Aspirin Non-responders in Thai Ischemic Stroke/TIA Patients

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Background: *Aspirin resistance has been defined as inability of aspirin to protect individuals from thrombotic complications or to produce an anticipated effect from laboratory tests of platelet function. Most reported information comes from Western patients with coronary artery disease and aspirin resistance is defined by laboratory criteria. The purpose of the present study was to look for aspirin non-responders in Thai patients who presented with acute/subacute ischemic stroke and transient ischemic attack (TIA).*

Material and Method: *The authors prospectively included acute ischemic stroke/ TIA patients who were treated at Thammasat Hospital from August, 2006 to July, 2007 and had already been on aspirin. Information about compliance of medication, reasons for taking aspirin, doses of aspirin, baseline characteristics, and stroke subtypes of the patients were collected.*

Results: *There were 194 acute/subacute ischemic stroke/TIA patients during the study period. Forty-six patients (23.7%), who had already been on aspirin (aspirin non-responder), while having new stroke/TIA, were studied. Eighteen patients were on aspirin 300-325 mg and 28 patients were on 81 mg per day. Most patients had taken aspirin 300-325mg/day as secondary prevention, while half of the patients taking aspirin 81 mg/d had diabetes mellitus and took aspirin as primary prevention.*

Conclusion: *Aspirin non-responders in ischemic stroke patients are common. Future study is required to clarify mechanisms of aspirin non-responders in Thai patients.*

Keywords: *Aspirin non-responder, Stroke, Thai*

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Aspirin is a well-established medication in treatment and prevention of atherothrombotic disease. However, despite aspirin treatment, a substantial number of patients experience recurrent ischemic episodes. Data obtained by various laboratory tests of platelet function indicated that aspirin does not attain adequate antiplatelet efficacy in a significant proportion of these cases[1]. Aspirin resistance has been defined as inability of aspirin to protect individuals from thrombotic complications or to produce an anticipated effect on one or more *in vitro* tests of platelet function[1,2]. Prevalence of aspirin resistance is 5.5-45% in patients with various cardiovascular diseases from previous reports[2]. Most reported information comes from Western patients with coronary artery disease and aspirin resistance is defined by laboratory criteria. The purpose of the present study was to look for aspirin non-responders in Thai patients who presented with acute/subacute ischemic stroke and transient ischemic attack (TIA).

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Material and Method

The authors included all patients who presented with acute/subacute ischemic stroke/TIA at Thammasat Hospital from August 2006 to July 2007 and had already been on aspirin. Patients with poor compliance with aspirin and patients who had underlying cardiac conditions which could cause these ischemic stroke events, such as atrial fibrillation, were excluded. Information about compliance with medication, reasons for taking aspirin, doses of aspirin, baseline characteristics, and stroke subtypes of the patients

were collected. Patients with a history of missing a dose within a week prior to the event and irregularly taking medications were defined as those with poor compliance with aspirin. Stroke subtypes were classified by TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria: large-artery atherosclerosis (LAA), cardioembolism (CE), small-artery occlusion (SAO), stroke of other determined cause (OC) and stroke of undetermined cause (UND).

Results

There were 194 acute/subacute ischemic stroke/TIA patients during the study period. Eight patients with cardiac conditions (6: atrial fibrillation, 2: value replacement), which aspirin was not the prophylactic drug of choice in these conditions, were excluded. Forty-six patients (23.7%), who had already been on aspirin (aspirin non-responder), while having new ischemic stroke, were studied. Baseline characteristics of aspirin non-responders were presented in Table 1. Eighteen patients had been on aspirin 300-325 mg/day and 28 patients on aspirin 81 mg/day. Four patients were on a combination of aspirin and other antiplatelet drugs (2: aspirin 81 mg/clopidogrel 75 mg, 1: aspirin 300 mg/clopidogrel 75 mg, 1: aspirin 300 mg/dipyridamole 300 mg per day). Enteric-coated aspirin was used in 8 patients (17%). Most of the patients had taken aspirin 300-325mg/day as secondary prevention because they

