

Aspirin Resistance: A Review

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Abstract— Aspirin is valuable medicine used for the prevention and treatment of coronary artery disease. Its antithrombotic mechanism is believed to be inhibition of the biosynthesis of thromboxane (and thus platelet activation) by inactivation of platelet cyclooxygenase-1 (COX-1). But in significant number of patients clotting occurs despite of taking regular Aspirin resulting in Aspirin resistance. Aspirin resistance in different studies varied from 8% to 45%. This Aspirin resistance is either of due to inadequate intake of Aspirin, Concurrent intake of certain NSAIDS, Concurrent cigarette smoking, certain diseases like Diabetes and Arteritis, Increased platelet sensitivity to collagen and ADP, Biosynthesis of thromboxane, Increased turnover and vascular endothelial cells, Over expression of COX-2 in RNA, Generation of β_2 -iso PGF2 alpha binds to thromboxane receptors, Polymorphism in Ia/IIa, Ib/V/IX and IIb/IIIa receptors, COX-1, COX-2 thromboxane-A₂ synthetase or other arachidonate metabolism enzymes, Factor XIII etc. It can be diagnosed by Bleeding time, Selection-P. over expression, measurement of urinary concentration of the metabolite II-dehydrothromboxane B₂ indicate the level indicate the level of TXA₂ generation etc. Its resistance may lead to acute coronary syndrome, Acute Myocardial Infraction and/ or cardiovascular death in these coronary artery disease patients. Combining with other antiplatelet agents with other precautions like avoid concurrent use of NSAIDS, avoid cigarette smoking, taking proper dose of aspirin etc may prevent Aspirin resistance.

Keywords— Aspirin Resistance, Atherothrombotic vascular event, Acute Myocardial Infraction

1. Introduction:

Aspirin is one of the valuable drug used for the prevention and treatment of coronary artery disease, the single leading cause of death worldwide. Aspirin reduces the death worldwide. Aspirin reduces the odd of serious Atherothrombotic vascular events and death in a broad category of high risk patients by Duarter.

Aspirin was synthesized by Felix Hoffman¹ in 1897 and for the 1st time in 1948 it was proposed that it might be beneficial in the treatment of coronary artery disease². The ISIS-2 trial in 1988 confirms the crucial role of aspirin in treatment of Acute Myocardial infraction by showing 20% decrease in mortality with use of Aspirin.

Aspirin acts primarily by interfering with biosynthesis of TXA₂, Prostacyclin & other prostaglandins. It irreversibly inhibits COX-1 by Acetylation of Serine -530 and induces a long lasting functional defect in platelets. The resultant decrease in production of TXA₂ & PG₂ account for much of Aspirin antithrombotic effect³. Plasma half life of Aspirin is only 20 min in circulating blood. It is rapidly deacylated convert salicylate in vivo.

2. **Evolution of Aspirin Resistance:**

Aspirin is used by millions of patients for the prevention and treatment of coronary artery disease, the single leading cause of death in the world. The primary antithrombotic mechanism is believed to be inhibition of the biosynthesis of thromboxane (and thus platelet activation) by inactivation of platelet cyclooxygenase-1 (COX-1). A recent meta analysis reported that among high risk vascular patients, Aspirin therapy was associated with a 34% reduction in nonfatal myocardial infarction, a 25% reduction in nonfatal stroke and 18% reduction in all cause mortality⁴. However it appears that Aspirin's antiplatelet effect may not be uniform in all patients. A Significant number of these patients manifest breakthrough events despite regular intake of Aspirin. The occurrence of clotting in patients taking regular Aspirin has been attributed to the failure of Aspirin blocking its target and is a hot topic in cardiovascular disease today. This has resulted in the emergence of the phenomenon of Aspirin resistance.

3. **Definition of Aspirin Resistance:**

Aspirin resistance is a poorly defined term. Aspirin resistance has been used to describe several different phenomena. One is the inability of aspirin to protect patients from ischaemic vascular events. This has also been called Clinical Aspirin resistance. Aspirin resistance has also been used to describe an inability of Aspirin to produce an anticipated effect on or more tests of platelet function, such as inhibiting biosynthesis of thromboxan⁵, inhibiting platelet aggregation⁶ and causing a prolongation of the bleeding time⁷. This has been called Biochemical Aspirin resistance.

