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Evaluation of aspirin resistance in elderly people in rural population in India

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ABSTRACT

Lowdose aspirin remains the gold standard therapy in the prevention of myocardial infarction, ischaemic stroke, and vascular death among patients at high and low risk of these events. . In aspirin 'resistance' the change is not in the drug target, and the effects can fluctuate over time and are at least partly reversible by increasing the dose. Biochemical Endpoints for in Vivo and ex Vivo Tests were done. Aspirin dose 325 to 1,300 mg daily were administered to previous ischaemic stroke patients to investigate the extent of inhibition of platelet aggregation. Signal-dependent de novo synthesis of COX1 occurring over time in aspirin-treated platelets after persistent activation has been suggested to provide an additional source of aspirin-insensitive thromboxane biosynthesis.

Key words: Aspirin, Thromboxane B₂, Platelet aggregation, Drug resistance.

INTRODUCTION

Lowdose aspirin remains the gold standard therapy in the prevention of myocardial infarction, ischaemic stroke, and vascular death among patients at high and low risk of these events [1]. These characteristic events depend on antiplatelet action of aspirin and thus are measured by bleeding time. The discovery of thromboxane A₂ led to a full description of the pharmacologic effects in humans in the early 1980s [2,3].

Drug resistance is defined as being the result of microbes, viruses or cancer cells changing in ways that reduce or eliminate the effectiveness of agents used to cure or prevent infection or

disease [4]. Genetic changes affect the drug targets (eg. Enzymes, transmembrane proteins, and pumps), leading to reduced or no drug activity. Drug exposure is generally the trigger, and the effect is often drug-specific and is reversible only slowly. The changes can be detected by specific laboratory tests and the results can have a direct impact on clinical decisions about changing drug therapy.

The features of so-called aspirin resistance differ notably from those of drug resistance as defined above. In aspirin 'resistance' the change is not in the drug target, and the effects can fluctuate over time and are at least partly reversible by increasing the dose .

Although newly formed platelets express both COX 1 and COX 2, [5] mature platelets express only COX 1. While COX 1 is highly sensitive to low doses of aspirin, [2,3] COX2 is inhibited only by doses high enough to have analgesic or anti-inflammatory effects. A change in drug target, as implied by the definition of drug resistance, could involve COX1 polymorphism affecting Arg120, Ser529, or both. These polymorphisms could explain a fixed percentage of drug resistance in any given population.

The genetic variability COX 1 explains both increased and decreased responses to aspirin. Alternatively, enhanced platelet regeneration and an increased proportion of newly formed platelets expressing COX2 in response to chronic aspirin administration could explain time-dependent changes in platelet sensitivity to inhibition by a low dose of drug [6].

MATERIALS AND METHODS

Assessment of Platelet Function:

The aspirin 'resistance' has relied on ex vivo measurement of the following techniques: light transmittance aggregometry in platelet rich plasma, the platelet function analyzer PFA-100, which was developed as a bedside, rapid, whole-blood assay and the verifyNow Rapid Platelet Function Assay [7]. Each of these techniques challenges the capacity of blood platelets to respond to an aggregating stimulus, such as arachidonic acid, added at variable concentration in a largely artificial environment. These showed the antiplatelet action of aspirin [8].

Biochemical Endpoints for in Vivo and ex Vivo Tests:

Adequacy of platelet COX1 inhibition by low-dose aspirin was measured by serum thromboxane B₂ by ELISA before aspirin administration and used standardized threshold as a reference. Measurement of urinary 11-dehydro-thromboxane B₂ provides a noninvasive, time-integrated index whole-body thromboxane A₂ production.

RESULTS AND DISCUSSION

This study was conducted by the Department medicine of Bhaskar Medical College, Yenkapalli, Ranga Reddy district, Andhra Pradesh, India. This prospective observational study was done by the Department of Pharmacology of the college. There were 306 elderly patients above 40 years. 200 were males and 106 were females.

Aspirin dose 325 to 1,300 mg daily were administered to previous ischaemic stroke patients to investigate the extent of inhibition of platelet aggregation.

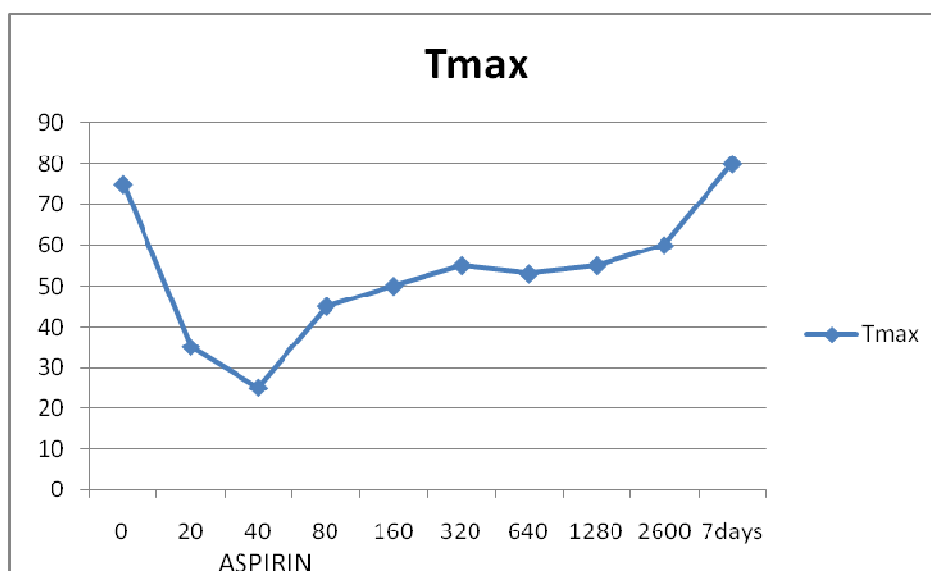
Table 1: Inhibition of platelet aggregation measured with at 325 mg of Aspirin from 2 weeks to 33 months

