

A Neglected Possible Clinical Management for Surgery for Patients at Risk of Peri-Operative Thrombosis

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Abstract

Background: Excessive bleeding occurs when anti-thrombotic drugs for patients with thrombotic risk are administered in the context of surgical operations and trauma.

Purpose: Analysis of data from the published literature on the mechanism of occlusive arterial thrombosis and evaluation of the most likely drug intervention that might circumvent this problem.

Results: Activation of platelets by haemodynamic factors appeared to be more important than plaque rupture and arterial endothelial factors in the process of arterial thrombosis within arterial stenoses. The process was accelerated by the well established serotonin to serotonin positive feedback thrombus growth mechanism. Much animal experimental data attest to the inhibition of this process by 5HT_{2A} receptor antagonism. Serotonin is not involved in the hemostasis of wounds.

Conclusion: Pure serotonin 5HT_{2A} antagonists will not increase traumatic bleeding and can be administered during surgical operations and the peri-operative period.

Keywords: Wound Hemostasis; Anti-Thrombotic Therapy; Platelet Shear Stress; Serotonin; 5HT_{2A} Receptor Antagonism

Introduction

Surgeons and accident specialists have grave concerns about anti-thrombotic therapies that cause increased bleeding. In non-cardiothoracic surgical operations, one faces more complicated problems in prevention and treatment of peri-operative thrombosis than in orthopaedic operations, and that is complicated enough, with different recommendations for different types of patient [1]. This and most of the literature on this subject are concerned with anti-coagulation for venous thrombosis and pulmonary embolism. A more general case is the recommendations for stopping anti-coagulation before planned operations [2]. In cardiovascular surgery, one may well be more concerned with dual antiplatelet therapy for arterial disease, which at least leads to less bleeding, but excess bleeding nevertheless [3,4]. After risk stratification analysis, various therapeutic pathways include continuing or discontinuing all antiplatelet agents or maintaining one antiplatelet agent and discontinuing the other [4]. All sorts of schemes to avoid operative bleeding are being tried. One example is that of

Marcos, et al. who discontinued clopidogrel and in some cases also acetylsalicylic acid 5 days prior to the planned intervention; the patients were admitted 2 to 3 days before the intervention [5]. A tirofiban infusion was then administered and discontinued 4 h before intervention. Nevertheless 6 of 36 patients sustained bleeding events, 5 of which required a blood transfusion. So problems remain.

Relevant Pre-Clinical Data

An experimental model of coronary arterial thrombosis in the anaesthetized dog developed by Folts demonstrated inhibition of such thrombosis by aspirin [6,7]. There followed a number of publications from the Folts and Willerson groups confirming this and other influences of thrombus growth in the coronary artery [8]. The papers from the Willerson group included a suggestion that ketanserin was effective in this preparation (ketanserin was a crude drug with antagonistic properties to alpha-1 adrenergic receptors) and serotonin 5HT₂ receptors, producing an hypothesis that 5HT₂ receptors might be a potential anti-platelet drug. I noticed that a histology figure in one of these papers apparently showed no effect on the haemostatic layer of platelets bound to fibrinogen. Discussion of this with Folts, led to scepticism owing to the mixed actions of ketanserin such as a risk of arrhythmic death due to QT prolongation. Folts' laboratory confirmed powerful inhibition of coronary thrombosis growth by the ritanserin [9].

One needed a drug of this class that could be used to treat arterial thrombosis without unwanted effects. There were many available that showed anti-thrombotic activity. Most drugs with anti-serotonin properties were developed for the treatment of brain disorders such as anxiety and depression. It became possible to try out one of these, ICI 170809, in the Folts model [10]. This drug not only inhibited thrombus growth but did so to such an extent that the thrombus eventually dispersed altogether (Figure 1). In addition it was effective when thrombus growth rate was accelerated with adrenaline [10]. In addition, if one allowed the thrombus growth to go to complete occlusion and reopened the artery with the thrombolytic tPA, re-occlusion occurred which was abolished by the administration of a 5HT_{2A} antagonist [11] (Figure 2).