An appropriate definition of Aspirin resistance may be "the lack of anticipated response to a therapeutic dose of Aspirin (75-150 mg/day for at least five days in a compliant patient), that can be demonstrated by a specific, valid and reliable laboratory measure of the antiplatelet effect of Aspirin and which correlate significantly, independently, and consistently with an increased incidence of atherothrombotic vascular events⁸. The definition may be refined in the future to include proven genetic determinants (for example, platelet polymorphisms), which mediate Aspirin resistance and risk of Ischaemic events.

4. **Prevalence of Aspirin Resistance:**

Exact prevalence of Aspirin resistance among patients taking aspirin, is not known because of inavailability of proper test at all centres. Studies have reported a prevalence of Aspirin resistance in healthy volunteers and in manifestations of atherosclerosis in frequencies ranging from 5.5% to 63%⁹. A study done by Metha et al¹⁰ showed that 30% of patients had minimal inhibition of platelet aggregation after a single 150mg dose of aspirin. Gum & CO workers¹¹ reported a 5% incidence of Aspirin resistance as defined by optical platelet aggregation. Chen et al¹² reported a 19.2 % incidence of Aspirin resistance as defined by the Ultegra RPFA, among 151 patients with coronary artery disease. The overall prevalence of Aspirin resistance in different studies varied from 8% to 45%.

5. Mechanism of Aspirin Resistance:

There are some possible causes of recurrent Ishaemic vascular events among patients taking Aspirin. The mechanism of Aspirin resistance are:

- Clinical :
 - (a) Inadequate intake of Aspirin (poor compliance)
 - (b) Inadequate dose of Aspirin
 - (c) Concurrent intake of certain NSAIDS (for example-Ibuprofen, Indomethacin), possibly preventing the Access of Aspirin to Cyclooxygenase-1 binding site¹³
 - (d) Concurrent cigarette smoking
 - (e) Diabetes and hyper cholesterolema- by means of producing free radicals decrease response to antiplatelet therapy
 - (f) Arteritis
 - (g) Embolism from the heart
- Biological/ Cellular Factor :
 - (a) Alternative pathways of platelet activation:-
 - (i) Platelet activation by pathways that are not blocked by Aspirin (eg. Red cell induced platelet activation, stimulation of collagen, ADP, epinephrine and thrombin receptors on platelets)
 - (ii) Increased platelet sensitivity to collagen and ADP
 - (iii) Biosynthesis of thromboxane by pathways that by not blocked by Aspirin (eg. By COX-2 in monocytes and macrophages and vascular endothelial cells)
 - (b) Increased turnover and vascular endothelial cells.
 - (c) Over expression of COX-2 in RNA
 - (d) Generation of β_2 -iso PGF2 alpha binds to thromboxane receptors.
- Genetic [14] Polymorphism :
 - a) Polymorphism in involving platelet glycoprotein Ia/IIa, Ib/V/IX and IIb/IIIa receptors and collagen and VWF receptor genes.
 - b) Polymorphisms of COX-1, COX-2 thromboxane-A₂ synthetase or other arachidonate metabolism enzymes
 - c) FACor XIII Val 34 Lev polymorphism, leading to variable inhibition of Factor XIII activation by low dose Aspirin.
 - d) Patients displaying either the P1A1/A2 or P1A2/A2 polymorphism have been shown to be less responsive to the anti-platelet effect of Aspirin¹⁴.

6. Types of Aspirin resistance:

Weber et al¹⁵ classified Aspirin resistance into three types :

A. Aspirin resistance type I (Pharmacokinetic type) -

There is no effect on collagen induced platelet aggregation or thromboxane formation while taking Aspirin 100 mg/day while there is inhibition of platelet aggregation in Vitro suggesting intra and inter individual variability of pharmacokinetics.

B. Aspirin resistance type II (Pharmacodynamic type) -

It is characterized by the inability of Aspirin to inhibit platelet thromboxane formation both in Vivo and in Vitro.

C. Aspirin resistance type III (Pseudo resistance) -

It is characterized by inhibition of thromboxane formation in Vivo but not in Vitro. This type of Aspirin resistance was designated as "Pseudo resistance" because in these patients, Aspirin exerted the expected pharmacodynamic effects.

7. Diagnosis of Aspirin resistance and its validity:

- (1) Measurement of urinary concentration of the metabolite 11-dehydrothromboxane B₂ indicate the level indicate the level of TXA₂ generation. Eikelbloom et al¹⁶ indicated that Aspirin treated patients, urinary concentration of 11-dehydroTXB₂ predict the sure risk of MI or cardiovascular death.

