drastic changes in platelet structure. For example, arachidonic acid derivatives may leave the platelet to be biochemically altered by vessel endothelium.

There is general agreement that in vivo platelet function is optimal only when platelets can undergo a release reaction, although the biochemical mediators and the clinical difference between the consequences of the different types of release are not known. Released ADP can potentiate the initial stimulus and recruit more platelets. Concomitant structural alterations of the platelet can influence the coagulation factors to produce thrombin more efficiently and, ultimately, fibrin.

Platelets and the Vessel Wall

At present, we cannot distinguish between the platelet's response to a severed blood vessel and the response to an altered but continuous vessel wall. In this sense we assume that the platelet reactions to promote hemostasis and thrombosis are the same. In acute events occurring within seconds to minutes, platelets can change blood flow patterns by becoming physical aggregates partially or completely occluding blood flow, by releasing a variety of vasoactive materials, or by promoting fibrin formation. The latter two are the more important events.

The effects of platelets and their release reaction have been studied most thoroughly in the pulmonary circulation where the induction of release produces a rise in pulmonary vascular resistance and an increase in physiological shunting. Blood in the cisterna magna causes cerebral arterial vasospasm unless the platelets have been depleted of vasoactive amines. Recently, much more potent vasoactive materials derived from platelets have been described. Thromboxane A2 causes vasospasm and induces the release reaction, prostaglandin I2 has the opposite effect, and both are derived from arachidonic acid. Platelets may induce immediate vessel wall changes, although the exact biochemical nature and the consequences of these effects are not known. A deficiency of platelets can produce gaps between endothelial cells and allow...
Intracellular Events in Platelets

The physical events of platelet adhesion, aggregation, and shape change and the biochemical events of release are mediated, in part, by all three "second messenger" groups: the cyclic nucleotides, the divalent cations, and the prostaglandins and their intermediates. The exact interrelationships among these messengers are still under intensive investigation.

Most, if not all, of the biochemical inducers of the release reaction affect specific membrane receptors which modify the platelet pools of one or more of the "second messengers," each of which may then modify the others. Depression of membrane adenylate cyclase may diminish c-AMP pools which, in turn, may modify prostaglandin production because of diminished phosphorylation of proteins or other mechanisms. Alternatively, many of the inducers may activate specific membrane lipases, releasing arachidonate ions into the cytoplasm where enzymatic conversion by one of several parallel pathways will produce physiologically active derivatives, such as thromboxanes A2 and B2 and prostaglandins D, E2, F2a, G, H, and the precursor to I2. These modified arachidonate molecules may have numerous effects on the state of the thrombasthenin molecule, on membrane adenylate cyclase activity, and/or on the distribution of intracellular calcium.

Cell-Cell Interactions Involving the Platelet

Platelets exist among erythrocytes and leukocytes which have more inertia. Consequently, while erythrocytes flow in the middle of the bloodstream and avoid the endothelial wall, platelets are constantly bouncing between the endothelium and the heavier blood cells. The cells may interact in many ways. For example, red cells can leak small portions of their vast stores of ADP; leukocytes contain proteases or produce peroxides that can modify the platelet; and endothelial cells can change intermediates of prostaglandin synthesis produced in the platelet from vasoconstrictor to vasodilator compounds. These cell-cell interactions, as well as differences between release of stored cytoplasmic constituents and differences between acute and chronic changes induced by the platelet in the vessel wall, may explain why drugs which have definable pharmacological effects on platelets and which should produce a desired biological effect must be empirically evaluated.

Platelets and Transient Ischemic Attacks

Several studies have shown that platelets are abnormal in people who have had TIAs. Enhanced reactivity has been demonstrated in vitro and in vivo, using measurements of platelet retention, circulating platelet aggregates, platelet coagulant activity, platelet aggregating agents, and platelet turnover studies. Abnormally high platelet counts are also associated with strokes (and bleeding in general), but with strokes this finding is unusual.

Antiplatelet Agents

Several drugs given for other illnesses may also affect platelet function, but they are not usually considered APAs. These include carbencillin, clofibrate, heparin, hydroxychloroquine, propranolol, and chlorpromazine. The more generally recognized APAs include nonsteroidal anti-inflammatory drugs such as aspirin, profen derivatives, tolmetin, and indomethacin, all of which are believed to inhibit the cyclo-oxygenase enzyme in platelets, preventing synthesis of prostaglandins, endoperoxides, and thromboxanes. Sulfinpyrazone may be a competitive inhibitor of this same enzyme, or alternatively, this drug's mechanism of action may be due to stabilization of the erythrocyte membrane, preventing a leak of ADP. Dipyridamole prevents degradation of c-AMP by inhibiting one of the platelet phosphodiesterases.

While continued efforts are being made to define the biochemical reactions that are modified by APAs, large multicenter trials are taking place with some of these drugs to demonstrate modification of diseases potentially mediated by thrombosis, e.g., atherosclerosis, TIAs, and coronary artery disease. These drugs pose unusual dilemmas to physicians. Use of one of them — aspirin — is so prevalent that if an effect in preventing TIAs is shown, there will always be a question as to whether a properly controlled trial was done. If atherosclerosis is to be prevented by APAs, these drugs will have to be taken chronically for many years. How does one evaluate the efficacy of these drugs? APAs may not have a very dramatic effect on the incidence of TIAs; however, these drugs are relatively free of side effects (although we must not forget the lesson learned from "phenacetin nephritis").

Therapy

In September, 1977, the Canadian Trial comparing aspirin, sulfinpyrazone and aspirin, and a placebo for prevention of recurrent TIAs was terminated. Aspirin taken twice a day was shown to protect individuals, especially males, from recurrences and infarctions. Three recent, extensive reviews,*+ one limited to the modification of cerebral ischemic disease by drugs,^ discussed previous trials in detail and reached the conclusion that at present no definitive recommendations could be made. In contrast to aspirin, dipyridamole or clofibrate alone produces no beneficial effects in patients with TIAs.

Because vasoactive and platelet-active materials
can pass between aspirin-affected and aspirin-nonaffected cells to recruit all platelets, it may be advisable to take aspirin twice a day. “Complicated migraines” may also be responsive to APAs although the data are not complete. There is no evidence to suggest that stroke-in-evolution, completed strokes, or atherosclerosis itself should be treated with antiplatelet drugs, except perhaps when stroke-in-evolution is associated with repeated embolization of platelet material.

References