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REVIEW

Aspirin resistance: Fact or fiction? A point of view

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Abstract

Aspirin is a wonder drug that has been used for well over 100 years for its analgesic and antipyretic effects. For the past three decades, it has increasingly been used for the prevention of primary and secondary cardiovascular events. Lately, it has been suggested that a significant number of individuals taking aspirin have become resistant to this drug. The phenomenon of "aspirin resistance" is based on the observation of clinical events in some patients taking aspirin, and/or a diminished platelet aggregation inhibitory response to aspirin therapy. Unfortunately, laboratory assays used to monitor the efficacy of aspirin are far from accurate and the results are not reproducible. Furthermore, results of different platelet function tests are often not congruent. In addition, platelet aggregation studies show marked inter-individual and intra-individual variability. Patients with coronary heart disease take many drugs that interfere with the effect of aspirin on platelet aggregation. Besides inhibiting formation of thromboxane A_2 from arachidonic acid, aspirin has a host of platelet-independent effects that complement its platelet inhibitory effects. Laboratory assays designed to measure platelet function do not take into account these pleiotropic effects of aspirin. In our view, use of the term "aspirin resistance" based on inadequate knowledge of imperfect laboratory tests does a disservice to physicians and patients.

INTRODUCTION

A substance called salicilin was first isolated from the bark of willow tree by Reverend Edmund Stone in 1763[1]. In 1897, acetylsalicylic acid was marketed by the Bayer Company as Aspirin® as an analgesic[2,3]. When other non-steroidal anti-inflammatory drugs (NSAIDs) were introduced in the 1950s, the popularity of aspirin declined. In the 1970s and 1980s, research revealed potent anti-platelet and cyclooxygenase (COX) inhibitory actions of aspirin. Soon thereafter, aspirin started being used as a first-line drug in patients with a variety of cardiovascular disease states.

The Antithrombotic Trialists' Collaboration[4] showed a 12% reduction in major vascular events in primary prevention trials. This was primarily driven by a reduction in myocardial infarction. There was no significant effect of aspirin on the incidence of stroke or vascular mortality. The reduction in major coronary events was similar in both primary and secondary prevention trials [relative risk (RR) 0.82 for primary prevention and RR 0.80 for secondary prevention]. The absolute benefit of aspirin in primary prevention trials was 0.06% per year and in secondary prevention trials was 1% per year. There was a significant 20% reduction in stroke in secondary prevention trials. In

a recent meta-analysis of six studies of aspirin in primary prevention in patients with diabetes mellitus[5], however, no significant reduction in the risk of cardiovascular or all-cause mortality was identified. Although there was a heterogeneity in the rate of myocardial infarction and stroke, aspirin reduced the risk of myocardial infarction in men [odds ratio (OR), 0.57; 95% confidence interval (CI): 0.34-0.94], but not in women (OR, 1.08; 95% CI: 0.71-1.65), and there was no benefit of aspirin against stroke in men or women. Nonetheless, it is now generally accepted that aspirin exerts a powerful effect against cardiovascular events in all secondary, and in some primary, prevention trials. Hence this drug is used in patients with known coronary heart disease and forms the background medication in all patients undergoing coronary, carotid, renal or peripheral artery revascularization.

This issue of "aspirin resistance" is of much interest to patients and physicians, since aspirin is perhaps the most widely used drug worldwide. Almost 30 million people, or 36% of the adult population in the United States, consume 10-20 billion aspirin tablets each year either alone or with other antiplatelet drugs to protect their hearts and brains from platelet-rich clots, the leading cause of heart attacks and strokes.

A recent Medline search by the authors using the words "aspirin-resistance" revealed 364 published articles between 1993 and 2009, 116 published articles using the words "aspirin-resistance coronary disease", and 52 published article using the words "aspirin-resistance stroke".

Antiplatelet therapy, whether it consists of aspirin, clopidogrel, other antiplatelet drugs, or their combination is essentially unmonitored for efficacy. Whether it should remain unmonitored or if the dose or type of drug/s should be tailored for the individual patient is subject to debate. In this context, "aspirin resistance", if there is such a phenomenon, becomes very important.

