Aspirin: Expectations and Limitations

Gundu HR Rao*

South Asians (Indians, Pakistanis, Bangladeshis and Sri Lankans) have the highest incidence of Coronary Artery Disease (CAD) compared to any other ethnic group in the world. According to World Health Organization reports, India tops the world, in number of diabetic (Type-2) patients. This number is supposed to double in the next two decades, majority of the patients suffering from CAD and Diabetes use aspirin for secondary prophylaxis. Aspirin is the most cost-effective drug for secondary prophylaxis. In recent years, there has been considerable concern that those taking aspirin for prolonged periods of time may develop resistance to the action of this drug. If this phenomenon is true, then those who are resistant to aspirin need alternate drugs for protection against the development of acute vascular events. In this editorial, we will make an attempt to describe how aspirin works as an anti-platelet drug, and speculate on the expectations of clinicians and describe its limitations.

Blood platelets play a very important role in the pathogenesis of heart attacks and stroke. Therefore, several million individuals all over the world take aspirin, an irreversible inhibitor of the cyclooxygenase enzymes, for the prevention of heart attacks and stroke. Aspirin, as a therapeutic drug, has been in use for over a hundred years. Its use as an anti-platelet drug was recognized in the early '70s. For the secondary prophylaxis of acute vascular events, it is the most useful and cost effective drug. A large number of clinical studies using aspirin has demonstrated that at any given risk, irrespective of the diseases state, aspirin at low to medium dose (80-160 mg) is as effective as any other anti-platelet drug.

However, in recent years, there is considerable concern regarding development of aspirin resistance in certain group of patients suffering from heart disease. According to an article in the New York Times (Andrew Pollack, 2004), anywhere from 5-40% of the individuals taking aspirin for secondary prophylaxis are non-responders. Aspirin resistance is poorly understood and is ill-defined. However, if there is a real lack of aspirin effect on platelet function in any patient, then it is important for him/her to know the existence of such a condition, so that alternate therapy can be recommended. According to some physicians, non-compliance seems to be a significant mediator of poor outcome. Platelets exposed to aspirin may exhibit variable response to different agonists. Although this phenomenon is described as aspirin resistance, the lack of a uniform definition or specific diagnostic method makes it difficult to detect this condition, under clinical situations. Aspirin resistance has been described in cardiovascular diseases, cerebrovascular diseases and peripheral arterial diseases. How much of this observed phenomenon is due to aspirin resistance is debatable because many studies have used platelet function tests to determine aspirin resistance. In the absence of a specific reliable assay to monitor aspirin resistance, the results obtained from some of these studies are misleading and add to the confusion. There is a great need for the development of a simple, platelet-specific, rapid, cost-effective assay for monitoring aspirin resistance in high-risk individuals.

Studies from our laboratory using aggregometer have demonstrated that by and large, aspirin resistance is a rare phenomenon in normal healthy individuals. In our platelet function testing studies over three decades, we have come across aspirin insensitivity in only one subject. In this subject, the platelets were deficient in cyclooxygenase activity and as such failed to respond to arachidonate, as they were incapable of metabolizing AA to PG endoperoxides and thromboxane. Researchers from the Artificial Heart Institute, Salt Lake City, Utah, published a report indicating that the bovine platelet cyclooxygenase is not inhibitable by oral dose of aspirin. We examined this phenomenon and found that if the aspirin was administered as a suppository through the anal route, the drug was quite effective in inhibiting platelet cyclooxygenase. In the earlier study since aspirin was administered orally it was probably metabolized in the stomach to salicylic acid before reaching the circulating blood. Salicylic acid is not an inhibitor of cyclooxygenase.

To demonstrate drug-induced refractoriness to aspirin, we used a short acting inhibitor, Ibuprofen. This drug when used first antagonized the action of aspirin, In other words, in individuals administered with ibuprofen, aspirin did not have any effect on the platelet function. We hypothesized that Ibuprofen was interfering with action of acetyl salicylic acid at the active site of the enzyme. When the active site is occupied by another drug, aspirin will not be able to...
interact with this site and acetylate the amino acid. Since Ibuprofen is a short acting drug, platelets regain their response to arachidonate by next morning. If there was any effect of aspirin on these platelets, the platelets would fail to respond to arachidonate with aggregation even the next day.

We at the University of Minnesota have discovered an intrinsic phenomenon called “membrane modulation” which is capable of securing irreversible aggregation of drug-induced refractory platelets; the novel mechanism is modulated by the stimulation of the alpha-adrenergic receptors and restores the sensitivity of drug-induced refractory platelets to the action of agonists. This observation may partially explain why none of the currently available antiplatelet drugs are effective in the total prevention of in vivo platelet activation and formation of thrombi. Aspirin and Clopidogrel only inhibit one of the many platelet activation mechanisms. Therefore, they do not offer full protection from the risk of acute vascular events. Furthermore our studies have demonstrated that when aspirin-treated platelets are subjected to interact with exposed sub-endothelial cell matrix under flow conditions, there is more adhesion and aggregation of aspirin-exposed cells than normal platelets. Though aspirin reduces the thrombus formation on the exposed cell matrix components, it does not prevent the formation of massive aggregates. Furthermore, when epinephrine was used in such flow conditions, adrenergic receptor modulation restored the ability for thrombus formation of aspirin-exposed platelets.

