PLATELETS AND VASCULAR OCCLUSION

Therapeutic opportunities in vasoocclusive disease


ABSTRACT  There is evidence that aspirin is partially effective in the prophylaxis of various vasoocclusive disorders. This article reviews pharmacologic opportunities for improvement over and above the therapeutic effect of aspirin. It is concluded that several rational possibilities merit consideration, in particular, the use of combinations of drugs that affect the thrombotic process at different points. Such strategies will ultimately require validation by clinical trial.


VASCULAR OCCLUSIONS, especially in the arterial circulation, are the principal source of mortality and morbidity in Western society. Occasionally the cause is a generalized disease process that affects blood flow (e.g., hyperviscosity states such as macroglobulinemia or polycythemia) or blood vessel walls (e.g., giant cell arteritis or syphilitic vasculitis). Such diseases offer specific points of therapeutic attack. Recently the pathophysiology of hypercoagulable states associated with protein C deficiency, antithrombin III deficiency, and the lupus anticoagulant have been elucidated.1-3 Such insights provide new therapeutic approaches to these disorders and no doubt further instances of such specific entities will be discovered in the future. However, overwhelmingly the most common pathology in the arterial circulation is the atheromatous plaque and related thrombosis.

Atheromatous plaques are very common, but they are usually clinically undetectable. Risk factors for their development, such as cigarette smoking, raised blood pressure, or abnormal blood lipids can be determined by screening an asymptomatic population. Drug treatment aimed at these etiologically significant conditions in high-risk groups may reduce the risk of overt vascular disease (see Dollery and Bulpitt4 and Oliver5 for reviews). However, some studies have recorded negative results, for example the multiple risk factor intervention trial,6 and at present treatment is of proven benefit only in very high-risk groups. The majority of vascular catastrophes occur in individuals who do not fall into such groups.7 It may be possible to improve this situation if new risk factors are identified. In particular, components of the coagulation pathway (factors VIIc, VIIIc, and fibrinogen) may prove to be powerful predictors of cardiovascular death.8 However, it is likely that effective primary prevention will depend either on treating everyone or on developing detection techniques that are sufficiently noninvasive and cheap to be used in screening large asymptomatic populations. Such techniques could in principle be either structural or biochemical. However, structural techniques such as Doppler ultrasound are likely to be too time-consuming and expensive for mass screening.

The recent finding of raised levels of the urinary metabolite of prostacyclin in patients with severe atheromatous disease9 suggests that a biochemical approach to detecting the extent of atheroma is not impossible, although other markers of arterial damage may prove to be more sensitive. Whether some such method would be worthwhile as a screening technique will depend on its ability to identify a subgroup at particular risk and to follow changes in response to a therapeutic measure. Some interventions (such as stopping smoking) are so clearly advantageous that there is no need to restrict them to a population at particular risk. Some dietary measures (such as avoidance of gross excesses of fats and cholesterol) probably fall into the same category, whereas others (e.g., increased consumption of food rich in eicosapentaenoic acid) are more contentious, and certainly require further study. This is also true of most drugs that might be used in the primary prevention of atheromatous disease.

This article concentrates on possibilities for drug therapy, and particularly on drugs acting on the eicosanoid cascade that may modify platelet/vessel wall interactions. The platelet is an attractive target for pharmacologic attack, first because of its role in thrombosis. The probable efficacy of aspirin in the secondary prevention of myocardial infarction10 and of
stroke and death in patients experiencing transient ischemic attacks is encouraging in this context. Second, platelets are also implicated, albeit indirectly, in the development of the atheromatous plaques themselves. Thus, experimental intimal proliferative lesions in rabbits do not occur in thrombocytopenic animals. Pigs with von Willebrand’s disease in which platelets fail to adhere to the subendothelium develop fewer atheromatous lesions than do control pigs both on normal and high-cholesterol diets. It has been suggested that platelet-derived growth factor may be the stimulus to the smooth muscle cell proliferation that is central to the development of atheroma, although the evidence for this is limited to observations on cultured cells. Whether or not platelet-derived growth factor proves to be an important link between platelets and atheromatous plaques, antiplatelet drugs can influence atheroma formation, at least experimentally: proliferative arterial lesions caused by homocystine infusions in baboons were prevented by dipyridamole.