HOW DOES ASPIRIN WORK?

Aspirin acts on platelets by acetylating the COX enzyme at position serine 529 resulting in the reduced formation of cyclic endoperoxides [prostaglandin G_2 (PGG_2) and PGH_2] from arachidonic acid[6]. The inhibition of the constitutive COX enzyme is irreversible[6,7]. Since platelets are anucleated cells and cannot generate a new COX enzyme, the action of aspirin lasts for the entire lifespan of the platelets which is 7-10 d. The COX enzyme is required for the production of the prostanoid thromboxane A_2 (TXA_2) from cyclic endoperoxides in platelets. TXA_2 is a very potent stimulus for platelet aggregation.

Besides arachidonic acid, platelets are activated in response to epinephrine, collagen, thrombin, and adenosine diphosphate (ADP) (Figure 1). When there is injury to the vascular intima, circulating platelets are exposed to subendothelial collagen, proteoglycans, fibronectin and other adhesive proteins. The resulting changes in platelets can be divided into adhesion, secretion and aggregation. For adhesion, von Willebrand factor is necessary and serves as a bridge between collagen and platelets through its receptor glycoprotein (Gp) Ⅰb/Ⅸ[8]. This causes release of cytosolic Ca^{2+} which facilitates the second phase or secretion. In this phase there is release of alpha and dense granules. P-selectin released from alpha granules causes adhesion of monocytes and neutrophils to activated platelets[9]. Dense granules release ADP, a potent mediator of the third phase of platelet activation, namely platelet aggregation. ADP acts through the platelet specific receptor P2Y1 and mediates the action of phospholipase A_2 on membrane phospholipids[6]. This releases arachidonic acid, which is converted to endoperoxides *via* constitutive COX (COX-1); activation of TXA_2 synthase enzyme then converts endoperoxides to TXA_2 in platelets[10]. In addition to ADP and TXA_2, other stimuli, such as 5-hydroxytryptamine and epinephrine can initiate aggregation *via* specific receptors. The cytosolic release of Ca^{2+} also causes a conformational change in platelet GpⅡb/Ⅲa receptors which allows the platelets to bind to fibrinogen[6]. These stimuli lead to a build-up of Ca^{2+}, which causes an autocatalytic reaction of platelet aggregation.

Table 1 Cyclooxygenase-independent effects of aspirin

On platelets
Partially inhibits ADP2Y12 receptor activation responsible for residual arachidonic acid induced platelet activation[11]
Blocks NF-κB activation that facilitates platelet inhibition by neutrophils[12]
Anti-inflammatory effect
Inhibits release of reactive oxygen species[13]
Inhibits release of elastase and soluble ICAM-1[13]
Inhibits formation of malondialdehyde[13]
Inhibits formation of oxidized LDL antibodies[14]
Reduces inflammatory cell activity[13]
Anti-oxidant effect
Inhibits oxidized LDL formation[14]
Blocks transcription of LOX-1[15,16]
Scavenges hydroxyl radicals[17]
Induces synthesis of ferritin[18]
Inhibits nitric oxide synthase[19,20]
Inhibits expression of redox sensitive transcription factor NF-κB[19,20]
Acetylates proteins and prevents their oxidation[21,22]
Endothelial function modification
Prevents adhesion of neutrophils and monocytes[23]
Induction of VCAM-1, ICAM-1 and E-selectin[24,25]
Miscellaneous effects
Inhibits vascular smooth muscle cell function[26]
Inhibits angiogenesis[27-29]
Inhibits γ-carboxylation of coagulation factors[30]

ADP: Adenosine diphosphate; NF-κB: Nuclear factor-κB; ICAM-1: Intracellular adhesion molecule-1; LDL: Low density lipoprotein; LOX-1: Oxidized LDL receptor.

