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Serotonin Reuptake Inhibitors and Cardiovascular Disease

Philip R Belcher*, Angela J Drake-Holland and Mark I M Noble

*University of Glasgow, Department of Cardiac Surgery

Royal Infirmary

10 Alexandra Parade

Glasgow G31 2ER

UK

Cardiovascular Medicine

University of Aberdeen

Aberdeen Royal Infirmary

Foresterhill, Aberdeen AB25

Corresponding Author: Dr PR Belcher

University of Glasgow, Department of Cardiac Surgery

Royal Infirmary

10 Alexandra Parade

Glasgow G31 2ER UK

Telephone +44 (0)141 211 4336

Facsimile +44 (0) 141 552 0987

Email pbelcher@clinmed.gla.ac.uk

Abstract

Selective serotonin re-uptake inhibiting drugs (SSRIs) are widely used for endogenous depression. In addition to depleting the nerve terminals of serotonin they also lower blood platelet serotonin levels. Platelet aggregation is a major component of acute coronary syndromes, including sudden death, and also of limb ischaemia. Platelet-released serotonin causes constriction of diseased blood vessels. The recent literature has revealed a number of reports of association between treatment of depression with SSRIs and reduced events caused by intra-arterial thrombosis. The effects of serotonin and serotonin depletion upon intracoronary thrombosis, diseased blood vessels, blood platelets and bleeding are discussed with recommendations for future research into the potential cardiovascular benefits of SSRIs and serotonin 5HT_{2A} antagonists.

The serotonin theory of platelet-rich thrombus growth

Platelets are the richest source of serotonin in the body outside the brain. The source of the serotonin is extra-platelet, being acquired by means of the cell membrane serotonin uptake mechanism. Inhibition of this mechanism by serotonin reuptake inhibitors (SSRIs) causes depletion of platelet serotonin [1]. The high concentrations of serotonin located in the dense granules are released upon platelet activation, and act upon platelet serotonin 5HT_{2A} receptors to activate more platelets, thus constituting a positive feedback or “snowball” mechanism leading to thrombus growth. The serotonin theory [2-5] supposes that this serotonin mediation is essential for thrombotic occlusion of diseased coronary arteries owing to fact that such occlusion are abolished by

antagonism of the platelet 5HT_{2A} receptor [6, 7] even when the major stimulus of adrenaline is applied [8] and in the circumstances where thrombolysis has failed to clear a complete thrombotic occlusion [9]. Examination of patients undergoing angiography showed that a high 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 [10]. 5HT_{2A} antagonism was advocated in the treatment of coronary artery disease [11] in which some positive preliminary results were published [3]. A further aspect of the theory relevant to such a proposal concerns the fact that serotonin is not present in the arterial wall or tissues and does not participate in the mediation of haemostatic platelet layers. Thus, platelet-rich thrombus growth which can cause myocardial infarction and unstable angina are inhibited, but there are no bleeding side effects as seen with all other anti-platelet therapies. However, by chance, the frequent use of SSRIs to treat depression after acute coronary syndromes (because other antidepressants are cardiotoxic) has led to the realisation that these drugs also reduce the consequences of platelet-rich thrombus growth. In this case, the benefits arise from the fact that there is less serotonin in the platelets to be released upon activation, and thus there is less serotonin to activate other platelets through their 5HT_{2A} receptors.

Figure 1 about here

Serotonin receptors

Serotonin is a neurotransmitter in the central nervous system which directly activates 5HT receptors. Serotonin receptors come in 7 types with numerous subtypes, most of which are associated with the central nervous system. For the purposes of this review we will only examine 5HT_{1A}, 5HT_{1B}, and 5HT_{2A} as these are the most important receptors found outside the central nervous system, where serotonin acts as a local hormone. The multiplicity of receptor subtypes explains the disparate effects of serotonin on the cardiovascular system [12]. Serotonin is released into the plasma from nerves, chromaffin cells and platelets. It is taken up by liver, endothelium and platelets where it is stored in the dense granules (Figure 1). Normal levels of serotonin in plasma are very low and at the limits of measurement techniques [13]. Serotonin release by platelets is the main source of serotonin in the plasma as the platelet contains large amounts of dissolved serotonin; in addition the dense granules have a very high concentration of serotonin. The normal adult platelet concentration of serotonin is $3.81 \pm 0.87 \text{ nmoles} \cdot 10^9 \text{ platelets}$ [14]. Serotonin is classified as a weak platelet agonist [15] but, when combined with other agonists of platelet aggregation, amplifies the response. Local concentrations of serotonin in the region of a coronary stenosis, which causes shear stress upon the platelet, are very high and form the basis of the amplification of the platelet activation and aggregation reactions [16]. See Figure 2.