New therapeutic avenues may arise from the application of new drugs or from more rational use of existing ones. Antiplatelet drugs offer opportunities of both kinds. Their value in secondary prevention must be judged against existing therapies (aspirin, anticoagulants, β-blockers), in terms of efficacy, adverse reactions, and cost. In the case of primary prevention, controlled studies will be needed, such as the study of aspirin in British doctors in progress under the direction of Sir Richard Doll. Antiplatelet drugs include the following categories: (1) cyclooxygenase inhibitors, (2) thromboxane synthase inhibitors, (3) thromboxane receptor antagonists, (4) antiaggregatory prostaglandin (PG) agonists, and (5) platelet phosphodiesterase inhibitors. What prospects do these drugs offer for a greater effect on valvular disease than that on aspirin?

**Cyclooxygenase inhibitors.** Can the value of aspirin therapy be improved by the use of low doses (20 to 40 mg/day)? Conventional doses of aspirin may inhibit both platelet (proaggregatory) and vascular (antiaggregatory) prostanoids, posing an “aspirin dilemma.” Low doses are more selective, at least in healthy subjects. The use of such drugs should have advantages in reducing adverse effects. Whether it will also increase efficacy has been challenged. We agree with Patrono that this question can only be answered by clinical investigation rather than by philosophical discourse, while acknowledging that the size (and cost) of clinical trials large enough to achieve adequate statistical power to detect effects of realistic magnitude will be considerable.

It is unlikely that other cyclooxygenase inhibitors will have greater efficacy than aspirin, but it is possible that some may be of value in specific circumstances such as renal impairment or gastric intolerance. In this context the selectivity of sulindac in sparing renal cyclooxygenase in vivo is noteworthy. This selectivity has recently been questioned. However, in patients with mild renal impairment ibuprofen caused a fall in glomerular filtration, whereas sulindac, in a dose that caused substantial inhibition of platelet thromboxane synthesis, had no effect on renal function or prostaglandin production. The combined lipoxygenase/cyclooxygenase inhibitor BW 755C does not inhibit gastric prostacyclin synthesis and is not ulcerogenic in rats at doses that do inhibit the formation of PGs in inflammatory exudate, raising the possibility of cyclooxygenase inhibitors that specifically spare the stomach.

**Thromboxane synthase inhibitors.** It was hoped that this class of drug, exemplified by dazoxiben, would be an improvement over cyclooxygenase inhibitors for two reasons. First, it would circumvent the “aspirin dilemma” referred to above, since vascular PG synthesis would be unimpaired. Since low-dose aspirin therapy achieves selective inhibition of platelets at low cost, this rationale is not so attractive as at first appeared. A second reason these drugs could be superior to cyclooxygenase inhibitors is that by diverting endoperoxide precursor from platelets to vessel wall, they might augment prostacyclin synthesis. The occurrence of such “steal” has been repeatedly demonstrated in appropriate conditions in vitro and has even been demonstrated in vivo. If, as appears likely, prostacyclin functions locally at sites of endothelial disruption where platelets are in direct apposition to subendothelium, this mechanism is of great potential importance and may well be underestimated in studies of healthy subjects. Thus, recent evidence shows that PGI synthase is present in high amounts in aortic smooth muscle as well as endothelium but with much lower amounts of PGH synthase in smooth muscle. A supply of platelet PGH to smooth muscle cells will therefore circumvent the rate-limiting step in PGI synthesis in this tissue. However, a problem with the use of thromboxane synthase inhibitors is that the endoperoxide intermediates themselves are agonists on thromboxane receptors and are therefore proaggregatory in their own right. This problem may not be insuperable, however, as discussed below.

**Thromboxane receptor antagonists.** Several drugs fall in this group, including EP 045, which does not affect thromboxane synthesis and does not contract smooth muscle while inhibiting platelet aggregation.
alone, drugs of this class may be no more effective
than low-dose aspirin, although they might be safer.
However, in the light of the above discussion, it is
clear that they have real potential for use in combina-
tion with a thromboxane synthase inhibitor. Thus, by
blocking thromboxane receptors, the proaggregatory
actions of the endoperoxides will be prevented while
permitting endoperoxide diversion and hence aug-
mented local vascular prostacyclin production.