ASPIRIN CAN ACT THROUGH COX-INDEPENDENT PATHWAYS BESIDES A COX-DEPENDENT PATHWAY

Aspirin has a myriad of effects that are not limited to platelet inhibition through COX enzymes (Table 1). In platelets, there is residual arachidonic acid-induced platelet activation in aspirin treated patients even after controlling for

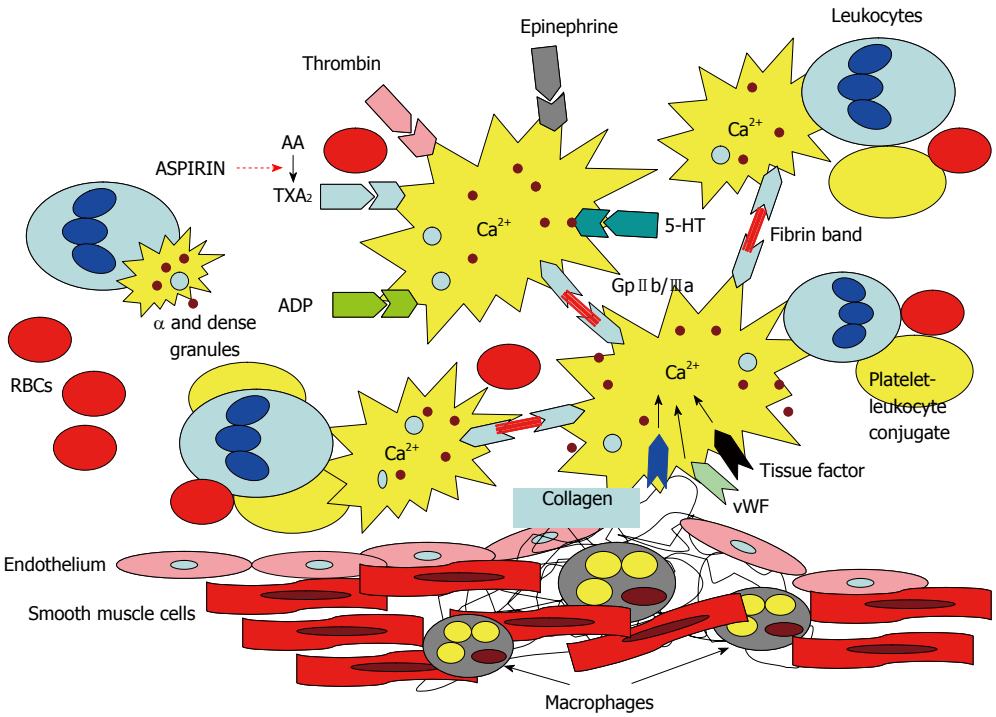

Figure 1 Pathways of platelet aggregation. Platelets can be activated in response to collagen, von Willebrand factor (vWF) and tissue factor when there is injury to the endothelial lining. A host of other stimuli, such as adenosine diphosphate (ADP), 5-hydroxytryptamine (5-HT), epinephrine and thromboxane A_2 (TXA_2), can initiate aggregation *via* specific receptors. The end-point is the rise in cytosolic Ca^{2+} which induces platelet activation/aggregation. Externalization of glycoprotein (Gp) Ⅱb/Ⅲa receptors causes fibrin bands to bind to different platelets. Aspirin interferes with the conversion of arachidonic acid (AA) to TXA_2 and inhibits the rise in cytosolic Ca^{2+} and subsequent platelet aggregation.

non-compliance and under-dosing. This platelet activation is independent of the COX pathway and is dependent on ADP P2Y1 and P2Y2 receptors[11]. Through the nitric oxide/nuclear factor-κB (NF-κB) pathway aspirin facilitates the inhibition of platelet activation by neutrophils[12].

Other agents that inhibit COX expression or activity, such as NSAIDs, or the direct TXA_2 synthase and receptor inhibitors inhibit platelet aggregation, but do not show the same beneficial effect against vascular disease as aspirin, suggesting unique vascular properties of aspirin, independent of the COX-TXA_2 pathway[31].

Activation of inflammatory pathways is intimately related to the pathogenesis of atherosclerosis as well as the precipitation of acute vascular events. Aspirin reduces inflammatory cell activity, release of elastase and soluble intracellular adhesion molecule-1 (ICAM-1), and formation of malondialdehyde and oxidized low density lipoprotein (LDL) antibodies[13].