Figure 2 (5ht2) about here

Aggregation experiments have shown that the released serotonin from platelets interacts with the platelets' own 5HT_{2A} receptors and that this determines the aggregatory response to other agonists; blockade of the 5HT_{2A} receptor also counteracted aggregation induced by ADP, adrenaline and thrombin thus suggesting a major role for serotonin and the platelet serotonin receptor in the genesis of intracoronary thrombosis [17]. See Figure 2.

The role of serotonin in intravascular thrombosis

The beneficial effects of 5HT_{2A} receptor blockade in animal models of intracoronary thrombosis have been well shown. Using the Folts model in which a critical stenosis overlies damaged endothelium, 5HT_{2A} antagonism was effective in abolishing intracoronary platelet-rich thrombosis [6, 7, 18, 19]. When used as an adjunct to thrombolysis in the Folts model, selective 5HT_{2A} blockade improved flow even after withdrawal of the thrombolytic agent and normalisation of coagulation variables and bleeding time, which suggest good safety margins as well as therapeutic effectiveness of this class of agents [9]. There is also evidence to suggest that 'demand-induced myocardial ischaemia' in the presence of coronary arterial stenosis, involves platelet activation and or microvascular vasoconstriction due to serotonin released from platelets [20]. Both recovery of ST segment change and mechanical function are improved in the presence of 5HT_{2A} receptor antagonism [20]. The presence of circulating platelet aggregates increases in sheep with degenerating biological valves but the use of a 5HT_{2A} antagonist dramatically decreased the numbers of platelet aggregates [21]. Reports of gastric

bleeding associated with the use of SSRI antidepressants [22, 23] consisted of 7 isolated case reports [22]. A population-based case-control study has shown that SSRIs increase the risk of upper gastrointestinal bleeding by threefold. The risk was similar with all the inhibitors confirming that it was a class effect and there was a clinically relevant interaction between SSRIs and non-steroidal anti-inflammatory drugs. The conclusions should not be accepted without a double blind cross-over placebo controlled clinical trial with measurements of bleeding time, especially as major thoracic surgery in animals was not accompanied by either clinical bleeding or increased bleeding time [9].

Ketanserin possesses 5HT_{2A} receptor blocking effects as well as α -1 adrenergic antagonistic properties [24]. Ketanserin has been shown to decrease thrombotic complications in peripheral vascular disease [25, 26]. In another study of patients awaiting coronary interventions for over one year, the effects of prophylaxis by aspirin or ketanserin were compared. The aspirin group suffered significantly more infarcts thus indicating a superior protective effect of 5HT_{2A} receptor blockade [3]. Unfortunately, ketanserin has proarrhythmic properties, when used in combination with potassium-losing diuretics, which make it unsuitable for routine clinical use [27]

Role of serotonin in vascular smooth muscle control

(a) Normal vessels

Arterial relaxation can be caused by endothelium-independent, or by endothelium-dependent, vasodilators. The effect of the latter is to release

nitric oxide (NO) which relaxes the vascular smooth muscle. In normal circumstances the aggregating platelet releases serotonin which reaches 5HT_{1A} receptors on the endothelium; this triggers the release of NO leading to vascular smooth muscle dilatation. This response contributes to the protective function of the intact endothelium in the prevention of unwanted coagulation of blood in vessels with a normal intima (Figure 2). Serotonin has, however, been shown to be a potent constrictor of epicardial vessels although it has no significant effect on resistance vessels when compared with phenylephrine [28]. In blood vessels which have suffered endothelial loss and regeneration, or arteries which have atherosclerosis, the endothelial secretion of NO is considerably reduced which favours the occurrence of vasospasm [29]. In patients with vasospastic angina, transcardiac gradients of serotonin were significantly higher than those seen in control subjects [30].