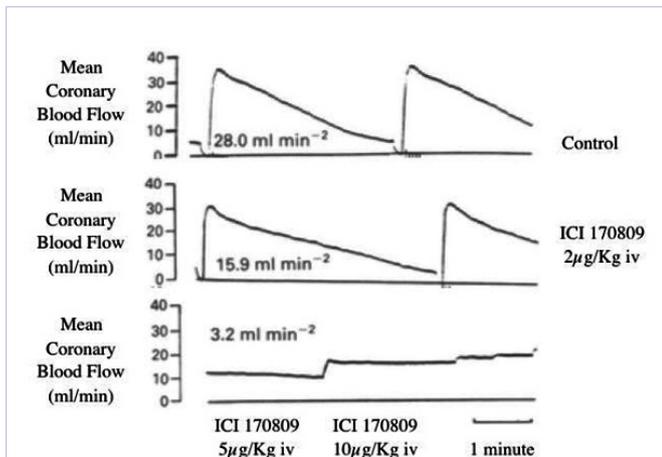


Figure 1: Records of mean coronary blood flow in the stenosed circumflex coronary artery of the anesthetised dog adapted from McAuliffe, et al. with permission. Thrombus growth is assessed by the slope of the falling blood flow as growing thrombus occludes the lumen. In the top control panel, flow is declining by 28.0 ml/min/min. In the middle panel after intravenous administration of 2µg/Kg of the 5HT_{2A} antagonist, the rate of decline of flow is reduced to 15.9 ml/min/min. In the bottom panel after intravenous administration of 5µg/Kg, the rate of decline of flow is reduced to 3.2ml/min/min, and after intravenous administration of 10µg/Kg, the thrombus embolises, causing increased flow..

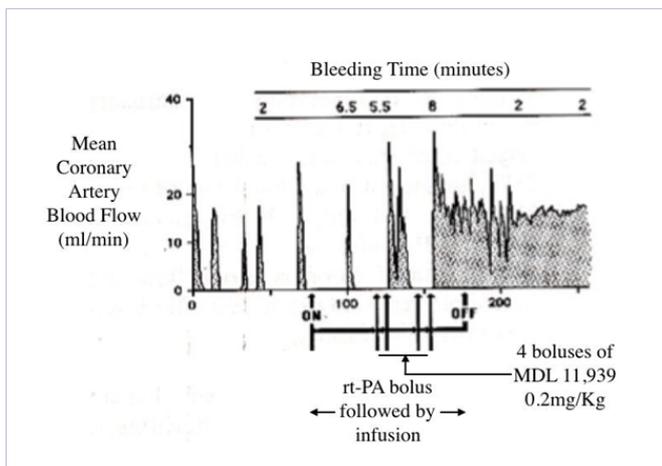


Figure 2: Records of mean coronary blood flow in the stenosed circumflex coronary artery of the anesthetised dog adapted from Belcher, et al. with permission. The baseline shows the passing of time in minutes. In this experiment, the stenosis in the coronary artery caused thrombus growth and occlusion of the artery with occasional small spurts of flow. A bolus of the thrombolytic drug rt-PA of 200µg/Kg, followed by an infusion at 1.5 mg/Kg/hour was minimally effective in restoring flow. When this was supplemented by 4 boluses of the 5HT_{2A} antagonist MDL 11,939, Full flow was restored. Note that bleeding time increased from 2 minutes to 8 minutes in the presence of rt-PA but returned to 2 minutes after stoppage of the thrombolytic during full flow restored by 5HT_{2A} antagonism.

Does 5HT₂ antagonism leave the haemostatic layer of blood cells and fibrinogen intact? A hint that there might be something in that idea is the result of bleeding time measurements in the study of Belcher, et al. which showed an increase during thrombolysis but normal values during 5HT₂ antagonism after recovery from

thrombolysis [11]. But before going into that, it is necessary to explain why thromboses occur within stenoses in the first place.