Aspirin has significant antioxidant properties. Accordingly, it protects LDL-cholesterol from oxidation. Oxidized LDL is now recognized to be a more potent mediator than native LDL in atherogenesis[32]. Aspirin also exerts some of its antiatherogenic effect *via* a reduction in oxidized LDL formation[14]. The salicylate moiety in aspirin blocks the transcription of Oxidized LDL receptor 1, a receptor for oxidized LDL, in endothelial cells[15] and platelets[16]. Aspirin can also scavenge hydroxyl radicals[17]. Aspirin has been demonstrated to induce synthesis of ferritin that sequesters free cytosolic iron which is the main catalyst for oxygen radical formation[18]. Lastly, aspirin induces a small reduction in blood cholesterol[33].

Aspirin inhibits cytokine-inducible nitric oxide synthase gene expression, an effect that involves the activation of redox-sensitive transcription factor NF-κB[19,20]. *Via* its acetyl moiety, aspirin can acetylate ε-amino groups of lysine residues in proteins and prevent their oxidation[21,22]. This effect of aspirin on proteins is important in limiting both lipoprotein and fibrinogen oxidation[21,22], with resultant reduction in inflammation in patients with vascular disease[34].

Aspirin improves the dysfunctional state of the endothelium[23] and prevents the adhesion of neutrophils and monocytes to the activated vascular endothelium. This effect is mediated *via* inhibition of NF-κB activation and induction of various adhesion molecules, such as vascular cell adhesion molecule-1, ICAM-1 and E-selectin[24,25]. In clinical disease states, aspirin has been shown to normalize nicotine-induced endothelial dysfunction[35] and to restore the forearm vasodilatory effect of acetylcholine in hypercholesterolemic patients[36].

Aspirin, in high concentrations, inhibits growth of human vascular smooth cells in culture[26]. This property of aspirin may have a salutary effect after percutaneous intervention in terms of restenosis at the site of angioplasty or stent placement. Aspirin can reverse hypoxia-induced coronary vasoconstriction[37], a mechanism that contributes to aspirin's effect on vascular tone following percutaneous coronary intervention.

Aspirin also has a modest anticoagulant effect. Salicylate, a metabolite of aspirin, can inhibit γ-carboxylation of coagulation factors Ⅱ, Ⅶ, Ⅸ and Ⅹ[27-29]. The fibrinolytic activity of blood increases with aspirin and is mediated by acetylation of the ε-amino groups of lysine residues.

Both COX-1 and COX-2 are important in the regulation of angiogenesis. Aspirin inhibits angiogenesis, which is an essential step in the growth of atherosclerosis. This inhibitory effect of aspirin is mediated *via* inhibition of mitogen-activated protein kinase activity on endothelial cells[30].

WHAT IS "ASPIRIN RESISTANCE"?

There is no consensus definition of "aspirin resistance". This phenomenon has been described based on clinical assessment or on the results of laboratory tests that assess platelet activation. A recent article in the European Heart Journal has aimed at obtaining a consensus definition for aspirin resistance. The clinical definition of "aspirin resistance" relates to the occurrence of thromboembolic events despite aspirin intake. In the laboratory, "aspirin resistance" has been defined as the failure to inhibit platelet reactivity despite taking antiplatelet drugs. However clinical resistance to aspirin has often been termed 'treatment failure'. Not all patients with 'treatment failure' have laboratory evidence of aspirin resistance and *vice versa*[38].

The reported prevalence of "aspirin resistance" is variable[39-74] with a rate of approximately 8.3% in healthy adults (Table 2). In subjects with one or more risk factors its prevalence ranges from 0.7% to 23.4%. In patients with stable coronary artery disease, again a wide range has been noted, with the prevalence as high as 29%. In patients with acute myocardial infarction, congestive heart failure and peripheral vascular disease, and in others undergoing coronary artery bypass grafting or percutaneous coronary intervention, the reported prevalence of "aspirin resistance" has been as high as 50%-70%. However, based on the results from a combination of three of the most commonly used laboratory tests (VerifyNow®, optical aggregometry, PFA-100®), the prevalence rate is approximatively 2% in patients with transient ischemic attacks and stroke[74].