(b) Diseased vessels

Synergistic vascular contractile effects between serotonin and other vasoconstrictor substances within the circulation may play an important role in hypertension, peripheral vascular disease and coronary arteries [31]. In arteries with evidence of atherosclerosis or dysfunctional endothelium, serotonin caused vasoconstriction which could not be prevented by aspirin but could be prevented by ketanserin, a drug with 5HT_{2A} receptor blocking properties [24]. Patients with coronary artery disease do not possess the normal vasodilator response to infused intracoronary serotonin and in patients with vasospastic angina, doses of serotonin that dilate normal vessels can cause occlusive vasospasm [32]. If the endothelial layer is absent, no NO is released and serotonin can reach the 5HT_{2A} receptors of smooth muscle

which cause vasoconstriction. Serotonin release by platelets produces a positive feedback to promote further platelet activation with more serotonin release, vasoconstriction and platelet aggregation (Figure 2).

The presence of atheroma or other damage to the endothelium augments the constrictor response to serotonin [33, 34, 35]. This may be acute or chronic with evidence of damaged endothelium possessing a “memory”. Other chemical factors such as oxidised low density lipoproteins may also potentiate agonist-induced vasoconstriction [36, 37]. The presence of a significant coronary artery stenosis exposes further effects of serotonin, namely decreased endocardial flow [38], which could be attenuated but not abolished by the 5HT₁ antagonist methysergide [39]. Serotonin has also been shown to constrict intramural penetrating arteries with resultant subendocardial ischaemia [40]. Serotonin can constrict coronary collateral vessels which may be important in patients with angina where significant portions of the myocardium can be collateral-dependent [41].

Fig 3 about here

Long term modification of endothelial responses

What influence does serotonin have upon the endothelial cell itself?

Investigators of the mitogenic effect of vasoactive compounds have evaluated incubation of serotonin and the stable thromboxane A₂ (TXA₂) analogue U46619 on endothelial cells. U46619 was without effect by itself whereas serotonin promoted cell proliferation which was potentiated by U46619 [42].

Interestingly, the mitogenic effect can be blocked by preloading the cells with the fish oils eicosapentaenoic acid and docosahexaenoic acid thus providing cellular support for the cardiovascular benefits of fish oil in the diet [43]. The same investigators have shown that thrombin and serotonin act synergistically in promoting vascular smooth muscle proliferation at much lower concentrations than each would induce proliferation independently [44]. Further work demonstrated that even low concentrations of very low density lipoprotein, intermediate density lipoprotein or low density lipoprotein from hypercholesterolaemic plasma can significantly potentiate the mitogenic effect of serotonin [45]; as serotonin is released in high concentrations by platelets at sites of vascular damage this suggests an important mechanism for medial thickening. Vascular endothelium seems never to regenerate properly and the new endothelium has reduced ability to synthesise NO. In experiments with pigs that had coronary endothelial damage, intracoronary serotonin repeatedly caused marked vasoconstriction compared to an undamaged control artery [46]; in rabbits with carotid endothelial damage, the abilities of the vascular smooth muscle were unchanged but endothelium-dependent relaxation was severely impaired [47]. This effect has been shown to persist for at least three months following endothelial damage [48]. In the isolated coronary artery of the dog serotonin causes constriction but 5-carboxamidotryptamine (a 5HT₁ receptor agonist) caused relaxation which could be suppressed by removal of the endothelium. In monkey and human arterial segments both serotonin and 5-carboxamidotryptamine caused contraction [49]. Following focal endothelial loss arteries have been shown to have an increased endothelium-dependent constrictor response to serotonin,

but this was not seen with endothelium-independent constrictors such as ergonovine, noradrenaline or U46619 [50]. In the diseased human coronary artery, the normally endothelium-dependent vasodilators, acetylcholine and serotonin, caused vasoconstriction of diseased vessels and also the vessels of symptomatic patients who were without obvious coronary artery disease [51].

Genetic studies

Heightened membrane expression of glycoprotein IIb/IIIa and P-selectin receptors, assessed by Western blotting has been previously reported in depressed patients without heart disease [52]. There is some evidence for the T102C polymorphism as the cause of increased expression of 5HT_{2A} receptors; such increased expression is more prevalent in coronary thrombosis patients than in controls [53]. Another line of investigation has been to look at the serotonin transporter gene which, when it shows polymorphism of the promoter region, is associated with raised cholesterol levels and cardiovascular disease [54]. This gene has also been shown to play a role in susceptibility to coronary artery disease particularly when combined with smoking [55]. Though Coto *et al* were not able to confirm an association between myocardial infarction and 5HT_{2A} receptor gene polymorphism, they did find an age-related association between myocardial infarction and the homozygous ss deletion of the 5HT transporter gene polymorphism [56]. Mutant mice lacking the tph1 gene controlling (with tph2) tryptophan hydroxylase (the rate-limiting enzyme for serotonin synthesis)

have large hearts and develop heart failure [57]. It is not clear which action of the non-neural serotonin system is responsible for this protective effect.

