Effect of Aspirin and Ticlopidine on Platelet Deposition in Carotid Atherosclerosis: Assessment by Indium-111 Platelet Scintigraphy

Yoshinari Isaka, M.D., Kazufumi Kimura, M.D., Hideki Etani, M.D., Akira Uehara, M.D., Osamu Uyama, M.D., Shotaro Yoneda, M.D., Takenobu Kamada, M.D., and Masahito Kusunoki, M.D.

SUMMARY The antiplatelet effects of aspirin and ticlopidine were studied by a dual-tracer method, using Indium-111 labeled platelets and technetium-99m human serum albumin, in a group of 12 patients with suspected ischemic cerebrovascular disease. The magnitude of platelet accumulation at the carotid bifurcation was expressed as the ratio of radioactivity of Indium-111 platelets deposited on the vascular wall to those circulating in the blood-pool (PAI, platelet accumulation index), 48 hr after injection of labeled platelets. PAI values were measured before (baseline studies) and after the antithrombotic therapies (aspirin studies: 325 mg bid for 22.3 ± 1.3 days, ticlopidine studies: 100 mg tid for 21.8 ± 2.1 days). At the baseline, the mean PAI value at 24 carotid bifurcations in the patient group was 15.7 ± 15.3% (mean ± S.D.) compared to -4.3 ± 9.1 at 24 carotid bifurcations in 12 normal subjects (p < 0.01). We defined the upper limit for a normal PAI (%) value to be +13.9, namely the mean PAI plus 2 SD for the carotid bifurcation in normal subjects and used this value for semiquantitative analysis. At the baseline, significant elevation of PAI (more than 13.9%; positive scintigram) was observed at 12 of 24 vessels, while 12 other regions were negative (less than 13.9%). In the lesions with positive scintigraphic results at the baseline, the mean PAI (%) value from the baseline, aspirin and ticlopidine studies was 29.5 ± 7.0, 11.2 ± 8.5 (p < 0.01 versus baseline) and 21.4 ± 21.3 (not significant from baseline), respectively. The regions with negative scintigraphic findings (PAI < 13.9%), accumulated few, if any, labeled platelets and antithrombotic therapy had no significant influence on PAI (baseline 1.9 ± 5.0; aspirin 1.0 ± 8.3; ticlopidine 0.1 ± 7.6). Our results suggest that a moderate dose of aspirin (325 mg bid) inhibits platelet deposition on carotid atheromatous lesions in vivo in patients with recent cerebral ischemia while the ticlopidine therapy (100 mg tid) was less conclusive than that of aspirin. The procedures described in this study may be useful for evaluation of antithrombotic drugs on platelet deposition at carotid atherosclerotic lesions.

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OCCLUSIVE DISEASE of the internal carotid artery is an important cause of stroke. 1 Transient attacks of cerebral ischemia (TIAs) may result from microemboli released from thrombi deposited on atheromatous lesions. 2 The platelet is known to play an important role in the genesis of arterial thrombus formation and atherosclerosis. 3 This idea has led to several clinical trials utilizing oral aspirin therapy in patients with recent cerebral ischemia. 4-6 The effect of antithrombotic drugs in altering the platelet-vessel interaction at carotid atherosclerosis, however, remains largely undetermined.

Indium-111 platelet is an ideal tracer for evaluation of platelet-vessel wall interaction in vivo, by its half-life, decay by electron capture and high photon abundance. 7

Among the antithrombotic drugs, aspirin 4-6 and ticlopidine, 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothiophene-(3,2-c) pyridine hydrochloride, 8,9 are most commonly used in various thrombotic disorders and the therapeutic effectiveness of them has been reported. 4-8

In the present study, we investigated the effect of a moderate dose of aspirin (325 mg twice daily) and ticlopidine (100 mg three times daily) on platelet deposition at the carotid atheromatous lesions, semiquantitatively, by means of a dual tracer method, using Indium-111 platelets and Technetium-99m human serum albumin (HSA). The magnitude of platelet deposition was expressed relative to the platelet-derived radioactivity circulating in the blood pool (PAI, platelet accumulation index). 10