Laboratory evaluation of platelet activation

Most of the variability in the prevalence of "aspirin resistance" is due to different platelet function tests that are used to assess platelet activation. The tests used include light transmission aggregometry, whole blood aggregation, flow cytometry and point-of-care tests. Indirect measurement of TXA_2 formation include serum TXB_2 and urinary 11-dehydro-TXB_2. However, measurement of TXA_2 metabolites does not take into account formation of TXA_2 by non-platelet sources, such as endothelial cells, leukocytes and renal tissue[11].

Light transmission and impedance aggregometry have been the gold standard for measuring platelet aggregation function. Many point-of-care assays have been developed to study platelet activation. Some of these assays assess COX-dependent pathways and others include COX-independent pathways. The most common of these point-of-care assays are VerifyNow® and PFA-100®. A comparison between PFA-100®, platelet aggregometry and GpⅡb/Ⅲa flow cytometry found little correlation between the results obtained from these three methods[75]. Some investigators have also used measurement of aspirin metabolites and bleeding time to assess the efficacy of aspirin.

Table 2 Reported prevalence of "aspirin resistance"

	Prevalence (%)	Ref.
Healthy adults	8.3	[38]
Risk factors	0.7-23.4	[39,40]
Stable CAD	0.4-29.2	[41-48]
CVD	12.5-56	[49-55]
CABG	7.1-54	[56-60]
PCI	12.7-26.2	[61-64]
MI	0.5-70.1	[65-70]
CHF	55.0	[71]
PVD	9.6-60	[72,73]

CAD: Coronary artery disease; CVD: Cardiovascular disease; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; MI: Myocardial infarction; CHF: Congestive heart failure; PVD: Peripheral vascular disease.

PFA-100® assay

This test uses cartridges coated with platelet agonists (either collagen/ADP or collagen/epinephrine). The time for platelet plug to close the central opening (closing time) is used as a measure of platelet reactivity[10,76]. This test is thought to simulate platelet function *in vivo* and can be considered an *in vitro* equivalent of bleeding time[76]. "Aspirin resistance" is defined as: closing time < 193 s using collagen/epinephrine, and < 121 s using collagen/ADP as agonists[44]. This test is unfortunately not aspirin-specific. It correlates well with light transmission aggregometry.

VerifyNow® assay

This is a point-of-care platelet aggregation test that correlates with the results obtained with light transmission aggregometry. Response to aspirin is reported in aspirin resistance units. The extent of COX inhibition is believed to be measured by this assay[77,78]. "Aspirin resistance" is usually taken as ⩾ 550 units[46].

Light transmission and impedance aggregometry assays

Light transmission aggregometry measures optical density of plasma after platelet aggregation with an agonist. The problem with this test is lack of standardization as to the choice of agonist/s and their concentration. For example, platelet aggregation in a given person may be abnormal in response to ADP 1-5 μmol/L, but completely normal using higher concentrations. Furthermore, there is a marked variability in aggregation response to different agonists. Impedance aggregometry has the same principle, but utilizes whole blood instead of plasma and measures

electrical impedance instead of light transmission[10]. This test assesses the role of blood components including leukocytes and clotting factors besides platelets in thrombus formation as a mild electrical current is passed through the whole blood. Again, the ideal agonist for thrombus formation has not been defined.

TXA_2 metabolites

Serum TXB_2 and urinary 11-dehydro-TXB_2 are metabolites of TXA_2. They have been used to assess "aspirin resistance". These are COX-1 dependent tests and are not platelet specific and do not necessarily reflect platelet reactivity. Serum TXB_2 reflects TXA_2 formation by endothelial cells and leukocytes in addition to platelets. Urinary 11-dehydro-TXB_2 usually requires 24 h urine collection and reflects TXA_2 formation by renal tissues besides platelets and leukocytes[79]. These tests were initially quite popular, but have lost their popularity because of the time delay between aspirin intake and measurement in the laboratory.