Pharmacology

(a) General

The interest in drugs for the prophylaxis of migraine resulted in the production of pure 5HT_{2A} antagonists, which turned out to be of no benefit in this condition, but are predicted to be of value in intra-arterial thrombosis (see section on serotonin theory above). During the period of their development, improvements resulted in increased potency of the agents and coincidentally an increasing body of evidence that platelets, the vasculature and serotonin were implicated in coronary artery disease. 5HT_{2A} antagonists were found to have no effect on migraine but 5HT_{1B/1D} agonists such as sumatriptan which cause vasoconstriction of the cerebral vasculature are highly effective. They do possess minor systemic vasoconstrictor properties [58] and also minor constrictor effects on the coronary arteries acting through the 5HT_{1B} subtype receptor in people without coronary artery disease [59]. These effects do not appear to have any clinical significance but coronary artery or vasospastic diseases are contraindications to their use, although Macintyre's study was in patients undergoing diagnostic coronary angiography in which systemic and pulmonary artery pressures were raised and coronary artery vasoconstriction was seen in response to intravenous sumatriptan; heart rate and ECG morphology were unchanged [60]. Studies of receptor sub-types conclude that serotonin-induced contraction of coronary arteries is most probably mediated *via* the activation of both 5HT_{1B} and 5HT_{2A} receptors [61, 62]. Chest

pain has been reported following administration of sumatriptan-like drugs and there have been occasional incidences of myocardial infarction even with normal coronaries [63]. However, exercise test abnormalities are rare in patients with sumatriptan-induced chest pain [63] and there is little evidence of any relation to cardiovascular disease [64].

(b) Development of the use of SSRIs in depression following acute coronary syndromes

The older tricyclic antidepressants possess serious cardiovascular side effects and are contraindicated in depressed patients with an acute coronary syndrome [65]. The use of tricyclic antidepressants, but not SSRIs, is associated with an increased risk of myocardial infarction [66, 67]. On the other hand, SSRIs are well-established antidepressant drugs that have shown little evidence of cardiac toxicity, even in patients with heart disease. The recent Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) studied 364 depressed patients with acute coronary syndromes and documented no evidence of harm with sertraline treatment and showed a (non-significant) trend towards reduction in morbidity and mortality among the SSRI-treated patients [68]. Lower cardiovascular morbidity and mortality in SSRI-treated patients was reported in recent epidemiologic studies [66, 67, 68, 69, 70]. Further, a study of 137 post-stroke patients treated with sertraline who were followed up for one year also showed reduced mortality and morbidity [71]. More trials are required to establish these findings, but should not be confined to patients with depression. Unfortunately, SSRIs take time to deplete serotonin from the platelets, so that they cannot be expected to work

at once in an acute coronary syndrome, but only by treatment beforehand. It would therefore be necessary to start with trials of secondary prevention by SSRIs in patients with arterial disease, whether depressed or not.

Depression is a significant risk factor for ischæmic heart and cerebrovascular disease as well as mortality following myocardial infarction [72, 73]. The potential effects of SSRIs upon the cardiovascular system may therefore be very important. A recent study [74] draws attention to a potential benefit from these drugs in hypertensive patients 18 months after myocardial infarction; episodes of depression (negative affect) and hypertensive responses to depression were reduced in patients who had been prescribed SSRI drugs. The authors ascribed this decreased response to lessened sympathetic drive and its effects on cardiovascular reactivity [75, 76], but the investigators did not measure catecholamine levels. Unlike ketanserin (with α_1 adrenoreceptor antagonist properties), pure 5HT_{2A} receptor antagonists do not affect the blood pressure although it is suggested that serotonin may help maintain the chronic increase in peripheral resistance in hypertensive patients. If so, it could be due to increased responsiveness of the vessel wall to 5HT₁ serotonin-mediated vasoconstriction, and/or a reduced ability to clear serotonin from the blood [29]. Hypertension is, of course, only one of many independent risk factors targeted in secondary prevention following myocardial infarction. All the patients in the quoted study were also receiving aspirin and about half were prescribed ACE inhibitors and/or β -blockers; 80% received nitrates which are also known to suppress blood platelets [77]. In another hypertension study, blockade of the platelet serotonin receptor (5HT_{2A} receptor) with ketanserin in pregnancy, for the treatment of mild to moderate

mid-trimester hypertension, decreased the number of cases of pre-eclampsia and severe hypertension as well as reducing the incidence of placental abruption and perinatal mortality [78].

