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Antiplatelet drugs and thrombosis prevention: ticlopidine in perspective

Although already described 100 years ago[1], platelet aggregation has been extensively investigated only during the last 20 years. During the sixties the possibility was established of inhibiting platelet aggregation by drugs in current clinical use. Dipyridamole, sulphinpyrazone and aspirin were shown to prevent some of the multiple (perhaps too many) functions of platelets[2] and during the seventies numerous clinical trials were organized to assess their antithrombotic efficacy[3]. The results so far, however, are meagre. This might be due to inappropriate patient selection, to poor knowledge of the mechanism of action and clinical pharmacology of the drugs tested, to inhibition of platelet functions possibly irrelevant to thrombosis development, to all these reasons and/or others at present unknown.

The search for new compounds interfering more selectively and - it is hoped - more effectively with platelet function has been intense and fruitful. Two main groups of drugs been selected: the first includes original structures with obvious antiplatelet effects but whose mechanism of action is largely unknown; the second group includes chemicals with precise and well-documented biochemical effects but whose antiaggregating activity is less evident. Typical exemples of the two groups are ticlopidine and imidazole or pyridine derivatives, respectively.

Ticlopidine markedly prolongs the bleeding time[4-6] and the shortened platelet survival[7] and prevents the platelet aggregation induced by all stimuli tested[4-6,8], but does not interfere directly with any of the known biochemical pathways regulating platelet function (namely cyclic AMP levels and arachidonic acid metabolism)[4]. Imidazole and pyridine derivatives effectively block thromboxane-synthetase and thus prevent the formation of thromboxane A[9,10], which is considered the most powerful inducer of platelet aggregation and release reaction[2]. However, the antiaggregating effect of these compounds is somewhat dificult to show both in vitro[11,12] and after administration to normal subjects[13,14]. Yet, the bleeding time is slightly prolonged in volunteers taking an imidazole-derivative [9]. Thus ticlopidine still "lacks" a mechanism of action, and thromboxane-synthetase inhibitors a clearcut antiplatelet effect *. Both might happen to be effective antithrombotic drugs (perhaps combined?). It is against this historical and cultural background that the growing interest in ticlopidine must be viewed.

Ticlopidine differs from aspirin since it does not interfere with the (perhaps over emphasized) thromboxane/ prostacyclin "balance". No "ticlopidine dilemma" has therefore emerged analogous to the still unsolved "aspirin dilemma"[16]. Both drugs

*Prostacyclin is a potent antiaggregating compound (but also a strong vasodilator) and its mechanism of action is already known (it stimulates adenylate-cyclase, thus increasing platelet cyclic AMP levels 15). It is however highly unstable and the search is on for an analogue which can be given orally and has no hypotensive effect prolong bleeding time but the effect of ticlopidine is more marked and seems not to be sex-related[4-6]. Aspirin does not modify platelet survival[2], whereas ticlopidine does[7]. In this respect ticlopidine resembles both dipirydamole and sulphinpyrazone, neither of which, however, prolongs bleeding time[2]. As still occurs with coumarin-type oral anticoagulants, the clinician has a visceral fear of drugs affecting haemostasis. But how can a drug prevent thrombosis without carrying a potential risk of haemorrhage? (The recently described tissue-type plastinogen activator[17] might dissolve thrombi without inducing haemorrhage; this is because of its peculiar mechanism of action, namely very great affinity for fibrin-bound plasminogen and very low affinity for circulating plasminogen. To be active, therefore, plasminogen activator requires the presence of a thrombus, so it cannot be used to prevent thrombosis!). Despite its unequivocal effect on bleeding time, clinically relevant haemorrhagic complications seem not to occur in patients given ticlopidine[18,19].

As regards platelet aggregation tests, ticlopidine is unusual in its inhibitory effect on the prima-ry platelet response to ADP (the so-called first wave of aggregation) [1-6]. Only prostacy-

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clin when administered by intravenous infusion shares this property. However, the effect of ticlopidine lasts several days while that of prostacyclin is transient and disappears shortly after stopping infusion[2O].

