Review Article

Aspirin Resistance: A Review

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Abstract

The benefits of aspirin have been studied extensively and its place in therapy has been established through many landmark clinical trials. Despite the proven efficacy in clinical studies, there is a growing concern regarding patients who continue to experience vascular thrombotic events despite receiving aspirin therapy. The aim of this review is to give an overview of the various clinical studies, discussing possible mechanisms, diagnostic testing and the prevalence of aspirin resistance. In recent years aspirin resistance has been in focus and the mechanisms to determine aspirin resistance are being studied. Several laboratory studies have reported variations in response to aspirin treatment and also the platelet function has been demonstrated to be normal in a considerable proportion of patients taking aspirin daily. However according to the available data and ongoing research, it has been shown that about 20% of the patients are resistant to the antiplatelet effects of aspirin, or the doses they are taking are too low to affect platelet aggregation.

***Keywords*:** Aspirin, resistance, mechanism, clinical studies

Introduction

Aspirin resistance can be defined as the lack or decreased antiplatelet effect despite therapeutic doses of aspirin or the incidence of recurrent vascular events in patients taking aspirin. This term has been used interchangeably in the literature to describe biochemical as well as clinical phenomenon (Sanderson et al., 2005).

Failure of aspirin to suppress thromboxane production and therefore to inhibit platelet aggregation *in vitro* has been linked to inadequate protection against atherothrombotic events. Millions of people with heart disease who take aspirin need to know whether it is effective for them. Not finding out whether the patient is aspirin resistant would be comparable to diagnosing someone with high blood pressure, giving him medication and then not monitoring his blood pressure.

However aspirin resistance, also called 'aspirin non-responsiveness' or simply treatment failure, is a heterogeneous phenomenon still without a generally accepted definition and with unclear clinical implications.

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Classification

Aspirin resistance may be classified as (Patrono, 2003).

i. Laboratory resistance (the failure of aspirin to inhibit platelet thromboxane-A2 production or inhibit platelet aggregation or persistent platelet activation, demonstrated by platelet function tests (biochemical aspirin resistance)

ii. Clinical resistance (the failure of aspirin to prevent clinical thromboembolic ischemic events in patients prescribed aspirin) or the recurrence of vascular events in patients prescribed usual therapeutic doses of aspirin (clinical aspirin resistance). The clinical concept is nonspecific and might be preferably labeled as *clinical treatment failure*.

Postulated mechanisms for aspirin resistance

Possible postulated mechanisms for aspirin resistance as reviewed by Cambria-Kiely and Gandhi (2002):

- Concurrent intake of certain NSAIDs
- Inadequate dose of aspirin
- Poor compliance
- Reduced bioavailability
- Enhanced platelet function

- Biosynthesis of TXA2 by pathways that are not blocked by aspirin, e.g. by COX-2 in monocytes and macrophages
- Increased platelet sensitivity to ADP and collagen
- Hypercholesterolemia, usually accompanied by increased thrombin generation
- Hypercoagulable states following MI and unstable angina
- Increased release of platelets from bone marrow in response to stress, i.e. after coronary artery bypass surgery, introducing to blood newly formed platelets unexposed to aspirin
- Genetic polymorphisms
- Transcellular arachidonate metabolism between aspirinated platelets and endothelial cells
- Inadequate blockade of red cell-induced platelet activation
- Polymorphism of platelet glycoprotein IIb/IIIa; carriers of PlA2 allele are less sensitive to antithrombotic action of aspirin in vivo
- Polymorphisms of platelet collagen receptors
- COX-2 variants in patients after coronary artery bypass surgery
- FXIII Val34Leu polymorphism leading to variable inhibition of FXIII activation by low-dose aspirin
- Increased platelet turnover
- Upregulation of non-platelet pathways of thromboxane production

Other probable factors

- Increased levels of norepinephrine (excessive physical exercise, mental stress)
- Smoking
- Oxidant stress and biosynthesis of 8-iso-PGF2a

The potential benefit of aspirin therapy may be significantly reduced in patients with aspirin resistance, creating a clinical and economic burden on the healthcare system. It is estimated that 29 billion aspirin tablets are consumed each year by Americans, with the most popular use of aspirin being the prevention of cardiovascular disease. However studies have estimated that 5% to 45% of patients taking aspirin are experiencing suboptimal antiplatelet effects (Gum et al., 2001).