Investigation of patients with diabetes and peripheral vascular disease have shown low intraplatelet serotonin levels associated with platelet hyper-reactivity [79], in contrast to the finding of decreased platelet reactivity seen with SSRIs [1]. Possibly this is due to over-release of serotonin from activated platelets, this was reflected in a 66% increase in plasma serotonin levels although these did not reach statistical significance [79].

Actions of SSRIs in the periphery

The purpose of SSRI drugs is to increase serotonin concentration in the nerve synapses within the central nervous system. This is achieved by prevention of reuptake into the nerve terminal and, because of loss of negative feedback control, there is overproduction of serotonin by the nerve terminal [80]

Blood platelets actively take up serotonin from the plasma but are incapable of its synthesis. SSRI drugs reduce the uptake of tritiated serotonin by platelets [81]. This has led to the use of blood platelets as a surrogate for the central nervous system in the study of these drugs [82]. The tricyclic antidepressants such as imipramine have been reported to decrease platelet serotonin concentration but do not inhibit uptake [83]. In a general practice study, in which normal patients were compared to depressive patients, those taking the SSRI drug fluoxetine had significantly decreased aggregatory response to submaximal collagen stimulation [1]; this study also showed a

significant decrease in serotonin concentration in platelet rich plasma associated with use of fluoxetine but not with the tricyclic antidepressant amitriptyline. It is attractive to suggest that lowered platelet serotonin content translates into less serotonin release during platelet activation at an intracoronary stenosis. A study into the effects of paroxetine (SSRI) revealed lower platelet factor 4 (PF₄) and β -thromboglobulin (β -TG) levels and suggests that reduced platelet aggregation *in vivo* may positively impact upon coronary artery disease-related mortality in this [84].

Is the mechanism of beneficent action of SSRIs in coronary disease platelet related?

Enhanced platelet activation has indeed been proposed as a possible mechanism contributing to the increased cardiac risk associated with the diagnosis of major depression [85, 86]. Circumstantial evidence is consistent with this prediction. Data have accumulated indicating that depression is associated with platelet activation and that the SSRIs [1, 85, 86] affect platelet function. SSRIs reduce platelet activity in patients on aspirin therapy and in patients with heart failure [87]. Platelet activity is also decreased by *in vitro* exposure to both sertraline (an SSRI) and N-desmethylsertraline, the non-active metabolite of sertraline [88]. Does this imply an effect on platelets which is not dependent on serotonin depletion? Paroxetine reduces the abnormality in platelet hyper-reactivity observed in depressed patients [89]. Patients with major depression exhibit reduction of serotonin transporter platelet binding sites by imipramine [90, 91] and an increase in serotonin 5HT_{2A} receptor binding sites on the platelet surface [92], as determined by

radioligand binding studies [93]. Enhanced platelet activity is also reflected in markedly elevated β -TG and PF₄ levels in patients suffering from depression and chronic ischemic heart disease [94]. The breakdown of serotonin is dependent on monoamine oxidase, which is increased in depressed patients [95]. Unfortunately, for the clarity of interpretation of modern studies, most patients with acute coronary syndromes are treated with aspirin and/or clopidogrel, but the accumulated evidence is strongly consistent with platelet activation as a major determinant of increased intra-arterial thrombosis in depressed patients.

Can SSRIs reverse platelet activation in patients with arterial disease?

A number of studies have been carried out using the SSRI sertraline which is a potent SSRI and a selective dose-related inhibitor of the serotonin transporter; by this mechanism serotonin 5-HT_{2A} receptors and other serotonin receptors in the brain are downregulated [96]. As with fluoxetine [1], sertraline depletes platelet serotonin [82]. There is also a reduction in SSRI radioligand binding [97]. Overall platelet thrombosis as determined *in vitro* by collagen stimulation is inhibited by sertraline [98], as is intracellular Ca²⁺ mobilisation [99]. A recent study assessed both platelet and endothelial markers in a post-acute coronary syndrome patient group in whom 89% received aspirin and 17% received clopidogrel or ticlopidine, while 29% received either warfarin or coumadin. In a double-blind comparison of sertraline and placebo, 6 or 16 weeks of sertraline treatment caused significantly greater reductions in β -Thromboglobulin, in spite of the concomitant antithrombotic therapy [86]. The differences were detectable

against a background of decreasing activation in the placebo group as a result of recovery from an acute coronary syndrome. Moreover, markers of endothelial function such as PECAM-1, 6-oxo-PGF_{1α} and VCAM-1 were unaffected, in line with the non-participation of vessel wall components in the serotonin theory (see above). The falls in PF4 and TXA₂ following acute coronary syndromes were similar in treated and placebo groups. In view of the opinion that β-Thromboglobulin and PF4 are inadequate descriptors of platelet function, and that the samples were collected in citrate (which involves unphysiologically low extracellular Ca²⁺ concentration) it would be worthwhile to repeat this study with measurements of platelet IIb/IIIa binding to fibrinogen in hirudinised samples.