Materials and Methods

Subjects

Twelve patients with suspected ischemic cerebrovascular disease (11 male and 1 female, mean age 57.9 ± 8.5 yrs, ranging from 38 to 69 yrs) participated in the study. Eleven patients had recent symptoms or signs of ischemic cerebrovascular disease. Clinical manifestations were transient ischemic attacks (TIAs) in 7, reversible ischemic neurological deficit (RIND) in 2, and completed stroke in 2. One patient was asymptomatic but had bilateral carotid bruit that was shown by cerebral contrast angiography to be caused by stenosis of the internal carotid artery. Clinical profiles of the patients are summarized in table 1. Informed consent was obtained from all subjects, under a
Cerebral Angiography

Before the platelet imaging study, bilateral carotid angiography was performed in all patients either by cutaneous direct puncture (1 case) or via the femoral artery (11 cases). The x-ray films were then interpreted by a staff neuro-radiologist and carotid bifurcations on each side were classified as normal, stenotic (lumen by a staff neuro-radiologist and carotid bifurcations on each side were classified as normal, stenotic (lumen reduced by more than 20%) or occlusive. The interval between cerebral angiography and first platelet imag-

Study Protocol

To assess the inhibitory effects of antiplatelet therapy on platelet deposition at carotid atheromatous lesions, patients were studied by platelet imaging at the baseline, while receiving aspirin (325 mg two times daily) and ticlopidine (100 mg three times daily), in the same order. Each antithrombotic drug was adminis-
ted for 4 wks and platelet imaging was performed 20 to 26 days after the administration of each antithrombotic drug (aspirin studies 22.3 ± 1.3 days; ticlopidine studies 21.8 ± 2.1 days). All of the patients were not receiving any anticoagulant or platelet-active drugs (warfarin, aspirin, ticlopidine, dipyridamole, sulfinpyrazone, indomethacin or other non-steroidal antiin-
flammatory drugs) in the preceding 3 wks before the baseline studies.

At each study, the patient was asked if any side effects had occurred and if he was taking the tablets regularly.

Platelet Imaging

Preparation of indium-111 oxine and platelet labeling were performed according to the method described by Heaton et al. The mean injected dose for all 36 studies was 326 ± 18 μCi (± S.D.) and a final label-
ing efficiency of 68.9 ± 12.3%. There was no signifi-
cant difference in injected dose between the baseline and subsequent antithrombotic-drug studies (baseline studies 345 ± 21 μCi, aspirin studies 392 ± 23 μCi, and ticlopidine studies 334 ± 18 μCi). For the blood-
pool study, HSA was labeled with technetium-99m by the method of Eckelman et al., using a commercial kit. The labeling efficiency, which was assessed by technetium-99m blood-pool scintigram was obtained after labeled platelet injection. Then, 10 mCi of technetium, containing 200,000 counts, were obtained by means of a large-field of view gamma camera.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Angiographic findings in ICA</th>
<th>Interval from last attack (months)</th>
<th>PAI (%)</th>
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<tbody>
<tr>
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<td>67</td>
<td>M</td>
<td>TIA</td>
<td>rt stenosis</td>
<td>3.06 (+)</td>
<td>Baseline</td>
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<td>M</td>
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<td>rt occlusion</td>
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<td>M</td>
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<td>Ticlopidine</td>
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<tr>
<td>4</td>
<td>54</td>
<td>M</td>
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<td>rt stenosis</td>
<td>16.3 (+)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>M</td>
<td>TIA</td>
<td>rt stenosis</td>
<td>30.3 (+)</td>
<td></td>
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<tr>
<td>6</td>
<td>54</td>
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<td>rt stenosis</td>
<td>32.9 (+)</td>
<td></td>
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<tr>
<td>8</td>
<td>69</td>
<td>M</td>
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<td>rt stenosis</td>
<td>19.2 (+)</td>
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<tr>
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<td>62</td>
<td>M</td>
<td>completed stroke</td>
<td>rt stenosis</td>
<td>32.4 (+)</td>
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<tr>
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<td>61</td>
<td>M</td>
<td>TIA</td>
<td>rt stenosis</td>
<td>37.2 (+)</td>
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<tr>
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<td>rt stenosis</td>
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</tr>
<tr>
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<td>38</td>
<td>F</td>
<td>TIA</td>
<td>rt stenosis</td>
<td>4.5 (-)</td>
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Table 1: Clinical Profile and Results of Semiquantitative Analysis in 12 Patients

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Abbreviations: M = male; F = female; TIA = transient ischemic attack; RIND = reversible ischemic neurological deficit; ICA = internal carotid artery; np = no pathological finding; + = PAI > 13.9%; - = PAI < 13.9%; * = clinically responsible lesion.
equipped with a medium energy parallel-hole collimator. Both energy peaks at 173 and 247 keV were used for indium-111 and that at 140 keV for technetium-99m.