Defective ADP-induced platelet aggregation on1y occurs "naturally" in patients with Glanzmann's thrombasthenia, a congenital functional platelet disorder[21]. Interestingly enough, ADP induces a normal "shape change" in platelets from these patients[21] and from individuals taking ticlopidine[5]. More striking is the observation that fibrinogen binding to platelet receptors is similarly impaired in Glanzmann's thrombasthenia[22] and in ticlopidine-treated platelets upon exposure to ADP[23]. Is this a clue to the mechanism of the antiaggregating action of ticlopidine? This is an attractive hypothesis in view of fibrinogen's fundamental role as cofactor of platelet aggregation induced by all physiological stimuli (with the possible exception of thrambin)[22]. Afibrinogenaemic patients have (moderately) prolonged bleeding time, impaired or absent platelet aggregation response to all inducers (with the possible exception of thrombin), but normal ADP induced platelet "shape change"[24]. This phenomenon is mediated by a platelet high affinity binding site of ADP (which is not affected by ticlopidine[5]). Binding of ADP to a low-affinity site (whose relevance for platelet function is less certain) is in contrast impaired by ticlopidine[5].

It seems therefore that ticlopidine might - to a moderate degree - induce a pharmacological form of congenital platelet dysfuction. Whether it interacts with the glycoproteins typically defective in platelet membrane of Glanzmann's patients[25], is still unknown.

Occasional reports have suggested several, often contrasting, effects of ticlopidine on platelet enzymes including adenylate-cyclase[26], phospholipases[27], thromboxane-synthetase and PGD , isomerase[28]. None of these effects however seems to[2]be implicated in the antiaggregating activity of the drug.

When administered to normal subjects or patients, ticiopidine takes 24-48 hours to produce measurable antiplatelet effect; this reaches a maximum after 3-4 days of treatment and disappears slowly after the last drug dose[4-6]. This suggests that; active metabolite(s) rather than the parent molecule may be responsible for the effects observed in vivo. Is there any clinical vidence of an antithrombotic effect of ticlopidine? Several trials are currently under way in patients with peripheral occlusive arterial disease, myocardial infarction and cerebral ischaemia and the results are awaited with much interest.

So far, an impressive antithrombic effect has been reported in uraemic patients under -going maintenance haemodialysis. Frequence of clot removal from arteriovenous shunts or vascular grafts ws significantly reduced by ticlopidine treatment (from 2.02 to 0.82 times/ patient/month) compared to the control group (from 1.43 o 1.06 tirnes/patient/month). The frequency of reconstructive surgery of vascular access also appeared reduced by ticlopidine (64% as compared to 26% in the control group)[19]. Promising results have been announced in patients with coronary artery disease: in 7 patients ticlopidine was associated with a significant reduction in the number of episodes of ECG evidence of ischaemia occurring without increase in heart rate and at night[29].

Encouraging results have also been obtain ed in patients with chronic arterial occlusive disease[30]. In a double-blind study, a greater overall improvement of elinical parameters (such as size of the ulcers, granulation and pain) was found in patients given ticlopidine (500 mg daily) than in a comparable placebo group.

As a conclusion of their pioneer studies on the effect of ticlopidine in man, O'Brien et al.[4] recalled that "the chance observation in 1933 that cattle eating spoilt sweet clover develop a bleeding tendency led to the worldwide employmen of coumarin anticoagulants to depress some aspects of blood coagulation, with a comitant decrease in the incidence of thrombosis. Ticlopidine given orally is the first drug studied that causes marked prolongation of bleeding time and it inhibits many platelet function tests. Since platelets contribute to thrombosis, it is reasonable o speculate that ticlopidine may also eventually play an important role in the control of thrombosis".

The forthcoming years will show whether this speculation can be supported by well-established clinical facts.

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