Table 1. Baseline characteristics of aspirin non-responders (n = 46)

Baseline characteristics	Mean (range)	Number (%)
Age (years old)	64 (25-87)	
NIHSS	11 (2-39)	
Sex		
Male		16 (35%)
Female		30 (65%)
Diagnosis		
Ischemic stroke		44 (96%)
Transient ischemic attack (TIA)		2 (4%)
Hypertension		35 (76%)
Diabetes mellitus		26 (57%)
Hyperlipidemia		30 (56%)
Coronary artery disease		8 (17%)
History of ischemic stroke		15 (33%)
History of TIA		2 (4%)
Current smoking		7 (15%)
Significant carotid stenosis (>50%stenosis)		6 (13%)
Presentation		
TIA		2 (4%)
Stroke subtypes		
Large arterial thrombosis and artery to artery emboli (LAA)		13 (28%)
Cardioembolism (CE)		5 (11%)
Small-artery occlusion (SAO)		26 (57%)

Table 2. Reasons for taking aspirin in aspirin non-responders (n = 46)

	Subgroup of aspirin 300-325 mg per day Number (%)	Subgroup of aspirin 81 mg per day Number (%)
Old ischemic stroke	11 (61%)	6 (21%)
Transient ischemic attack	1 (5.5%)	1 (4%)
Coronary artery disease	3 (17%)	5 (18%)
Primary prevention in diabetic mellitus patients	2 (11%)	16 (57%)
Unknown reason	1 (5.5%)	-
Total	18 (100%)	28 (100%)

had a previous ischemic stroke, TIA or coronary artery disease. Half of the patients, taking low dose aspirin (81 mg/d) had diabetes mellitus and took aspirin as primary prevention (Table 2).

Discussion

Aspirin is one of the main antiplatelets in prevention of thromboembolic vascular events. In a meta-analysis of 145 randomized studies in patients with coronary artery disease and cerebrovascular disease, 75-300 mg/day aspirin therapy significantly reduced the risk of non-fatal myocardial infarction 35% and the risk of vascular events 18%[3,4]. Aspirin is also the cheapest antiplatelet available in the market and is the most common antiplatelet prescribed in Thailand. In Asia, aspirin resistance is common as it has been reported 27.4% in Hong Kong Chinese patients with coronary artery disease[5]. Previous studies, using different laboratory methods in assessment of antiplatelet effects in ischemic stroke/ TIA patients who were on aspirin, showed that 5-60% of patients had normal platelet function (aspirin non-responders)[6-8]. It has been shown from previous prospective studies that decreased responsiveness to aspirin therapy is associated with an increased risk of atherothrombotic events; however not all of them had subsequent events. In this study, the authors defined aspirin non-responders as inability of aspirin to protect against recurrent thromboembolic events. Aspirin non-responders were found in 23.7% of patients who presented with acute/subacute ischemic stroke or TIA. This might not represent true prevalence of aspirin non-responders because the study was cross-sectional and was not designed to follow-up new thromboembolic events occurring in stroke patients. However, this emphasized the fact that at least 23.7% of patients who presented with ischemic stroke, aspirin could not prevent recurrent events and if the authors added laboratory data, the number might be higher than this.

Possible mechanisms of aspirin failure have been reported which are extrinsic mechanisms (wrong diagnosis, poor compliance, insufficient aspirin dose) and intrinsic mechanisms (genetic polymorphisms, augmented COX-2 expression, oxidative stress, promotion of aggregation by erythrocytes, activation by catecholamines, adenosine diphosphate, presence of vascular risk conditions, drug interactions, and increased platelet turnover)[1,2]. Patients with poor compliance were excluded. For the dose of aspirin, American Heart Association/American Stroke Association Council recommend aspirin 50-325 mg/d to reduce the risk of recurrent stroke and other cardiovascular events in patients with non-cardioembolic ischemic stroke or TIA[9]. The American Diabetes Association recommends the use of aspirin therapy 75-162 mg/d in all diabetic patients more than 40 years of age or who have additional risk factors for cardiovascular disease[10]. Aspirin doses and formulation may affect the antiplatelet function. Patients who take lower aspirin doses [$\leq$ 162 mg/d] and enteric-coated aspirin preparation have normal platelet function (evaluated by platelet function analyzer (PFA-100)) more frequent than patients taking higher doses and not enteric-coated aspirin[6]. All aspirin non-responders in this study had taken appropriate doses of aspirin per indication of treatment and only 17% had enteric-coated aspirin. Intrinsic mechanisms may explain the causes of aspirin non-responders in the study. Future study is required to clarify mechanisms of aspirin non-responders in Thai patients and laboratory methods may be needed to confirm failure of aspirin to produce anticipated antiplatelet effect.