**Semi-quantitative Analysis**

Platelet images were analyzed by semi-quantitative analysis to derive the scintigraphic thrombus to blood ratio (PAI, platelet accumulation index) from indium and technetium digitized images. Semi-quantitative analysis was performed according to the assumption that indium image consists of radioactivity carried in labeled platelets circulating in the blood-pool (In BP) plus that deposited on the atheromatous lesions (In D).\(^{10,13-16}\) Using blood-pool tracers (such as, technetium-99m HSA or red blood cells), the activity due to In BP can be, in effect, subtracted. The degree of platelet deposition at carotid bifurcation was then expressed as the ratio of radioactivity of platelets deposited on the vascular wall to that circulating in the blood pool (PAI) as previously reported.\(^{10}\)

Digitzed images in a 64 X 64 matrix were used for analysis. All the stored images were corrected by background subtraction, using 16 pixel (4 x 4) background areas outside the head. Regions of interests (ROIs) (16 pixels in area (4 x 4)) were then set to cover the aortic arch and both carotid bifurcations, using the same locations for two tracers. The ROI at the aortic arch served as a reference region. PAI values were calculated as follows:

$$\text{PAI} = \frac{\text{In}_B}{\text{In}_A} = \frac{\text{In}_{CB}}{\text{In}_{AA}} + \frac{\text{Tc}_{CB}}{\text{Tc}_{AA}} - 1$$

in which In \(_B\) equals the radioactivity of indium-111 in the ROI at the carotid bifurcation, In \(_A\) the radioactivity of indium-111 in the ROI at the aortic arch, and Tc \(_B\) and Tc \(_A\) the radioactivity of technetium-99m in the ROI at the carotid bifurcation and aortic arch, respectively.

For purpose of comparison, the PAI values in control subjects are also presented. Control group consisted of 12 healthy volunteers who had no symptoms of cerebral ischemia and no other atherosclerotic vascular disease with the mean age 58.5 yr (range 39-81). None of them had abnormal findings in carotid Doppler spectrum analysis; the data in control subjects have been previously reported.\(^{10}\)

**Statistical Analysis**

Effects of antithrombotic drugs were tested with one-way analysis of variance (ANOVA) and Bonferroni method.\(^{17}\) Comparisons of two groups were performed with the Wilcoxon signed ranks test. Values for test results are presented as mean ± standard deviation.

**Results**

The results of semi-quantitative analysis are summarized in Table 1. In the baseline study, the mean PAI value at carotid bifurcation was 15.7 ± 15.3% (range -7.9 to 37.2) compared with -4.3 ± 9.1 (range -23.6 to 9.9) at 24 carotid bifurcations in normal subjects (\(p<0.01\)). We defined the upper limit for a normal PAI (%) value to be +13.9, namely, the mean PAI plus 2SD, for the scintigraphic diagnosis. In the baseline study, significant elevation of PAI (more than 13.9%; positive scintigram) were observed at 12 of 24 carotid bifurcations. In such lesions, 8 lesions became within normal range (less than 13.9%; negative scintigram) while receiving aspirin, and 5 lesions became negative during ticlopidine therapy. In 12 lesions with positive scintigram, the mean PAI (%) value from the baseline, aspirin and ticlopidine studies were, 29.5 ± 7.0, 11.2 ± 8.5 and 21.4 ± 2.1, respectively (F<sub>33</sub> = 5.25, \(p<0.05\), ANOVA). The mean PAI value during aspirin therapy significantly decreased from the baseline (\(p<0.01\)), while no significant decrease was observed during ticlopidine therapy (fig. 1). In 12 regions with negative scintigram, there was little platelet deposition at the baseline with the mean PAI (%) of...
1.9 ± 5.0, and the mean PAI (%) value was not significantly affected by administration of antithrombotic drugs (aspirin studies 1.0 ± 8.3; ticlopidine studies 0.1 ± 7.6, \[F_3 = 0.21\]). A typical scintigram is shown in figure 2.