Antiaggregatory PG agonists. PGI₂ and PGD₂ act
on different receptors on the platelet to increase intracel-
lar cyclic AMP and inhibit aggregation. There is a
real prospect that a drug acting on such a receptor
could improve on the efficacy of aspirin. Thus, there
are stimuli to platelet aggregation, notably thrombin,
that are likely to be highly relevant in the context of an
evolving thrombus and are independent of platelet
thromboxane synthesis. Aspirin is unlikely to be help-
ful when such stimuli predominate, whereas all stimuli
to aggregation are inhibited by increased intracellular
cyclic AMP. However, there are difficulties with the
use of PGI₂ or PGD₂ themselves because of their
chemical and biological instability and because of their
effects on tissues other than the platelets. These diffi-
culties may be partly surmounted by the use of stable
analogues, e.g., BW 245C, which acts on PGD₂ recep-
tors³ and inhibits platelet function in man.³⁸ However,
to date such analogues have lacked selectivity for
platelet receptors and have caused flushing and other
signs of vasodilation. A major therapeutic prospect is
the development of an agonist specific for platelet as
opposed to vascular smooth muscle receptors, al-
though desensitization, which occurs at PGI₁ recep-
tors,³⁹ might limit the usefulness of such a drug.

Platelet phosphodiesterase inhibitors. These drugs
(e.g., dipyridamole) also increase platelet cyclic
AMP, but by inhibiting its degradation rather than
stimulating its synthesis. Dipyridamole has gener-
ally been disappointing when used in conjunction with
conventional (high) dose aspirin, perhaps because in this
circumstance antiaggregatory PGs are inhibited, so
their stimulus to platelet cyclic AMP synthesis is re-
duced. In some studies dipyridamole has been reported
to potentiate PGI₂,⁴⁰ although this has not been ob-
served during short (15 to 45 min) infusions of PGI₂ in
healthy volunteers.³¹ It is therefore logical to consider
the use of a platelet phosphodiesterase inhibitor in con-
junction with a platelet-selective long-acting antiag-
gregatory PG agonist, should such a drug become
available (cf the combined use of β₂-agonist and theo-
phylline in asthma). This also offers a potential means
of circumventing the problem of desensitization al-
luded to above by enabling the agonist to be given at
greater intervals without reducing its effect on cyclic
AMP.

Conclusion. Existing antiplatelet drugs and ones that
will likely soon be available offer real possibilities for
secondary and perhaps even for primary prevention of
vasoocclusive disease. Several logical combinations
suggest themselves. In addition to those discussed,
there is also the possibility of combining drugs effective
on other components of the thrombotic process
(e.g., anticoagulants) with a platelet selective PG
agonist. This possibility is particularly attractive, both
because of the evidence that levels of coagulation fac-
tors are predictors of risk of cardiovascular mortality,⁸
and because of the evidence that anticoagulants are
effective in the secondary prevention of myocardial
infarction.⁴² Furthermore, the coagulation system and
platelet function are interdependent in several ways.
Thus, for instance, thrombin stimulates platelet aggre-
gation and platelet-derived phospholipid accelerates
several stages of the coagulation cascade. There is thus
the possibility of synergy between anticoagulant and
antiplatelet drugs. The beneficial effect of β-blockers
may well be additive with antiplatelet therapy. It is
possible that in the future such combinations will be as
common as combination therapy is today in the treat-
ment of hypertension. However, for such an approach
to be applied with precision, an intermediate end point
that is a continuous variable (rather than quantal end
points of stroke, myocardial infarction, etc.) must be
devised. It is conceivable that prostacyclin and throm-
boxane metabolites or some other biochemical reflec-
tion of atheroma and platelet activation may provide
this. If so, the time may soon be ripe for the validation
of such strategies by clinical trial. The falling inci-
dence of stroke and myocardial infarction in several
populations makes the use of concurrent controls es-
sential in such trials. The magnitude of effect that can
reasonably be hoped for will entail large numbers of
subjects studied for several years¹⁰ so such trials will
inevitably be very costly. It is therefore crucial that the
right questions are asked.⁴³

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J M Ritter and C T Dollery

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