There is direct between urinary 11-dehydro TXB₂ levels and increased incidence of vascular events (Myocardial infarction, stroke, cardiovascular death).

- (2) Platelet aggregation studies : using platelet rich plasma (optical aggregometer) or whole blood (platelet function analyzer 100: PFA-100 are the usually employed method.

Poor platelet responsiveness to Aspirin was defined by Friend et al¹⁷, as aggregation of $\geq 50\%$ of platelets using the PFA-100 device Gum et al¹⁸ defined Aspirin resistance on the basis of the platelet aggregation assay. Platelet aggregation of $\geq 70\%$ with 10 μ M ADP and of $\geq 20\%$ with .5 mg/ml of arachidonic acid constituted Aspirin resistance. They also defined Aspirin semi responders as meeting one but not both of these criteria.

- (3) Measurement of Thromboxane A₂ & its metabolite :-

Measurement of TXA₂ and its metabolite represent the ability of Aspirin to inhibit the COX-1. A potential drawback regarding the measurement of the level of TXA₂ is that TXA₂ is also formed by inducible COX-2, which is not sufficiently inhibited by Aspirin.

- (4) Selection-P. over expression¹⁹

- (5) Bleeding time²⁰

8. Clinical significance of Aspirin resistance:

Biochemical Aspirin resistance and Semiresponsively exists in a significant number of patients presenting as acute coronary syndrome or cardiovascular death. The overall prevalence of Aspirin resistance in different studies varied from 8% to 45%. Eikelbloom et al²¹ studied the relationship of Aspirin resistance with increased risk of cardiovascular events. The study showed that there was a 3.5 times higher risk of cardiovascular death in Aspirin resistant patients.

Mueller et al²² studied 100 patients undergoing peripheral balloon angioplasty and reported an 87% higher risk of reclusion on follow up in Aspirin resistance patient.

Grundmann et al²³ found that 34% patients with recurrent cerebro vascular ischemic events were Aspirin non responders.

All the studies done till today showed a clear-cut significant increased risk of myocardial infraction, stroke, cardiovascular deaths in patients with Aspirin resistance. It requires further approaches for preventing these complications in Aspirin resistant patient.

9. Management of Aspirin resistance:

Aspirin resistance cannot be treated completely, but it can be decreased by some measures, taken during Aspirin therapy.

- (1) Take proper dose of Aspirin & take it regularly.
- (2) Avoid concurrent use of drugs eg. NSAIDS Ibuprofen, which block the action of Aspirin.
- (3) Avoid cigarette smoking
- (4) Adequate control of blood sugar & lipids.
- (5) Regular exercise probably prevents onset of Aspirin resistance
- (6) Combining with other antiplatelet agents:- Clopidogrel inhibits platelet aggregation via ADP receptor and therefore may represent an important therapeutic alternative.
- (7) Data from clopidogrel in unstable angina to prevent recurrent events (CURE) and blockage of the Glycoprotein 11b/111a receptor to avoid vascular occlusion (BRAVO) studies show²⁴ that increasing

10. What is next - Clopidogrel resistance:

Resistance to Aspirin and other antiplatelet drugs has also been described. "Clopidogrel Resistance" has been documented²⁵ Clopidogrel non responders were defined by "an inhibition of ADP (5 and 20 mol/L) induced platelet aggregation, that was less than 10% of the baseline value 4 hours after Clopidogrel 600 mg intake. Semi-responders corresponded to patients with an inhibition of 10 to 29%; and responders are patients with an inhibition over 30%. Upto 4.% of the patients undergoing coronary stenting developed thrombotic stent occlusion, despite intensive Clopidogrel treatment; the parallel with Aspirin resistance, seems striking. However, as there is no standard definition of Aspirin resistance, comparison between the results of different studies is difficult.