Why do thrombi form in Arterial Narrowing?

Experimentally, it was only stenoses that caused coronary thrombosis; there were no plaques full of lipid, so the conventional idea that plaque rupture is the cause of occlusive thrombus must be modified. Indeed, in my practice before retirement in 2000, half the patients with acute coronary syndromes had concentric lesions, and the eccentric lesions associated with plaques had widely variable anatomy. There is, however, one thing in common with all sites of occlusive thrombus, and that is a stenosis which causes very disturbed local haemodynamics [12]. Common to all these is the acceleration of blood velocity required to get the same flow through the stenosis as that through the normal sections of artery. The increased velocity, together with a variety of swirling hemodynamic abnormalities distorts the blood cells. In particular, platelets are subjected to shearing forces that activate them. Activated platelets release large amounts of serotonin from the dense granules.

A theory, to explain the large amount of serotonin in platelets, requires one to consider the fact that serotonin is a vital neurotransmitter in the central nervous system. It is synthesised in the gut, secreted into the blood stream and the central nervous system has to acquire it through the serotonin re-uptake mechanism (SSRI). Antagonists of this system are anti-depressive drugs like fluoxetine. Carcinoid syndrome is a disease in which too much serotonin is secreted by the gut and leads to pulmonary hypertension and right heart failure; therefore in normal people there needs to be a buffer to prevent plasma serotonin levels going too high. This is achieved by the same serotonin re-uptake mechanism, but now in the platelet membrane leading to storage in the dense granules. At the end of a platelet's life the serotonin is broken down to 5-Hydroxyindoleacetic acid (5HIAA) which is secreted in the urine, which is a test used to diagnose Carcinoid tumors).

During evolution, this useful system evolved before humans lived long enough to develop arterial atherothrombosis. The additional difficulty is that platelets can also be activated by serotonin via their 5HT_{2A} receptor. The serotonin released from sheared platelets then activates more platelets via this receptor so that one has a positive feedback effect. (negative feedback causes stability; positive feedback accelerates a process). This process is stopped by antagonising the 5HT_{2A} receptor.

Treating wounds without causing excess bleeding

Excess bleeding occurs from wounds in patients who are being treated with anti-thrombotic drugs, who may end up with "ozing coagulopathy" which can co-exist with thrombosis [13]. And trauma activates thrombosis leading to worry by surgeons about the possibility of perioperative thrombosis [14]. Essentially, these practitioners need a protection for their patients against thrombosis with no effect on operative bleeding. This approach might be the answer to this problems in view of

the experiments on 5HT₂ antagonists inhibiting thrombosis by leaving the haemostatic layer intact.

Arachidonic acid and its metabolites are part of tissue control of antigens and allergy control. The mechanism by which the active metabolites of Arachidonic Acid (AA), i.e., thromboxane A₂ and/or prostaglandin H₂ (TXA₂/PGH₂) induce platelet aggregation is not understood [15]. Without going into this complex subject, the point to be made here is that it is an ubiquitous group of substances in tissue containing blood capillaries and wound release of these substances; thromboxane in particular, causes platelet aggregation that helps to stop the bleeding. If one inhibits the system with aspirin, bleeding is increased. All metabolising cells in tissue have an energy system based on the phosphate compounds Adenosine Triphosphate (ATP), Adenosine Diphosphate (ADP) etc, as a group called purines: again, ubiquitous substances in tissue. These will be released by cutting into tissue and ADP in particular will cause platelet aggregation that helps to stop the bleeding, a process called hemostasis. If one inhibits the system with clopidogrel and other blockers of the P₂Y₁₂ platelet purine receptor, bleeding is increased. Serotonin also activates platelets, but there is no serotonin in tissue, only in any quantity in nerve cells. Thus antagonising the serotonin receptors in platelets in wounds has no effect because of lack of agonist.

Does Serotonin Antagonism Affect Haemostasis?

