



Aspirin Resistance

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Aspirin is the most commonly used antiplatelet drug indicated for primary and secondary prevention of coronary artery disease (CAD). Primary mechanism of antiplatelet action of aspirin is due to irreversible acetylation of the hydroxyl group of a single serine residue at position 530 within the polypeptide chain of platelet prostaglandin G/H synthase-1 (COX-1), resulting in decreased synthesis of thromboxane A₂ (TxA₂)-a potent vasoconstrictor and a platelet aggregator (1). Since platelets lack the biosynthetic machinery to synthesis fresh enzyme, so inhibition of COX-1 induced by aspirin persists during their life span (8-10 days). The plasma half life of aspirin is only 20 minutes; it is rapidly deacetylated to salicylate in liver. After a single dose of aspirin, platelet COX activity recovers by 10% per day in parallel with the entry of new platelets in the circulation. The usual anti-platelet aggregator dose of aspirin ranges from 75-325 mg/day.

A meta-analysis study by Sanmuganathan *et al* (2) showed that low dose aspirin therapy significantly reduced the incidence of cardiovascular events, myocardial infarction or stroke in patients with previous cardiovascular events. However despite the demonstrated benefit of aspirin in primary and secondary prevention, there are some individuals who do not derive the anticipated anti-platelet response from low dose aspirin therapy and manifest with break through atherothrombotic events. Various laboratory parameters to measure platelet aggregation have also shown that there is variability among individuals to the anti-platelet action of conventional doses of aspirin. Based on the clinical and laboratory evidence of reduced response to aspirin therapy in some individuals, the concept of aspirin resistance has emerged. Though no formal definition of aspirin resistance exists, it may involve clinical failure of therapeutic dose of aspirin (75-150 mg for at least 5

days) to protect individuals from arterial thrombotic events or laboratory methods indicating the failure of aspirin to inhibit platelet activity (3). The former is known as clinical aspirin resistance and the latter as biochemical aspirin resistance. There are conflicting reports on incidence and clinical relevance of this phenomenon. Previous studies have estimated that 8-45% of the population are aspirin resistant (4).

Weber *et al* (5), tried to classify aspirin resistance into three distinct types using laboratory test like collagen induced platelet aggregation and thromboxane formation in citrated platelet-rich plasma. In aspirin responders, oral in take of 100mg/day of aspirin for 5 days inhibited both collagen induced platelet aggregation and thromboxane formation by more than 95%. In type I resistance (pharmacokinetic type) oral aspirin was ineffective but in vitro addition of 100µM of aspirin resulted in complete inhibition of collagen induced platelet aggregation and thromboxane formation. In type II resistance (pharmacodynamic type) both oral treatment with aspirin and in vitro addition of aspirin resulted in incomplete inhibition of collagen induced platelet aggregation and thromboxane formation. In type III resistance (pseudo-resistance), platelet aggregation was induced by collagen despite of complete inhibition of thromboxane formation by oral aspirin treatment.

Various mechanisms responsible for resistance are :

1) **Reduced accessibility of aspirin to receptor site due to concomitant intake of other NSAIDs** (6). Drug interaction between NSAIDs and aspirin may be one of the cause for reduced availability of aspirin at receptor site (docking site on platelet COX-1). Like aspirin, these drugs also inhibit COX-1, but unlike aspirin they are reversible inhibitors of COX. Hence their antithrombotic effect last only for a short time. Since both aspirin and

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NSAIDs share a common docking site on COX-1, NSAIDs when administered along with aspirin may compete with it for the active site and may reduce its antithrombotic effect. However, selective COX-2 inhibitors do not pose such problem.

2) **Genetic polymorphism of enzymes like COX-1, COX-2 or thromboxane A2 synthase** which make them less sensitive to aspirin may be another possible cause of resistance. Aspirin resistance has been associated with the polymorphism of PLA2 gene that codes for platelet glycoprotein IIIa- a component of platelet glycoprotein IIb/IIIa (7). Patients with this sort of resistance may derive benefit from higher dose of aspirin or from antiplatelet drugs other than aspirin like clopidogrel (8).

3) **Increased reactivity of platelets towards other aggregating factors** (9). Platelets can be activated by pathways other than thromboxane which are not inhibited by aspirin. Over activity of these alternate pathways of platelet activation such as erythrocyte induced platelet activation, increased sensitivity to collagen, adenosine diphosphate, increased levels of von Willibrand factor, increased levels of noradrenalin and hyperlipidemia may be responsible for break through cardiovascular events despite aspirin therapy. Concomitant use of another antiplatelet drugs and life style modifications may be useful in these patients.

4) **Increased rate of entry of new platelets into the circulation** (10). Clinical conditions such as myocardial infarction and coronary artery bypass surgery are associated with increased rate of entry of new platelets into the circulation introducing newly formed non aspirinated platelets into blood stream. These new platelets with an increased fraction of active COX may be responsible for aspirin resistance. Higher doses of aspirin may be more effective in such patients.

5) **Alternate pathways of thromboxane synthesis** (11). Isoenzyme G/H synthase-2(COX-2) is usually not expressed in platelets but it can be expressed in the platelets after their activation by growth factors and mediators of inflammation especially in atheromatous plaque. Low dose aspirin significantly blocks platelets COX-1 but inhibition of COX-2 require higher doses(>500mg/d). Thromboxane A2 synthesised in platelets by COX-2 may be another possible cause of aspirin resistance. Platelets can also acquire thromboxane precursors such as prostaglandin H2 from monocytes and

endothelial cells and synthesize thromboxane A2, another possible cause of aspirin resistance.

6) **Poor patient compliance** (12).

To conclude aspirin is an effective and widely used anti-platelet aggregating drug for primary and secondary prevention of atherothrombotic events. However in recent years both clinical and ex-vivo evidence has accumulated showing failure of low dose aspirin to produce expected biological response. Since aspirin resistance could have important clinical bearing, it is required to develop reliable laboratory tests to identify patients at risk for aspirin resistance and to individualize the anti-platelet therapy. At present, there are few studies to document incidence and clinical relevance of this phenomenon; more investigations are required to understand the mechanism, prevalence and clinical importance of this phenomenon.

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