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Aspirin Resistance

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INTRODUCTION

The use of aspirin (in doses of 81-325 mg/day) for secondary prevention in cardiovascular disease reduces subsequent events by about 25%. Aspirin treatment failures may have multiple causes and aspirin resistance is emerging as an additional factor.

Aspirin resistance is the inability of aspirin to produce the expected aspirin effect on in vitro tests of platelet function. Aspirin inhibits the cyclooxygenase (COX) pathway in the platelet, reducing the production of thromboxane A₂ (T_xA₂), a transient biologic product which produces platelet aggregation and vasoconstriction. Laboratory tests which have been used to evaluate aspirin effects include the following: 1) inhibition of thromboxane (T_xA₂) synthesis, 2) inhibition of T_xA₂-dependent platelet aggregation (in platelet rich plasma or whole blood), 3) prolongation of bleeding or closure times and 4) analysis of the propyl gallate (c-PG) effect (which activates platelets through the COX pathway) in the Ultegra Rapid Platelet Function Assay (Accumetrics VerifyNow device).

With low aspirin doses, platelet T_xA₂ falls to < 95% after several days and this amount of inhibition is necessary to influence platelet function in other assays. However, the relationship between inhibition of T_xA₂ synthesis and inhibition of second phase aggregation response is not linear. Using various techniques, the incidence of aspirin resistance ranges from about 5-45%.

MECHANISMS:

Mechanisms for aspirin resistance include a lack of drug availability and acquired or

hereditary factors which influence platelet responses. Bioavailability may be affected by non-compliance or concomitant use of non-steroidal anti-inflammatory agents. Increased platelet turnover and increased platelet COX-2 expression have also been associated with aspirin resistance. In addition, platelet polymorphisms, such as the PIA1A2 phenotype, appear to influence platelet responses to aspirin.

TESTING:

Different platelet function assays have been used to evaluate aspirin resistance. These include bleeding times, platelet aggregation in platelet rich plasma and in whole blood, measurements of thromboxane synthesis, the PFA-100 (Platelet Function Analyzer, Dade) and rapid platelet function testing using an arachidonate like substance and bead agglutination in whole blood in the Accumetrics VerifyNow system.

The latter two tests (PFA-100 and the Accumetrics device) have the advantage of being easily done in routine laboratories with real time results. The Accumetrics VerifyNow system is FDA approved for this purpose. In this assay system, aspirin resistance is defined as an aspirin resistance unit (ARU) > 550. Using the PFA-100, aspirin resistance has been defined variously as the lack of prolongation of the collagen/epinephrine closure time or as good (collagen/epinephrine closure time >300 secs), partial (prolonged collagen/epinephrine closure time but < 300 seconds) and no response (normal collagen/epinephrine closure time).

CLINICAL IMPACT:

Retrospective and prospective studies in cardiovascular patients (using various

techniques to evaluate aspirin resistance) have been performed with varying doses of aspirin. These have included patients with cardiac disease, cerebral thrombosis, transient ischemic attacks and peripheral vascular disease. In general, aspirin resistance regardless of the laboratory test has been associated with a 1.8-10 fold increased risk of major adverse cardiovascular events. These results suggest that aspirin resistance is a real phenomenon with important clinical consequences.

TREATMENT OPTIONS:

Randomized studies concerning the management of aspirin resistance have not been performed. There is no consensus regarding the management of aspirin resistance. However, if a patient has evidence for aspirin resistance, it makes sense to a) educate the patient about compliance and b) remove interfering substances. Additional considerations may include increasing the aspirin dose (some patients respond to a higher dose) or using alternative antiplatelet therapy, with drugs such as clopidogrel or possibly Aggrenox.

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