One of the 5HT_{2A} antagonists with effects on thrombosis, ICI 170809, (synthesised by ICI Pharmaceuticals Division) was subjected to a number of tests of haemostasis. The drug, as with most serotonin-related drugs, was synthesised and tested for serotonin antagonism with the idea that it might be good for brain disorders. All the necessary tests for toxicity etc were proved satisfactory for volunteer and then clinical trials which were carried out in patients with depression and anxiety. The department responsible seems not to have studied the very early basic work reports on this substance which demonstrated that it did not pass the blood brain barrier! Obviously there could be no effect on depression or anxiety, nor was there! However, another of the laboratories in the organization, knowing that serotonin activates platelets carried out platelet aggregation tests and the effect on that of ICI 170809 [16]. Conventional testing of platelet aggregation shows serotonin to be only a weak agonist, blocked by 5HT₂ antagonists, but ICI 170809 is much more potent in inhibition of macro-aggregate growth because of the positive feedback effect [17]. They also managed to carry out a few unpaired comparisons of bleeding time on volunteers which showed no significant difference with controls. The organization, having aimed the drug for the CNS, dropped it.

Modern hemostasis experts have reservations about the accuracy of bleeding time in assessing haemostasis, but the author's opinion is that bleeding time is the relevant index for wound bleeding if measured in a standard way as performed by Noble, et al. [18]. This trial design was a double-blind, placebo controlled, paired crossover, with 99% power for showing a difference in skin bleeding time. n = 48 Caucasian patients, age

69.0 ± 6.6 years, 38 male, 10 female, with stable atherothrombotic disease and other stable chronic diseases, treated with aspirin and statin. There was no effect of ICI 170809 on bleeding time (p = 0.9729) nor on tests of hemostasis, (Ultegra point of care aggregation test and flow cytometry). The mean platelet count rose from 234.43 ± 67.264 to 246.43 ± 84.14 x10⁹ per litre, p = 0.024. It was concluded that ICI 170809, now renamed Th001 (Arteclere™) therapy appears to be a safe method for potential treatment and prevention of occlusive arterial thrombosis with no risk of increased bleeding [18].

Adverse events with anti-thrombotic treatment with 5HT_{2A} antagonism?

Sarpogrelate has been available for some time, but has not been used to my knowledge for the purpose that I have described, and I am not aware that other 5HT₂ antagonists, all of which inhibit thrombosis in animal arteries, have been thoroughly tested for passage of the blood brain barrier or effects, if any, on bleeding. ICI 170809, now renamed Th001(Arteclere™) does not pass the blood-brain barrier, an aspect that is important for confidence that brain serotonin functions will not be disturbed [19]. The hemostasis issue is crucial if 5HT_{2A} antagonism is to be used in surgery and trauma.

There were small rises in liver function tests within the normal range that would not have been detected in an un-paired study design [18]. This is in common with many other drugs metabolised by the liver, eg: paracetamol, statins. Thus, for Th001, some care is needed on this point. No concomitant medications were stopped, of which there were many, but obviously continued observation of possible drug interactions are needed. All adverse events were minor with no significant differences between placebo and drug administration periods.

Bleeding During Surgical Operations is Normal

Abundant evidence comes from the animal experiments described which involved thoracotomy and dissection of a coronary artery. Normal haemostasis was secured routinely with diathermy and ligation. Subsequently, there was no further bleeding from the wounds and no oozing coagulopathy.

The only evidence in humans is from myself (a traditional self experimenter). In two knee and one hip replacement with pre-operative loading with Th001, and no postoperative routine anticoagulation, no excessive operative bleeding was reported from three different blinded orthopaedic surgeons, and there was no drop in blood hemoglobin concentration.

Conclusion and Recommendation

5HT_{2A} antagonism before during, and after surgery and trauma, as protection against thrombosis, should not increase operative and postoperative bleeding. The surgical community should be applying pressure to organizations with funding for research and the pharmaceutical industry to undertake clinical trials of 5HT_{2A} antagonism during, initially, elective surgery, in which careful and comprehensive protocols are possible.