Thromboelastogram and impact cone and platelet analyzer

The thromboelastogram platelet mapping system is a point-of-care system that measures clot formation and lysis. This uses whole blood and requires pipetting. The impact cone and platelet analyzer is a point-of-care test that assesses shear-induced platelet adhesion[80].

Flow cytometric analysis

Monoclonal antibodies against platelet surface antigens, such as GpⅡb/Ⅲa, P-selectin, platelet monocyte aggregates, thrombospondin and CD-40 ligand can be used to measure expression of certain antigens. Expression of these antigens has been found to be lower in patients treated with aspirin than controls[81].

Rapid platelet function assay

In this test, blood is run through a transparent fibrinogen-coated cartridge with platelet agonists. When a thrombus forms on the surface, light transmission changes and reflects platelet aggregation[79]. This test is not aspirin-specific.

Platelet reactivity

Venous blood is mixed with either EDTA-buffer or EDTA-formaldehyde buffer; activated platelets are dispersed in the former and fixed in the latter. The mixture is then centrifuged and only non-activated platelets remain in the supernatant. Platelet count in the supernatant (*vs* the platelet count in blood) is a reflection of adherent platelets[79].

Bleeding time

This is the only *in vivo* test that measures platelet activation. It is independent of coagulation factors and is a reasonably good index of platelet function[79].

A recent consensus statement by the Working Group for antiplatelet drug resistance[38] states that the term laboratory resistance should be reserved for pharmacodynamic resistance resulting from changes in enzyme or receptor. Aspirin hyporesponsiveness is defined as more than 10%-20% with light transmittance aggregometry and more than 0 ohms with impedance aggregometry. For determining aspirin-specific effects, the recommended test is arachidonic acid-induced aggregation or serum TXB_2 levels. However, it should be noted that there is no evidence that any of these laboratory values are associated with an adverse cardiovascular outcome.

DOES "ASPIRIN RESISTANCE" REALLY EXIST?

The phenomenon of "aspirin resistance" is characterized by attenuated inhibition of platelet aggregation in some patients taking aspirin. The term "aspirin resistance" came into use because some patients manifesting this phenomenon had cardiovascular events, presumably on the basis of platelet activation[82]. However, a direct correlation between evolution of cardiovascular events and *ex vivo* platelet activation has never been demonstrated. Also, the reduced platelet response (aggregation inhibition) in studies showing "aspirin resistance" was identified by different methods in different studies; some used platelet-rich plasma, others used whole blood to assess platelet aggregation, and yet others used serum TXB_2 measurement. The concentration of agonists used for inducing platelet aggregation varied widely in different studies, and the agonists were different in different studies. Pitfalls in studying platelet activation with different stimuli have been described earlier. Some investigators have shown that "aspirin resistance" may be present in some individuals using one particular stimulus, but not another. In addition, a person with "aspirin resistance" may not have "aspirin resistance" a week or two later.

As mentioned earlier, there is residual platelet activation (primary wave of aggregation) which is unaffected by aspirin treatment and is independent of non-compliance and under-dosing of aspirin. The residual platelet aggregation may be quite marked in some individuals. As stated earlier, there are multiple pathways of platelet aggregation (Figure 1) and most laboratory tests assess only one or two of these pathways. Most of these pathways are not entirely TXA_2-dependent and, therefore, not aspirin-specific. Further, most studies on "aspirin resistance" did not measure baseline platelet function (i.e. before aspirin treatment). In our opinion, the wide variation in the prevalence of "aspirin resistance" reflects the underlying heterogeneity in platelet response from patient to patient.