REFERENCES

1. JACK DE. One hundred years of Aspirin lancet 1997: 350: 437-39.
2. Craven LL, experiences with Aspirin in the non specific prophylaxis & coronary thrombosis Mississippi Valley Med. J. 1953: 75: 38-44.
3. Fitz Geral GA: Parsing an enigma:- the Pharmacodynamics of Aspirin resistance Lancet 2003: 361: 542-44.
4. Antithrombotic trialists collaboration. Collaborative metanalysis of randomized trials of antiplatelet therapy for prevention of death, MI, stroke in high risk patients. BMJ 2002: 324: 71-86.
5. Ekelboom JW, Hirsh J et al. Aspirin resistance and the risk of MI, stroke, cardiovascular death in patients at high risk of cardiovascular outcomes. Circulation 2002: 105: 1650-5.
6. Gum PA, Kottke-Marchant K et al. A prospective blinded determination of the natural history of Aspirin resistance among stable patients with cardiovascular disease. J. Am Coll cardiol 2003: 41: 961-5.
7. De Gaetano G. Cerlettic. Aspirin resistance a revival of platelet aggregation tests. J. Thromb Haemost 2003: 1: 2048-50.
8. Bhatt DL. Topol EJ. Scientific and therapeutic advances in antiplatelet therapy. Nature Rev. 2003: 2: 15-18.
9. Poulsen TS, Kristensen SR, Atar D and Mickey H. A critical appraisal of the Aspirin resistance. Cardiology. 2005: 104: 83-91.
10. Mehta J. Mehta P. Burger C et al. platelet aggregation studies in coronary artery disease. Effect of Aspirin. Atherosclerosis 1978: 31: 169-175.
11. Gum DA. Kotike-Marchant K. et al. a prospective blinded determination of the natural history of Aspirin resistance among stable patients with cardiovascular disease. J. AM Coll cardiol 2003:41: 961-965.
12. Chen W.H., Lee P.Y. Ng W et al: Aspirin resistance is associated with a high incidence of Myonecrosis after non urgent percutaneous coronary intervention despite Clopidogrel pretreatment. J. Am Coll- cardiol: 2004: 43: 112-1126.
13. Catella-Lawson F, Reilly MP et al. Cyclooxygenase inhibitors and the antiplatelet effects of Aspirin N Engl J. Med. 2001: 345: 1809-17.
14. Carter AM. Ossei-Gerning N et al. association of the platelet P1(A) polymorphism of Glycoprotein 11b/111a, and the fibrinogen beta 948 polymorphism with myocardial infraction. Circulation 1997: 96: 1424-31.
15. Weber AA. Przytulski B. Schanz A et al. Towards a definition of Aspirin resistance: a typological approach platelets 2002: 13: 37-40.
16. Eikelboom JW. Hirsh J Weitz JL et al. Aspirin resistant thromboxane biosynthesis and risk of M1, stroke and cardiovascular deaths. Circulation 2002: 105: 1650-55.
17. Friend M, Vucenik I, Miller M. platelet. Responsiveness to Aspirin in patients with hyper lipidemia: BMJ 2003, 326: 82-3.

18. Gum DA, Kott Ke- Marchant K. Welsn PA et al. A prospective, blinded determination of the natural history of Aspirin resistance among stable patients with cardiovascular disease. *J. AM Coll Cadiol* 2003, 41: 961-5.
19. Kokschi M, Zeiger F. Wittig K. et al. Coagulation, fibrinolysis and platelet P. Selection expression in peripheral vascular disease. *Eur. J. Endovas Surg.* 2001, 21: 47-54.
20. Buchanan MR, Brister SJ. Individual variation in the effect of ASA on platelet function implications of the use of ASA clinically. *Can. J. CArdiol* 1995, 11: 221-227.
21. Eikelboom JW. Hirsh J Weitz JL et al. Aspirin resistance thromboxane biosynthesis and risk of cardiovascular events. *Circulation* 2002; 105: 1650-55.
22. Wang JC, Aucoin Barry D, Manu elian D et al. incidence of Aspirin resistance using the Uttegra Rapid platelet Function Assay. *Am J. Cardiol* 2003, 92: 1492-1494.
23. Grundmann K. Jaschonek K, Kline B et al. Aspirin non responders status in patients with recurrent cerebral ischemic attack.
24. Grotemeger KH, SchuraFinsk: HW et al. Two year follow up of Aspirin responder and Aspirin non responders. A pilot study including 180 post stroke patients. *Thromb Res.* 1993, 71: 397-403.
25. Muller I, BestaF. SchulZ C, Massberg S. Schonig A, Gawaz M: Prevalence of Clopidogrel non responders among patients with stable angina pectoris scheduled for elective coronary stent placement. *Throm Haemost.* 2003, 89: 783-787.