



Case Report

Preservation of Haemostasis with Anti-thrombotic Serotonin Antagonism

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Abstract

An enquiry into the lack of attention awarded to serotonin antagonism in the treatment of arterial thrombosis revealed that the mode of action of serotonin and its platelet receptor antagonists was an action upon thrombus growth, and not, as with other anti-platelet drugs upon the initiation of thrombosis. This lack of effect could explain why this approach has been considered not to be effective. However under conditions of arterial stenosis in which there is platelet activation by increased shear stress, and during the growth phase of arterial thrombi, serotonin 5HT_{2A} antagonism has been demonstrated to have great potency in dispersing thrombotic obstruction to blood flow. This mode of action, the lack of participation of serotonin in haemostasis, and the absence of serotonin in wounds accounts for the proven lack of effect of effect of pure specific 5HT_{2A} antagonists (i.e., not those with other actions) on operative bleeding and skin bleeding times. This lack of effect on haemostasis solves the dosing problem encountered with other anti-thrombotic drugs, with which drug concentration cannot be controlled with single fixed doses, leading to the association between increased anti-thrombotic efficacy and increased bleeding complications. Thus 5HT_{2A} antagonism appears to be the preferred approach, from the point of view of safety and lack of bleeding risk; this consideration applies particularly to thrombosis therapy in the context of traumatic accidents, surgical operations and invasive procedures such as angioplasty.

Introduction

The importance of control of intra-arterial thrombosis is enhanced if this process proves crucial to the development of atherothrombosis as well as to the terminal stages [1,2]. It is commonly thought that thrombosis and haemostasis are always linked, leading to the concept that anti-thrombotic therapy is inevitably associated with excess bleeding, also called 'bleeding risk' [3]. It is true that experience with anticoagulants, which inhibit the action of thrombin, either directly or via the coagulation cascade, and with anti-platelet agents, which inhibit the thromboxane, purine or glycoprotein receptors, has confirmed the bleeding risk with these approaches [4]. At the present time, no alternative approach has been accepted, but in the case of anti-thrombotic treatment of arterial thrombosis, in which thrombin antagonism is ineffective [5] an alternative approach is available, namely inhibition of the serotonin receptor [6-10]. This follows the recommendation of [11], that drugs which block events upstream of the final common pathway might be better antiplatelet agents than those that merely inhibit platelet aggregation.

The anti-serotonin approach

Serotonin (5-hydroxytryptamine, 5HT) is present in high concentration in blood platelets. In contrast to the thromboxane, purine or glycoprotein mediators, serotonin does not influence the formation of haemostatic layers, although it is implicated in shear-induced aggregation and thrombus propagation by positive feedback from



the large amount of intra-platelet serotonin. It is important to distinguish between the serotonergic receptor subtypes [12]. 5HT₁ receptors respond with endothelium dependent nitric oxide mediated vasodilatation; 5HT₂ receptors activate platelets and mediate smooth muscle contraction. Thus, in arterial lesions in which vascular smooth muscle is bared of endothelium, vasoconstriction exacerbates arterial occlusion by thrombus; relief of such vasoconstriction by 5HT_{2A} antagonists is a bonus. However, surprisingly to date, serotonin antagonism has not progressed to clinical application in spite of publications confirming the effects of such antagonism, [13].

Platelets are the richest source of serotonin in the body outside the brain. Serotonin is not the only molecule secreted by platelets; the other include ADP, ATP, GDP, pyrophosphate, magnesium and calcium [14]. Platelets acquire serotonin from the plasma by means of the cell membrane serotonin uptake mechanism [15], and store the serotonin in dense granules [14]. Inhibition of this mechanism by serotonin re-uptake inhibitors (SSRIs) causes depletion of platelet serotonin [16].

Serotonin dependence of acute arterial thrombosis and its inhibition by 5HT_{2A} antagonism

Upon platelet activation (especially with high shear) high concentrations of serotonin in the platelets are released from the dense granules [17] and act upon platelet serotonin 5HT_{2A} receptors to activate more platelets, thus constituting a positive feedback mechanism leading to thrombus growth [18]. The serotonin theory [8] supposes that this serotonin mediation is essential for thrombotic occlusion of diseased coronary arteries, owing to the fact that such occlusions are abolished by antagonism of the platelet 5HT_{2A} receptor [9,19] even when the major stimulus of adrenaline is applied [20] and also in the circumstances where thrombolysis has failed to clear a complete thrombotic occlusion [21].