Conclusion

Aspirin non-responders were found in approximately 24% of Thai patients who presented with acute/subacute ischemic stroke or TIA. Intrinsic mechanisms of aspirin failure may explain the causes of aspirin non-responders in this study.

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ภาวะไม่ตอบสนองต่อยาแอสไพรินในผู้ป่วยโรคหลอดเลือดสมองตีบและอุดตันในคนไทย

พรภัทร ธรรมสโรช

ภูมิหลัง: *ภาวะไม่ตอบสนองต่อยาแอสไพรินคือภาวะที่ยาแอสไพรินไม่สามารถป้องกันการเกิด thrombotic events หรือไม่สามารถยับยั้งการทำงานของเกล็ดเลือด จากการตรวจในห้องปฏิบัติการ ข้อมูลการศึกษาในภาวะนี้ส่วนใหญ่มาจากประเทศทางตะวันตก โดยศึกษาในกลุ่มผู้ป่วยโรคหัวใจขาดเลือด และการวินิจฉัยภาวะนี้จากข้อมูลทางห้องปฏิบัติการ*

วัตถุประสงค์: *ในการศึกษานี้คือศึกษาภาวะไม่ตอบสนองต่อยาแอสไพรินในผู้ป่วยโรคหลอดเลือดสมองตีบ และอุดตันในคนไทย*

วิธีการศึกษา: *เป็นการรวบรวมข้อมูลแบบไปข้างหน้าในผู้ป่วยโรคหลอดเลือดสมองตีบและอุดตันและได้รับประทานยาแอสไพรินเป็นประจำก่อนเกิดอาการในครั้งนี้ ซึ่งมาพบแพทย์ที่โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติในช่วงเดือนสิงหาคม 2549 ถึง กรกฎาคม 2550 ข้อมูลเกี่ยวกับขนาดยา เหตุผลในการกินยาแอสไพริน ข้อมูลพื้นฐานของผู้ป่วย ลักษณะตำแหน่งและสาเหตุของโรคหลอดเลือดสมองตีบและอุดตันของผู้ป่วยในครั้งนี้ จะถูกรวบรวมและศึกษา*

ผลการศึกษา: *ในผู้ป่วยจำนวน 194 คน พบภาวะไม่ตอบสนองต่อยาแอสไพรินจำนวน 46 คนหรือร้อยละ 23.7 โดยผู้ป่วย 18 คนได้รับประทานยาแอสไพรินขนาด 300-325 มิลลิกรัมต่อวัน ส่วนใหญ่เพื่อป้องกันการเกิดโรคแบบทุติยภูมิ ผู้ป่วยจำนวน 28 คน รับประทานยาแอสไพริน 81 มิลลิกรัมต่อวัน โดยมากกว่าครึ่งของกลุ่มย่อยนี้ เป็นโรคเบาหวานและได้รับยาเพื่อป้องกันการเกิดโรคแบบปฐมภูมิ*

สรุป: *จากการศึกษา พบว่าภาวะไม่ตอบสนองต่อยาแอสไพรินในผู้ป่วยโรคหลอดเลือดสมองตีบและอุดตันในคนไทยพบได้บ่อย และในอนาคตควรมีการศึกษากลไกการเกิดภาวะนี้ในคนไทยให้มากขึ้น*