The effect of antiplatelet therapy was also compared with the clinical findings in the patients, i.e., in the patients with bilateral carotid atherosclerotic lesions and recent symptoms of ischemic cerebrovascular disease, PAI values of more than 13.9% in the baseline study were evaluated between clinically responsible and non-responsible regions. In five lesions which were considered as clinically responsible, the mean PAI (%) value from the baseline, aspirin and ticlopidine studies was, 28.7 ± 8.1, 9.1 ± 5.3, and 15.9 ± 22.0, respectively (fig. 3). In four lesions which were considered as clinically non-responsible, the mean PAI (%) value at each study was, 33.7 ± 2.8, 14.4 ± 11.6 and 21.1 ± 24.3, respectively (fig. 3). There were no statistical differences in mean PAI (%) between clinically responsible and non-responsible regions at each study.

Discussion

In the present study, we demonstrated that a moderate dose of aspirin (325 mg twice daily) inhibits platelet deposition at the carotid atherosclerosis significantly, while the ticlopidine studies were less conclusive than those with aspirin.

Aspirin rapidly blocks prostaglandin production in vascular tissue, as well as, in blood platelets by inhibiting fatty acid cyclooxygenase. However, the optimal dosage for the antithrombotic efficacy of aspirin has been a subject of major controversy. In experimental studies, Buchanan et al reported an enhanced platelet deposition onto injured carotid arteries in rabbits after aspirin treatment (10 mg/kg intravenously). Wu et al reported that aspirin (30 mg/kg orally) prevents platelet deposition in the injured rabbit arterial wall, whereas 150 mg per kg, promotes platelet deposition. Ercius et al found that 10 mg per kg of aspirin (orally) dramatically inhibits platelet deposition at the endarterectomy site in a canine model, while a low dose of aspirin (0.5 mg/kg) was ineffective. In clinical platelet imaging studies, Ezekowitz et al reported patients with left ventricular thrombi who had positive scans during variable doses of aspirin (300 to 2400 mg/day). Powers et al reported that treatment with aspirin had no effect on the frequency of positive scintigrams in carotid atherosclerosis. However, Cunningham et al found an inhibition of early platelet deposition at angioplasty sites by aspirin therapy (650 mg/day).

It was assumed that such controversial results may arise from differences in thrombogenic stimuli in various thrombotic disorders. A number of randomized
clinical trials comparing aspirin with placebo in cerebrovascular disease show that the dose, proven to be effective in stroke prevention, is between 990 mg to 1300 mg per day. There is, however, little information regarding the effect of aspirin on platelet deposition at the carotid atherosclerosis in humans. So far as we know, the present study is a first report which evaluates the degree of platelet deposition in vivo in patients with cerebral ischemia before and after antithrombotic therapy. Platelet scintigraphy is a reliable method for evaluation of in vivo thrombogenicity. The daily lowest dose of aspirin which is required to inhibit platelet deposition in vivo can be determined by this method.

The present study also demonstrates that ticlopidine diminishes the hematologic activity at some carotid atherosclerotic lesions (5 of 12 lesions), while there was no significant difference in mean PAI value between before and after the therapy. Ticlopidine has been shown to be a potent platelet aggregation inhibitor. The effect of its action upon blood platelets is characterized by inhibition of the primary wave of platelet aggregation induced by ADP, while the effect on collagen-induced aggregation and platelet adhesiveness varies according to the investigator. In humans, ticlopidine in dosage similar to those used in this study (300 mg daily), inhibits several parameters of the functional response of platelets. We monitor the bleeding time of the patients at each visit by Duke's method; the mean bleeding time (min.) from the baseline, aspirin and ticlopidine studies were, 3.8 ± 1.1, 7.4 ± 1.4 and 7.1 ± 1.3, respectively. Thus, it was concluded that ticlopidine does not inhibit platelet deposition in vivo, in a dosage that significantly increases bleeding time. Many experiments using a variety of experimental models have shown a protective effect of ticlopidine on thrombus formation in vivo. In our study, the exact reason why ticlopidine gives a better platelet inhibition in some foci while not effective in others remains to be cleared. The mechanism by which ticlopidine inhibits platelet aggregation is not well understood. A larger number of patients is needed to establish the value of this antithrombotic agent as a prophylactic agent against thrombus formation in ischemic cerebrovascular disease.