Examination of patients undergoing angiography has showed that a high plasma serotonin level was significantly associated with coronary artery disease in patients younger than 70. In nearly four years of follow up, high serotonin levels were also associated with cardiac events. This association persisted after adjustment for conventional risk factors [22].

Unfortunately, most of the antagonists of the platelet the 5HT_{2A} serotonin receptor have encountered problems. These problems are not due to the receptor blockade, but have precluded their application to human arterial thrombosis. However, Th001 (Arteclere™) formerly known as ICI170809 [23], or AZ170809, has proved extremely potent as an inhibitor of intracoronary thrombus growth [20]. This drug appeared to be safe in a number of trials of toxicity, which are detailed in an Investigator's Brochure. Another important aspect of the McAuliffe results [20] and those of [19], is that arterial thrombi spontaneously disperse under the influence of 5HT_{2A} antagonism to clear the artery for full blood flow. We presume that this is due to intrinsic natural thrombolytic agents [24]. The possibility that the 5HT_{2A} antagonist ICI170809 itself has a lytic effect was disproved by experiments in Aberdeen (unpublished). Indeed clearance of thrombus by thrombolytic drugs such as tPA is followed in dogs by re-occlusion, which 5HT_{2A} antagonism prevents [21]. These results are compatible with the intrinsic anti-thrombolytic effect [24].

A potent reason for pharmaceutical groups to promote 5HT_{2A} antagonism is the involvement of 5HT_{2A} receptors in promoting thrombosis in diabetes [25]. This disease is now reaching epidemic proportions worldwide with cardiovascular complications being the leading reason for morbidity and mortality in diabetes mellitus.

Other 5HT_{2A} receptor antagonists have been available in the past that also showed efficacy in acute arterial thrombosis, e.g., ketanserin [26] ritanserin [9], LU 49938 [27],



MDL11,939, and LY53,857 [21], MDL 28,133A [28], DV-7028 [29], AT-1015 [30,31], APD791 [32-34]. The 5HT_{2A} antagonists presently available are Th001 (Arteclere™), a specific platelet receptor antagonist and nefazodone [35], an antidepressant now taken off the market with non-platelet effects and an unknown effect on thrombosis. At present, sarpogrelate [36] seems to be the only 5HT₂ antagonist in clinical application. It is used in a wide variety of cardiovascular diseases associated with thrombosis, but appears not to have been trialed in acute coronary syndromes. Th001 (Arteclere™) has had considerable exposure in humans, with a clean safety record. We find confusing those studies of drugs with mixed receptor subtype, e.g., SL65.0472 [10].

Why has the serotonin approach not been followed up?

This follows from the different mode of action of serotonin and its antagonists, namely activation by increased shear stress [37], and blockade of positive feedback of serotonin generating thrombus growth. Most reports on the effects of 5HT_{2A} antagonists do not consider shear stress as an activating stimulus, [13]. But, increased shear stress is the very haemodynamic stimulus that occurs in a stenosed artery, and accounts for thrombus formation in both eccentric and concentric coronary artery lesions. Confirmation that 5HT_{2A} receptors play a major role in high-shear rate thrombus formation is provided by [38]. When searching for possible antiplatelet drugs, pharmaceutical groups search for platelet aggregability that is often tested in citrated platelet rich plasma, in which calcium ions have been removed. With this approach, high aggregability is found to thromboxane and ADP, together with high potency of their antagonists, compared to little or no activity using serotonin and its antagonists. They thus incorrectly ignore the role of shear stress within stenoses and the involvement of 5HT_{2A} receptors in that process, and assume that serotonin antagonists are ineffective. This conclusion is made despite the McAuliffe's 1993 study [20], in which ICI170809 showed about ten times the potency of clopidogrel, the leading P₂Y₁₂ purine (ADP) receptor antagonist, in inhibition of growing thrombus *in vivo*.