Based on the available data on this subject, it is difficult to explain the mechanism by which individuals are developing resistance to aspirin. Published reports suggest that this occurs mostly in patients with vascular disease and in those who are on long-term aspirin regimen. It is essential to learn who is resistant to aspirin, so that appropriate alternate prophylactic therapy could be administered. Even those who are considered responders to the aspirin therapy may need additional protection, if their platelets are hyper sensitive to other agonists such as collagen or have a hyper coagulation pathway. Differences in the definition of aspirin resistance, variation in the detection methods used, and lack of data from large clinical trials has hampered the advancement of knowledge in this area.

In this issue of JAPI, Mardikar et al have described variability in response to single dose of enteric coated aspirin in high risk population. They conclude that this is the first study to report hypo and hyper response to the action of single low dose of aspirin. Similar to our earlier observations they found minimal inter-individual variability in the response of aspirin when tested with AA as the stimulant. In one of the largest clinical studies in Hungary, Robert Kiss and associates found similar minimal inter-individual variability in the response of platelets to the action of AA (Personal Communication). Then the question arises as to how to explain the poor outcome in patients taking aspirin. First of all we should stop using terms such as “semi responders”, “non-responders” or “resistant”, when expressing results from studies using non-specific platelet function studies. By and large, they all represent the inter-individual variability in the response of platelets to multiple stimuli in in vivo conditions.

We have to understand that thrombosis is a complicated process initiated by multiple stimuli. Aspirin or Clopidogrel inhibit only one of the platelet activation mechanisms. These drugs, even at higher doses, do not have any inhibitory action on other activation mechanisms. Furthermore, in addition to platelets, thrombogenic agents from vascular endothelium, various blood components, and coagulation factors, contribute to the pathogenesis of thrombosis. Therefore, it is essential to develop assays that monitor global hemostasis, so that one can identify individuals with a higher risk for thrombosis and provide alternate therapy.

A Minneapolis-based company, PlaCor Inc, has developed a device that can monitor global hemostasis. This device uses a drop of blood from a finger-prick to monitor platelet dependent activation of blood coagulation. No agonists are used for activating platelets. Blood is pumped back and forth on a stainless steel coil. Shear induced activation of platelets promotes clotting. Data obtained from three independent laboratories (n=160) is summarized below.

<table>
<thead>
<tr>
<th>Before and after 8 Days on ASA</th>
<th>10-50 Seconds</th>
<th>51-120 Seconds</th>
<th>&gt; 120 Seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>56%</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>Day 8</td>
<td>37%</td>
<td>21%</td>
<td>43%</td>
</tr>
</tbody>
</table>

In this study platelet reaction time (PRT) in seconds was monitored before aspirin ingestion and after 8 days of aspirin (325mg/daily) ingestion. On day 1 (Pre-aspirin), 56% of the individuals tested had a PRT of 10-50 seconds, 22% had PRT of 51-120 seconds and 22 % had greater than 120 seconds. Whereas, after 8 days of aspirin (325 mg/day) ingestion, PRT of the group under 10-50 seconds changed to 37% and those with greater than 120 seconds increased to 43%. It is interesting to note that in spite of daily aspirin ingestion of 325 mg, 37% of individuals still had a short PRT time. These studies clearly demonstrate the inter-variability in response to the action of aspirin. Data clearly demonstrates that not all individuals are protected equally by aspirin.

Several hundred clinical studies with aspirin have established the fact that aspirin at low dose (80-160mgs) is as effective as any other anti-platelet drug in providing protection against acute vascular events in a variety
of disease conditions. In view of these observations, expectations of clinicians were too high about the benefit of low-dose aspirin therapy. In recent years clinical studies have demonstrated that a significant number of individuals who are on aspirin therapy also have poor outcomes. Some studies have suggested that those at risk, could be protected better by increasing the dosage of aspirin or using low-dose aspirin more than one time a day. In some studies those at risk have been switched altogether to Clopidogrel to achieve better protection.

Aspirin is an irreversible inhibitor of platelet cyclooxygenase. However it has a short half life and is rapidly converted to salicylic acid in the blood. Salicylic acid is not an inhibitor of COX-1 enzymes. Therefore, platelets that are released after aspirin is converted to salicylic acid retain active COX-1 enzymes. Furthermore, our studies have demonstrated that epinephrine exposure of aspirin treated platelets restores the function of drug refractory cells to the action of other agonists. Aspirin and Clopidogrel inhibit only one of the several mechanisms of platelet activation and have no effect whatsoever on coagulation mechanisms. Therefore it is too much to expect 100% protection from these drugs. The need of the hour is to develop cost effective point of care devices that can monitor global hemostasis. It is also equally important to develop newer and potent anti-platelet drugs, if we need to resort to alternate therapy.

REFERENCES


Announcement

Nominations are invited from members of API for the post of Hon. Editor - Journal of the Association of Physicians of India.

The nominations should be proposed and seconded by two members alongwith seven copies of the Biodata and should reach by 15th July 2008, to the Hon. General Secretary of API, Dr. Sandhya Kamath, Unit No. 6 and 7, Turf Estate, Opp. Shakti Mill Compound, Off. Dr. E Moses Road, Near Mahalaxmi Station West, Mumbai - 400 011.
Tel.: 022 6666 3224; Fax : 24920263

Announcement

Eligibility Criteria for the Award of Fellowship of Indian College of Physicians

Full Format available on API and JAPI Website - www.apiindia.org and www.japi.org

Dr. Sandhya Kamath
Hon General Secretary, API & ICP

Dr. Falguni Parikh
Jt Secretary, API & ICP