There are multiple reasons for the phenomenon of diminished inhibition of platelet aggregation in patients taking aspirin (Table 3). Non-compliance is perhaps the most likely cause of "aspirin resistance"[49,83]. Use of concomitant medications, such as NSAIDs and proton pump inhibitors (PPIs), which affect COX enzyme kinetics, can contribute to "aspirin resistance". Age, gender

Table 3 Underlying causes of "aspirin resistance"

Abnormal pharmacokinetics
Non-compliance
Inadequate dosing
Tachyphylaxis
Interaction with other drugs, such as NSAIDs and PPIs
Clinical conditions
Advanced coronary artery disease, acute coronary syndromes, CABG
Diabetes mellitus
Heart failure
Infection/inflammation
Obesity
Genetic
COX-1 gene mutation
COX-2 overexpression
GpⅡb-Ⅲa polymorphisms
Molecular
Increased turnover of platelets
PGH_2 substrate is provided to platelets by monocytes or endothelial cells
Incomplete inhibition of TXA_2 formation
Increased platelet sensitivity to ADP and collagen
Increased COX-2 expression on platelets

COX: Cyclooxygenase; NSAIDs: Non-steroidal anti-inflammatory drugs; PPIs: Proton pump inhibitors; Gp: Glycoprotein; TXA_2: Thromboxane A_2; PGH_2: Prostaglandin H_2; ADP: Adenosine diphosphate.

and smoking also reduce the platelet inhibitory effect of aspirin[47]. Hormonal changes in women have been shown to enhance platelet activation, and thus women may be more prone to show "aspirin resistance"[84]; others have disputed the presence of this phenomenon[41]. There is also a diurnal as well as a seasonal increase in platelet activation related to catecholamine surge in the morning hours and during the winter months which may manifest as a diminished response to aspirin. Variation in pharmacokinetics is another cause of "aspirin resistance". Clinical conditions, such as diabetes mellitus, advanced coronary disease, chronic kidney disease, acute coronary syndromes, inflammation, obesity and bypass surgery, are characterized by an increased platelet aggregatory response to different stimuli, which may be characterized as "aspirin resistance". We have observed serum TXB_2 levels to rise with continued use of aspirin (unpublished data), perhaps a response to the increase in platelet turnover and/or activation of alternate sources of TXA_2 generation.

Genetic polymorphisms have been noted to contribute to the diminished effect of aspirin on platelet biology. Genetic polymorphisms involving GpⅢa (P1A1/A2 polymorphism)[41,85,86] and COX-1 and COX-2[85-87] can lead to a variable effect of aspirin on platelet function.

It is also important to recognize that in conditions that are associated with infection and inflammation, non-platelet sources such as monocytes, macrophages and endothelial cells, activate the COX-2 enzyme, resulting in increased formation of TXA_2 and increased levels of F2-isoprostanes. Such COX-1-independent mechanisms are especially relevant to patients with diabetes mellitus, hyperlipidemia, smoking and heart failure, all of which are associated with augmented lipid peroxidation of arachidonic acid and consequent overproduction of isoprostanes. Failure of usual doses of aspirin to completely inhibit TXA_2 may be misinterpreted as aspirin resistance.

MANAGEMENT OF DIMINISHED RESPONSE TO ASPIRIN

The 2005 position paper of the working group on aspirin resistance concluded that there was not enough evidence of clinical improvement in changing treatment in aspirin resistance[83]. Some experts have recommended increasing the dose of aspirin to overcome "aspirin resistance"[88,89]; others have refuted the usefulness of this approach[6]. We believe that while most patients have adequate inhibition of platelet aggregation with low doses of aspirin, others need higher doses. Which patients are in the latter group is not known. Accordingly, we tend to prescribe a 325 mg daily dose to patients with multiple risk factors with evidence of ongoing vascular injury and inflammation, and to those who show evidence of repeated coronary artery occlusion. Addition of other antiplatelet agents such as clopidogrel and prasugrel to aspirin therapy might also help. A recent study shows that addition of an omega-3 fatty acid can overcome "aspirin resistance"[90].

In general, the use of NSAIDs and PPIs in patients needing aspirin should be curtailed or kept at a minimum as these agents tend to reduce the availability of aspirin. There may well be other agents that influence the pharmacokinetics of aspirin. Point-of-care tests, in our view, are not helpful in defining who is "aspirin resistant" and who is not.

CONCLUSION

Aspirin is a remarkable drug that reduces cardiovascular events and limits atherogenesis and perhaps development. This drug works through a host of mechanisms which are complementary to its platelet inhibitory effect. As such, use of the term "aspirin resistance" based on imperfect test-tube measurements is a disservice to the legacy of this very useful compound.

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