The potential impact of aspirin resistance is highly significant since large populations of patients are taking aspirin and therapeutic failure due to aspirin resistance can have a major impact on the cost of treating patients with coronary heart disease and stroke.

The American Heart Association (AHA) estimates that $112 billion per year is spent on direct costs, including hospital, nursing home, physician and drug cost on these diseases. The cost on society adds another $88 billion per year in lost productivity and loss of future earnings. AHA also estimates that 2.4 million procedures, including angioplasty, PCI (percutaneous intervention) and cardiac revascularization are performed yearly. Since aspirin resistance prevalence is estimated to be between 5% and 45%, the cost of treatment and the number of interventions can be significantly reduced if patients can be identified with validated laboratory tests and treated appropriately according to their resistance to aspirin (Gum et al., 2001).

There is growing evidence that patients with laboratory evidence of aspirin resistance are at a greater risk of thromboembolic events than aspirin sensitive or aspirin responders.

Clinical Studies

A number of clinical studies have been done in an attempt to explain the phenomenon of aspirin resistance, but they seem to be insufficient in explaining the phenomena of aspirin resistance. Same research may yield different results and, the characteristics in different population exhibiting aspirin resistance may add to the complexity. Aspirin resistance cannot be explained by only one pathway. More studies are required to investigate the mechanisms in different population (Zhang and Zhang, 2007).

The first study to demonstrate variability in response to aspirin was published nearly 50 years ago. Since then numerous trials evaluating responsiveness to aspirin in a variety of different settings, have been undertaken. No trial till date has ever found a uniform response to aspirin despite using a wide range of techniques.

Various studies have reported a prevalence of aspirin resistance in healthy volunteers and in patients with various manifestations of atherosclerosis in frequencies ranging from 5.5% to 60%. So far only a few published papers have provided knowledge on the clinical relevance of aspirin resistance. Overall these trials support the hypothesis of an association between aspirin resistance and an increased risk of suffering future thrombotic complications.

In 2004, the New York Times reported that up to 40% of aspirin users are resistant to aspirin. Patients prescribed aspirin to prevent atherothrombotic vascular disease need to know if they are resistant to aspirin and if so, what the implications are.

Table 1. Prevalence of aspirin resistance reported in selected studies (Modified from Poulsen et al., 2005).

Authors	Sample size	Aspirin dose mg/day	Platelet analysis method used	% aspirin resistant	Aggregating agent used
Grotemeyer et al., (1993)	180	1500	Platelet reactivity index	33	Aggregation induced by blood collection
Helgason et al., (1994)	306	325	Optical	25	AA, ADP, Collagen, Epinephrine
Mueller et al., (1997)	100	100	Whole blood aggregometer	60	ADP, Collagen
Buchanan et al., (2000)	289	325	Bleeding time	55	
Peters et al., (2001)	19	100	PFA-100	63	Collagen, ADP, Epinephrine
Macchi et al., (2002)	72	160	PFA-100	29	Collagen/ Epinephrine
Andersen et al., (2002)	129	75-160	PFA-100	37	Epinephrine, ADP
Christiaens et al., (2002)	50	>75	PFA-100	20	Collagen/ Epinephrine
Hezard et al., (2002)	50	75-300	PFA-100, optical	52 19-38	ADP
Ziegler et al., (2002)	52	100	PFA-100	10	Collagen/ Epinephrine
Sane et al., (2002)	88	325	Flow cytometry,	57	Collagen, ADP
Macchi et al., (2003)	72	160	PFA-100	29	Collagen/ Epinephrine
Gum, et al. (2003)	326	325	PFA-100, optical	9.5, 5.5	AA, ADP
Wang et al., (2003)	422	81-325	Ultegra RPFA	23	ADP
Grundmann et al., (2003)	53	100	PFA-100,	34	Collagen/ Epinephrine
Chen et al., (2004)	151	80-325	Ultegra RPFA	19	Incidence of myonecrosis measured
Cotter et al., (2004)	82	100	TxB2	12	Measured health outcome
Alberts et al., (2004)	129	< 162 162-325	PFA-100	56 28	Analysed mean closure time
Prabhakaran et al., (2008)	71	Median dosage 1300mg/wk	RPFA	4.2	Aspirin reaction measured
Lim et al., (2009)		100	Ultegra RPFA	14.8	
Thomson et al., (2009)	63	75	Urinary 11 dehydrothromboxane	38.1	
Jian Cao et al., (2012)	304	>75	LTA TEG	8.2 20.4	
Liu et al., (2013)	246	≥ 75	LTA TEG	9.3 24.8	AA, ADP
Ibrahim et al., (2013)	74		Multiplate	16	
Azmin et al., (2013)	50	5 doses total 900mg	Multiplate	14	
Yaturu et al., (2014)	142	81	Urinary TBX2	53	
Chadha et al., (2015)	126	150	LTA	2	ADP, AA
Maleki et al., (2016)	370	80,81,100,325	Bleeding Time(IVY method) Urinary TXB2	37.6 64	