No conclusion concerning the relationship between inhibition of platelet deposition in vivo and its clinical significance can be reached in the present study. There were no statistical differences in mean PAI (%) between clinically responsible and non-responsible regions at the baseline and during the antithrombotic therapy. We found that the time interval from acute event to testing did not relate to the platelet deposition in the previous study. Since 3 of 8 regions which were negative during aspirin therapy became positive during the ticlopidine therapy, it is unlikely that our results were biased by intervals from ischemic events to the examination. Powers et al. found no correlation between the non-quantitative platelet scintigraphic findings and the previous or subsequent occurrence of transient ischemic attacks or cerebral infarction. Furthermore, the patients with symptomatic carotid artery disease are more likely to have bilateral disease than the asymptomatic. It now remains to be demonstrated whether platelet deposition at atherosclerotic lesions is responsible for the progression of the patients and whether inhibition of in vivo thrombogenicity by antithrombotic therapy in carotid atherosclerosis may prevent recurrent stroke attacks. Additional prospective studies are needed to resolve those problems.

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References

Reduction in Regional Cerebral Metabolic Rate of Oxygen During Human Aging

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FUMIO SHISHIDO, M.D., ATSUSHI INUGAMI, M.D., TOSHIHIDE OGAWA, M.D.,
MATSUTARO MURAKAMI, PH.D., AND KAZUO SUZUKI, M.D.*

SUMMARY To investigate changes in cerebral circulation and oxygen metabolism during aging, regional cerebral blood flow (rCBF), regional oxygen extraction fraction (rOEF), regional cerebral metabolic rate of oxygen (rCMRO2) and regional cerebral blood volume (rCBV) were measured using the 15O labelled gas inhalation technique and a multi-slice positron emission tomograph (PET) in 22 healthy volunteers, aged from 26 to 64 years old. The measurements were performed with subjects at rest, without sensory deprivation. The values of rCBF, rOEF, rCMRO2 and rCBV in more than 40 anatomical structures of the brain were evaluated by studying a large series of scans in each region of interest after the functional PET image was anatomically identified using x-ray computed tomographic images corresponding to the PET. In mean gray values, only CMRO2 showed significant reduction with age. CMRO2 significantly decreased with age only in the supratentorial, and much more in the left hemisphere. Especially remarkable was CMRO2 reduction in the left caudate region. Both CBF and OEF were variable and less age-dependent. It was concluded that CMRO2 could be reflecting healthy brain aging most properly.

MANY RESEARCHERS have investigated the effect of aging on cerebral circulation and metabolism. The 15O method developed by Kety et al. provided a global cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO2) simultaneously. Using the above method, several papers2-4 concluded that both CBF and CMRO2 reduced with age, although other reports5-9 denied age-related decline of either one or both parameters. Since the advent of the 133Xe non-invasive method, the decline of rCBF with advancing age has been shown.10-17

The recent development of positron emission tomography (PET) using the 15O steady state and the 18F-fluorodeoxyglucose methods made it possible to perform the quantitative measurement of rCBF as well as regional cerebral metabolic rate of oxygen (rCMRO2) and glucose (rCMRGlc). Frackowiak et al.18 first reported that CBF and CMRO2 are reduced significantly in elderly subjects. They concluded later that CBF reduction with age was significant, but that CMRO2 was not significant.19 Pantano et al.20 also found similar results. Kuhl et al.21 indicated that rCMRGlc correlated negatively with age, but Duara et al.22, 23 and de Leon et al.24 did not show age-related change of rCMRGlc in healthy subjects.

This paper describes the age dependency of rCBF, regional oxygen extraction fraction (rOEF), rCMRO2

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