A second factor that deterred pharmaceutical groups from the serotonin antagonism approach is that the first 5HT₂ antagonist caused multiple problems due to its non-5HT₂ properties. One of these was alpha-1 antagonism causing a drop in arterial pressure leading to trial in hypertension! Pure 5HT₂ serotonin receptor antagonism has absolutely no role in the treatment of hypertension [39]. The other adverse effect of ketanserin was more serious, that of prolongation of the cardiac action potential and QT interval, causing deaths from arrhythmias. Since that time serotonin antagonists have been rigorously investigated, e.g., Th001 (Arteclere™), with the result that there is a clear absence of any cardiac electrophysiological changes attributed to serotonin or Th001 (Arteclere™).

Superiority of the serotonin approach in haemostasis

Those performing research on 5HT₂ antagonists since the 1980s when ketanserin became available, have observed that the haemostatic layer of blood cells bound to fibrinogen is unaffected. All the early work with these compounds involved experimental surgery on animals, and it was of note that, unlike similar experiments with other anti-thrombotic drugs, there was no excess bleeding, and no oozing coagulopathy. This makes these drugs particularly attractive to surgeons wanting to protect their patients from arterial thrombosis in the peri-operative period [40]. So, it is possible that, contrary to received opinion, the anti-thrombotic activity of 5HT_{2A} antagonists can be accompanied by an absence of effect on haemostasis. That this can be the case follows from the fact that the anti-thrombotic action only comes into effect during the thrombus growth phase of the occlusive arterial thrombosis process, the lack of participation by serotonin in the haemostatic process and the absence of serotonin in wounds.

Some drugs called 5HT_{2A} receptor antagonists have been claimed to prolong bleeding when cutting off the tails of mice [41], or rats [30,42], both containing veins. These claims need to be confirmed by correct methodologically controlled skin bleeding time measurements in man as performed by [43]. This study carried out at Aberdeen Royal Infirmary by [43], an MHRI approved report in the public domain that is now published, investigated indices of haemostasis in 48 patients with stable arterial disease. This stability enabled the investigators to design a statistically paired, randomised cross-over trial of placebo versus Th001 (Arteclere™). Lack of effect on haemostasis was confirmed by a series of ultragra and flow cytometry tests. Skin bleeding time showed no significant difference. Another important aspect of this study was that the dosing used for the Th001 (Arteclere™) arm (10mg bd for 2 weeks) produced a considerably higher plasma drug concentration than that producing complete arterial clearance in the McAuliffe study [20]. This is an important consideration when investigating dosing of other anti-thrombotic drugs.

The dosing problem with anti-thrombotic therapy

The efficacy of drug action is a function of drug concentration according to the classical concentration-effect relationship (Figure 1).

When drugs affect both thrombosis and haemostasis, a single fixed dose regime, e.g., 75mg clopidogrel gives different concentrations for different body masses. A large patient may be inadequately treated whereas a small patient may have bleeding complications. Only a lucky patient may receive a dose giving the correct concentration, but only by chance (Figure 2). Sensitivity to a given drug concentration varies from patient to patient. A patient with the blue concentration-effect curve in figure 3 will be inadequately treated, whereas one with the green relationship will have high bleeding risk. The ideal solution is to use a pure selective 5HT_{2A} antagonist such as Th001 (Arteclere™) which only affects thrombosis and not haemostasis; then one can give a high dose (right hand arrow in Figure 3), that is safe for all patient weights and sensitivities.

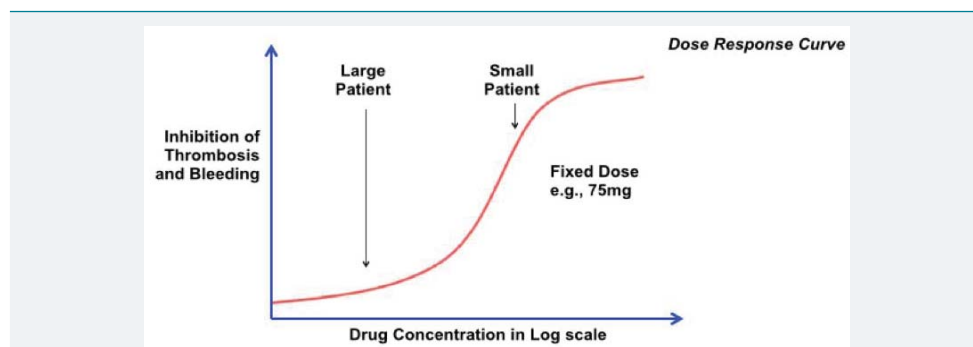


Figure 1: When drugs affect both thrombosis and haemostasis, a single fixed dose regime, e.g., 75mg clopidogrel gives different concentrations for different body masses. A large patient may be inadequately treated whereas a small patient may have bleeding complications.