Ultegra RPFA=Ultegra Rapid Platelet Function Assay, PFA-100=Platelet Function Analyser-100
MEA=Multiple electrode platelet aggregometry.

Friend et al., (2003) defined aspirin resistance as poor platelet responsiveness to aspirin and therefore aggregation of ≥ 50% of platelets. Gum et al., (2001), defined aspirin resistance based on the aggregating agents used. The percentage aggregation by using different stimulating agents was measured. Aggregation of ≥ 70% with 10 μM ADP, and of ≥ 20% with 0.5 mg/ml arachidonic acid, constituted aspirin resistance. This study shows that the aggregating or the stimulating agents also need to be considered while defining aspirin resistance.

Weber et al. (1999, 2002) classified aspirin resistance into three main categories. Type-1 (pharmacokinetic type) entails the inhibition of platelet thromboxane formation *in vitro* but not *in vivo*. Type-2 (pharmacodynamic type) is characterized by the inability of aspirin to inhibit platelet thromboxane formation both *in vivo* and *in vitro*. Type-3 (pseudoresistance) involves thromboxane-independent platelet activation. The results also suggested that the inducible isoform of cyclooxygenase in platelets, COX-2, confers aspirin resistance, although this opinion was challenged by Patrignani et al. (1999).

It is clear that further large prospective studies are needed to further clarify the clinical significance of aspirin resistance.

Hence aspirin resistance and aspirin non-responsiveness are the terms used for describing both the failure of aspirin to

protect individuals from severe vascular events and to cause inhibition of platelet function. Several studies utilizing a broad range of platelet function tests have shown that some subgroups of individuals exhibit a reduced or completely missing antiplatelet response to aspirin. The clinical significance of aspirin non-responsiveness for the prediction of clinical endpoints remains, however, to be determined. Thus far, only a few prospective clinical trials have demonstrated a possible relationship between aspirin non-responsiveness and subsequent vascular events. Most platelet function tests used in respective clinical studies cannot be reliably performed in clinical routine and are not interchangeable for monitoring antiplatelet treatment. There is a need for a simple and reliable assay for predicting the clinical efficacy of antiplatelet therapy (Patrono, 2003; Sanderson et al., 2005).

Several studies have demonstrated, using various platelet function tests (PFTs) that subgroups of patients taking acetylsalicylic acid (ASA) failed to produce the desired antiplatelet effect. Several different methods like optical aggregometry, platelet aggregation in whole blood, platelet function analyzer (PFA-100), platelet reactivity test or platelet aggregate ratio, flow cytometry and thromboxane B2 generation have been used to determine platelet function and hence aspirin resistance. The widespread clinical use of these platelet function tests is substantially limited due to complex preanalytic factors, reduced specificity and poor reproducibility and hence, there is a need for a simple and reliable assay for predicting the clinical efficacy of antiplatelet therapy (Haubelt et al., 2005).

Although formal diagnostic criteria are lacking, aspirin resistance generally describes the failure of aspirin to produce an expected biological response or the failure of aspirin to prevent atherothrombotic events. Aspirin resistance has been reported to occur in 5% to 60% of the general population, therefore, its detection is potentially of clinical importance (Benedek et al., 1995; Buchanan et al., 1995).

Conclusion

Estimates suggest that the prevalence of aspirin resistance is between 5.5% and 60% depending upon the definition used and parameters measured and also the methods used to measure platelet aggregation. Only a limited number of clinical studies which are of a sufficient scale, well designed, and prospective, with aspirin used at standard doses have convincingly investigated the importance of aspirin resistance. Also, most studies do not sufficiently address the issue of non-compliance to aspirin as a frequent, yet easily preventable cause of resistance to this antiplatelet drug. The clinical implications of aspirin resistance needs to be explored in various cardiovascular disease states, including diabetes mellitus, hypertension, heart failure, and other similar disorders where platelet reactivity is enhanced.

Conflict of Interests – None Declared

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