| Baseline (n=306) | complete inhibition (n=228) 75% | partial inhibition (n=78) 25% |
|---------------------|------------------------------------|----------------------------------|
| 2 weeks | 70% | 30% |
| 6 months | 62% | 38% |
| 12 months | 50% | 50% |
| 18 months | 45% | 55% |
| 24 months | 35% | 65% |
| 33 months | 25% | 75% |

Table 2: Inhibition of platelet aggregation measured with 325 mg/day to 1300 mg/day of Aspirin

| (n=100) | Complete inhibition | Partial inhibition |
|-------------|---------------------|--------------------|
| 325 mg/day | 25% | 75% |
| 650 mg/day | 22% | 78% |
| 1300 mg/day | 18% | 88% |

Figure 1: Percentage of bleeding time decreased with different doses of aspirin



It was noted that 100 mg of Aspirin for 1 week to a person had TXB_2 with the value > 80 micrograms/ml. Before treatment the serum TXB_2 was 200-600 ng/ml ± 50.89 . With 75 mg enteric coated aspirin TXB_2 was 2.2 ng/ml ± 0.54 . There was 99% inhibition with 100 mg of aspirin

showing TXB₂ as 10ng/ml \pm 2.53. There was 95% inhibition with 75mg of aspirin showing TXB₂ as 30ng/ml \pm 5.67. Urinary 11-dehydro-thromboxane B₂ was reduced by 60-80%.

The degree of inhibition of TXB₂ concentration (table 3) translates into homogeneously complete suppression of arachidonic acid induced platelet aggregation *ex vivo* [9,10]. Inadequate inhibition of platelet COX1 activity by low-dose aspirin is a rare phenomenon in patients who adhere to therapy. Tantry *et al* have reported that only 1 among 223 patients with coronary artery disease had less than complete inhibition of arachidonic acid induced platelet aggregation [11]. FitzGerald *et al* reported the intriguing finding that ADP-induced platelet aggregation was maximally inhibited by 40 to 80 mg aspirin daily, but values returned to baseline with chronic administration at higher doses of up to 2,600 mg daily.[3] Figure.1.

Urinary 11-dehydro-thromboxane B₂ excretion provides a noninvasive, time-integrated index of whole-body thromboxane A₂ production [11]. Platelets are not the only source of thromboxane A₂ biosynthesis and therefore, the urinary excretion of 11-dehydro-thromboxane B₂ is reduced incompletely by 60% to 80% following aspirin administration [3]. Thus, persistent metabolite excretion in aspirin-treated patients could provide a useful index of the degree to which aspirin-insensitive thromboxane A₂ biosynthesis is occurring. The underlying mechanisms include COX2 expression in inflammatory cells endowed with thromboxane synthase and a higher percentage of COX2-expressing platelets [11].

Moreover, signal-dependent *de novo* synthesis of COX1 occurring over time in aspirin-treated platelets after persistent activation has been suggested to provide an additional source of aspirin-insensitive thromboxane biosynthesis [12]. These mechanisms involve alternative sources of thromboxane A₂ biosynthesis that are either poorly sensitive (expression of COX2) or nonexposed (*de novo* synthesis of COX1 after aspirin clearance) to aspirin inhibition, neither of which would fit with the traditional concept of drug resistance.

Aspirin-insensitive thromboxane A₂ biosynthesis has been described in patients with post-stroke dementia [13-16]. The clinical relevance of this aspirin-insensitive activity has been explored by Eikelboom *et al*, who performed a nested case-controlled study of baseline urinary 11-dehydro-thromboxane B₂ excretion in relation to the occurrence of major vascular events in aspirin-treated, high-risk patients enrolled in the Heart Outcomes Prevention Evaluation (HOPE) trial [17]. After adjustment for baseline differences, the odds for the composite outcome of myocardial infarction, stroke, or cardiovascular death increased with each increasing quartile of 11-dehydro-thromboxane B₂ excretion, with patients in the upper quartile having a 1.8-times higher risk than those in the lower quartile. One limitation of this study, however, was the inability to differentiate between adherence to the aspirin regimen (or avoiding the use of NSAIDs) and aspirin-insensitive sources of thromboxane A₂ biosynthesis [18].

CONCLUSION

The definition of a threshold level of metabolite excretion to aid assessment of the adequacy of platelet COX1 inhibition by aspirin (as implied by a commercially available kit) is, therefore, simply not feasible to assess aspirin resistance. Therefore further investigation is needed.

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