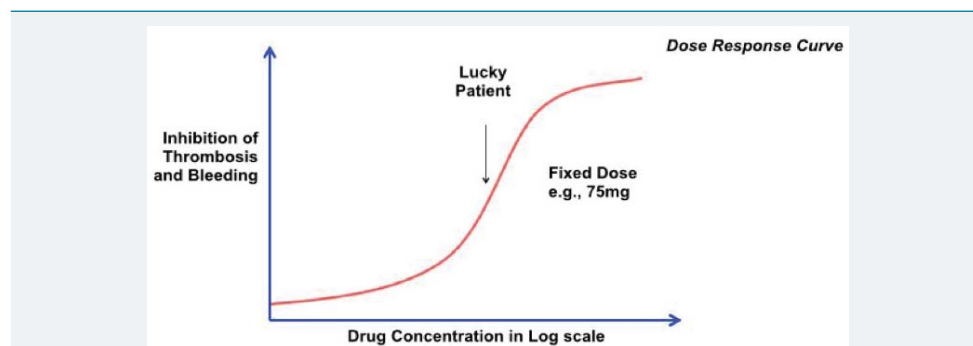


Figure 2: A lucky patient may receive a dose giving the correct concentration, but only by chance.

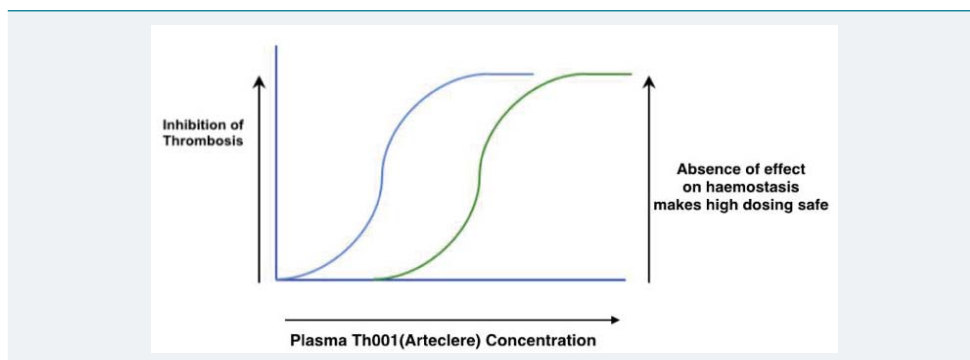


Figure 3: Patients' sensitivities to a given drug concentration varies. A patient with the blue concentration-effect curve will be inadequately treated with P_2Y_{12} antagonists or anti-coagulants, whereas one with the green relationship will have high bleeding risk. Overdosing with a $5HT_{2A}$ antagonist with no effect on haemostasis avoids these problems (right hand arrow).

Conclusion

$5HT_{2A}$ antagonism is proposed as the ideal solution to the problem of bleeding associated with treatment of arterial thrombosis. In the development of this approach, it is important to use a pure selective $5HT_{2A}$ antagonist such as Th001 (Arteclere™) which only affects thrombosis and not haemostasis. The reason for this conclusion is that thrombosis in arterial stenoses is activated by increased shear stress causing release of serotonin from platelets that then activates more platelets, setting in train the serotonin dependent positive feedback mechanism. This process is blocked by antagonism of the platelet $5HT_{2A}$ receptor. Because of the absence of effect of $5HT_{2A}$ antagonism on haemostasis, one can give a high dose that is safe for all patient weights and drug sensitivities. Of the $5HT_{2A}$ antagonists that have been investigated, Th001 (Arteclere™) has had a large exposure in human volunteers and patients and has not caused significant adverse effects.

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