ASPIRIN RESISTANCE: AN UNSETTLED ISSUE

Maqbool H. Jafary

The concept of “aspirin resistance” was proposed in the mid-1990s and it has been discussed in the medical literature ever since. However, the exact definition of aspirin resistance is still elusive. A variety of definitions have been put across. Probably the simplest one is, “occurrence of vascular events despite the use of recommended doses of aspirin”. However, the issue is more complex than this and it has led to further classifying the meaning of the resistance into various types. One is the inability of aspirin to protect patients from the ravages of atherosclerosis-induced ischemic vascular events. This is what has been dubbed as ‘clinical aspirin resistance’. The other is ‘biochemical aspirin resistance’ related to the chemical tests and is described as the inability of aspirin to have an anti-platelet effect on one or more tests of platelet function.

Biochemical aspirin resistance is dependent on the tests which may not necessarily be biochemical in nature. These tests include inhibiting platelet aggregation, effect on biosynthesis of thromboxane and causing prolongation of bleeding time. Even if all the presently performed tests were to be readily available everywhere, these are either non-specific or they have uncertain sensitivity. At present clearly there is no universal consensus about them. More over, the clinical relevance of the tests still needs to be locked in through standardization, validation and documented correlation with the definitive clinical events with the help of double blind clinical trials in cardiovascular medicine.

Recently, however, some evidence of the clinical relevance is coming forward. George Karasopoulo et al. in a systematic review and meta-analysis, have concluded that patients who are resistant to aspirin are at a greater risk of clinically important cerebro-vascular morbidity in the long term compared to patients who are aspirin sensitive. However, in this study the method of determination of aspirin resistance has not been specified and it relies on aspirin resistance ‘however measured’ before admission to hospital, without regard to the fact that apparent lack of effect with aspirin may have been due to poor compliance. Poor compliance, amongst others, has been shown to be an important factor contributing to an apparent aspirin resistance. KA Schwartz et al. for example, have reported that only one of seventeen patients (6%) given aspirin under supervision did not show a response to aspirin. The authors in Karasopoulo study have themselves highlighted the limitations of the systematic review and meta-analysis as the poor compliance can distort the results of meta-analysis. Thus confounding of compliance with outcome can make the final conclusions questionable.

The prevalence of aspirin resistance is another debated issue. In a review of 34 full articles and eight abstracts by MM Hovens et al. overall aspirin resistance was reported to be 24% with prevalence in individual studies ranging from 0% to 57%. However, the authors point out that aspirin resistance of one person in four may be the worst case scenario. As there is a problem of definition of aspirin resistance
and methodology used, it is likely that the prevalence figures will decrease rather than increase once the more conservative definitions and defined methods are in place. They also raise the issue of compliance as many studies included in the analysis have not taken this factor into consideration. Poor compliance, they observe, certainly contributes to higher apparent aspirin resistance. Another study, by Gum et al, estimated the frequency of resistance to be 5.2% in patients with cardiovascular disease. The Antithrombotic Trialists’ study reported the incidence to be 13%.11

Non-compliance as the cause of apparent resistance, in spite of reservations in some quarters as the reason of the problem, is generally accepted as an important factor. Compliance with the intake of a longer term therapy with aspirin is a significant issue all over the world, West or East, regardless of the fact whether it is linked with the resistance issue or not. In AAUS study in Pakistan, only 50% patients were on aspirin at discharge from the hospital after the treatment of acute coronary syndrome.12 Other than compliance, there are factors which may have definitive correlation with the resistance. Aspirin resistance has been shown in platelet A2 polymorphism13 and attempts are ongoing to locate a gene responsible for the resistance as the genetic basis of the resistance has been postulated. It has also been reported in patients taking Ibuprofen and Cox-2 inhibitors like celecoxib and rofecoxib, in vitro.14 Aspirin resistance has also been observed in the presence of cholesterol >220mg/dL,15 in smokers and in those taking ginkgo biloba and ginseng.16 An alternate pathway for platelet activation not affected by low-dose aspirin has also been suggested as a reason for the apparent resistance.5 In diabetes, the heightened platelets reactivity is known to be a significant phenomenon which may also account for less than optimal effect of aspirin.

In the light of the presently known facts, it seems clear that aspirin failure or resistance is a reality, as the vascular events of varying magnitude do take place in patients at higher risk.11 However, there are several unsettled issues about this phenomenon: a) we have to wait for consensus on definition of aspirin resistance, b) exact mechanism of aspirin resistance still remains to be elucidated, c) specific and sensitive tests for aspirin resistance need to be developed and agreed upon and d) more data is required to guide aspirin therapy on the basis of platelet function test results. Till the time these issues are settled the physicians should, however, adapt the most efficient strategy to prevent aspirin failure by using appropriate dose (75-150mg per day), maintain a high level of compliance and avoid combining aspirin with drugs which may inhibit anti-platelet effects of aspirin e.g., Ibuprofen, Cox-2 inhibitors, ginkgo, ginseng etc. In high risk situations like PCI, CABG and unstable angina, a combination of aspirin with other anti-platelet agents like clopidogrel should be considered.17

Declaration of conflict of interest: The author has no conflict of interest; he has not received any grant or honorarium from any source. The educational activities of Pakistan Aspirin Foundation, however, are presently supported by Atco Laboratories, Karachi.

REFERENCES