Clinical platelet function testing

Clinical platelet function testing has been fraught with difficulty, but in view of the importance of platelet function in assessment and prognosis, some attempt should be made to standardise methods. Vacutainer[®] sampling is unsuitable as suction from a vein through a small bore needle will activate the platelet artefactually. There is considerable disparity in techniques of assessing platelet function. Because of the importance of serotonin in the development and amplification of the platelet aggregatory response, we attempted to mimic the clinical situation as closely as possible by using normocalcæmic whole blood. To maintain normocalcæmia the anticoagulant used is recombinant hirudin; this is a pure thrombin inhibitor which has no intrinsic anti-platelet activity and has been shown to be ineffective when platelets are under conditions of high shear and exposed to collagen [100].

The advantage of normocalcæmia is because low Ca^{++} concentration favours TXA_2 production and TXA_2 -dependent secretion during aggregation induced by weak agonists such as ADP or adrenaline [101,102, 103, 104]. TXA_2 production causes additional platelet stimulation and aggregation by positive feedback and thus aggregatory responses in acalcaemic conditions can be spurious. The technique we employ uses low dose (sub-maximal) collagen as the agonist; this simulates the exposure of subendothelial collagen in the damaged vessel wall. At normocalcæmia it has been shown that TXA_2 formation and release of ADP and serotonin largely account for platelet aggregation with collagen in vitro, as determined by platelet counting [105]. Thus, collagen provides a global means of assessing impairment in vitro since these mediators may be altered through several different mechanisms or changes in expression of the integrin receptors involved in adhesion and aggregation, as well as changes in platelet sensitivity to TXA_2 , ADP and adrenaline [105]. This technique has also been applied to investigation of the heparin-induced platelet dysfunction which is encountered clinically and has been demonstrated to be a failure to form large stable aggregates, despite microaggregation being unaffected [106, 107, 108, 109, 110]. Single platelet counting is labour intensive, but many of the simpler tests are unsatisfactory. Binding of the platelet IIb/IIIa receptor to fibrinogen can be measured using cell cytometry or an automated fibrinogen-binding test using the Ultegra[®] rapid platelet function assay (Accumetrics, San Diego, CA, USA). Unfortunately, these assays have not been used so far with samples anticoagulated with hirudin to maintain normocalcaemia, although there appears to be no technical difficulty in so doing.

The future

To where should research into the effects of SSRIs on patients with vascular disease lead?

Figure 4 about here

What is the potential for therapeutic intervention involving the serotonin system in non-depressed patients with arterial disease?

Recent confirmation that acute events are associated with activation of the platelet serotonin system was obtained from the fact that excessive transcatheter accumulation of serotonin appears to play a role in the conversion of chronic stable angina to an unstable coronary syndrome [10].

Blockade of this system during acute coronary syndromes (or acute limb ischaemia) is therefore an obvious therapeutic intervention to be tried. In view of the time required for SSRIs to achieve antiplatelet effects in acute coronary syndromes, it may be difficult to obtain ethical clearance for a comparison of these agents with those that block the serotonin system directly.

In view of the lower platelet serotonin levels reported with SSRI treatment, the evidence of decreased platelet aggregability and the decreased hypertensive responses seen with the use of SSRIs, three lines of research open up:

1. First, monitoring of cardiovascular events should be possible in these patients and can be related to the drugs' antihypertensive effects.
2. Second, the antiplatelet effects of these drugs should be monitored and compared to patients not taking SSRIs. It is now possible reliably to

measure platelet function in whole blood 24 hours after sampling; this would allow remote testing of a large number of patients [111, 112].

3. Third, the possibility of interactions with aspirin and stomach bleeding merits further investigation. It may be that the withdrawal of aspirin could be carried out safely in these patients who would remain protected by their SSRI drug. This of course could be tested by the platelet aggregometry technique as described in the section above.

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