References

1. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopaedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e278S-e325S. doi: 10.1378/chest.11-2404
2. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e326S-e350S. doi: 10.1378/chest.11-2298
3. McKeivitt FM, Randall MS, Cleveland TJ, Gaines PA, Tan KT, Venables GS. The benefits of combined anti-platelet treatment in carotid artery stenting. *Eur J Vasc Endovasc Surg*. 2005;29(5):522-527.
4. Oprea AD, Popescu WM. Perioperative management of antiplatelet therapy. *Br J Anaesth*. 2013;111(Suppl 1): i3-i17. doi:10.1093/bja/aet402
5. Marcos EG, Da Fonseca AC, Hofma SH. Bridging therapy for early surgery in patients on dual antiplatelet therapy after drug-eluting stent implantation. *Neth Heart J*. 2011;19(10):412-417. doi: 10.1007/s12471-011-0197-y
6. Folts JD, Rowe GG. Cyclic reductions in coronary blood flow in coronary arteries with fixed partial obstruction and their inhibition with aspirin. *Fed Proc*. 1974;33:413.
7. Folts JD, Crowell EB, Rowe GG. Platelet aggregation in partially obstructed vessels and its elimination with aspirin. *Circulation*. 1976;54(3):365-370.
8. Folts JD. Experimental arterial platelet thrombosis, platelet inhibitors, and their possible clinical relevance. *Cardiovasc Rev Rep*. 1984;3:370-382.
9. Torr S, Noble MIM, Folts JD. Inhibition of acute platelet thrombosis formation in stenosed canine coronary arteries by specific serotonin 5HT2 receptor antagonist ritanserin. *Cardiovasc Res*. 1990;24(6):465-470.
10. McAuliffe SJ, Snow HM, Cox B, Smith CC, Noble MIM. Interaction between the effects of 5-hydroxytryptamine and adrenaline on the growth of platelet thrombi in the coronary artery of the anaesthetised dog. *Br J Pharmacol*. 1993;109(2):405-410.
11. Belcher PR, Drake-Holland AJ, Noble MIM. Antagonism of the platelet 5HT2 receptor in the presence of thrombolysis. *Int J Cardiol*. 1994;43(1):11-20.
12. Westerhof N, Stergiopoulos N, Noble MIM. *Snapshots of Hemodynamics*. First Edition, Kluwer Academic Publishers, Dordrecht. 2005, Second Edition Springer Dordrecht, 2011.
13. Hunt BJ. Bleeding and coagulopathies in critical care. *N Engl J Med*. 2014;370(9):847-859. doi: 10.1056/NEJMr1208626
14. Atlee JL. Activation of thrombosis by trauma and surgery. In *Complications in Anaesthesia*. Elsevier Health Sciences. 2007:361-974.
15. Marone G, Kagey-Sobotka A, Lichtenstein LM. Effects of arachidonic acid and its metabolites on antigen-induced histamine release from human basophils in vitro. *J Immunol*. 1979;123(4):1669-1677.
16. Millson DS, Jessop CL, Swaisland A, Haworth S, Rushton A, Harry JD. The effects of a selective 5HT2 receptor antagonist (ICI 170809) on platelet aggregation and pupillary responses in healthy volunteers. *Br J Clin Pharmacol*. 1992;33(3):281-288.
17. Menys VC. Collagen induced human platelet aggregation: serotonin antagonism retards aggregate growth in vitro. *Cardiovasc Res*. 1993;27(11):1916-1919.
18. Noble MIM, Ford I, Cameron G, Drake-Holland AJ. The novel anti-thrombotic drug with no-bleeding excess (NOBLE 1 study). *J Cardiol Cardiovasc Therapy*. 2017;6(2):1-6. doi: 10.19080/JOCCT2017.05.555684
19. Yamakawa J, Takahashi T, Itoh T, Kusaka K, Kawaura K, Wang XQ, et al. A novel serotonin blocker, sarpogrelate, increases circulating adiponectin levels in diabetic patients with arteriosclerosis obliterans. *Diabetes Care*. 2003;26(8):2477-2478.