Echocardiography, and 24-hour cardiac Holter among the stroke after the onset of stroke, respectively. In group 2, five patients had mor in all patients, and we observed no major differences on CT, pared the effects of aspirin and ticlopidine on baseline and activated calcium concentration ([Ca^{2+}]) are believed to be involved, but this possibility has not been studied in stroke. Accordingly, we com-
pared with the aspirin- and ticlopidine-treated patients, neither treatment inhibited platelet activating factor-induced responses. Compared with the aspirin-treated group, the ticlopidine-treated patients had a higher baseline [Ca^{2+}] and less inhibition of collagen- and platelet activating factor-induced responses. Taken together, our results suggest that while ticlopidine inhibits some measurements of platelet [Ca^{2+}], the effects are less pronounced than with aspirin. Therefore, mechanisms other than platelet inhibition may need to be considered as contributing to the relatively greater clinical benefit of ticlopidine over aspirin.

Ticlopidine has favorable antithrombotic effects on leukocytes and erythrocytes, which interact with platelets during thrombus formation. Therefore, the experimental observations that ticlopidine reduces platelet-dependent neutrophil activation and increases the stability of erythrocyte membranes may be clinically important. Recent observations that experimentally induced leu-
kopenia is associated with reduced volume of infarction raise the possibility that ticlopidine-induced leukopenia seen in some pa-
tients may have therapeutic benefit. Ticlopidine reduces blood fibrinogen and decreases blood viscosity, which may also con-
tribute to its beneficial effect. In conclusion, we have shown that ticlopidine, compared with aspirin, has a less pronounced effect in reducing platelet [Ca^{2+}]. Besides platelet inhibition, other mechanisms may contribute to the greater clinical efficacy of ticlopidine over aspirin.

Effect of Ticlopidine and Aspirin on Platelet Ionized Calcium in Ischemic Stroke

To the Editor

Ticlopidine, 5-(o-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, a newer antiplatelet drug, has recently been shown to be better than aspirin in the secondary prevention of cerebral ischemia. The exact mechanism by which ticlopidine exerts its antiplatelet effect is unknown. Changes in platelet ionized calcium concentration ([Ca^{2+}]) are believed to be involved, but this possibility has not been studied in stroke. Accordingly, we com-
pared the effects of aspirin and ticlopidine on baseline and activated platelet [Ca^{2+}] in patients with ischemic stroke.

Fifty-one ischemic stroke patients were studied; 22 had not taken antiplatelet drugs for at least 14 days before or after the onset of stroke (Group 1), 17 were on aspirin in a dosage of 325 mg daily for 4.2±2.1 (mean±SD) years (Group 2), and 12 were taking ticlopidine 500 mg twice daily for 2.5±1.9 years (Group 3). The groups were reasonably matched for age, major stroke risk factors (hypertension, diabetes, and smoking), and for concurrent other medications. Ischemic stroke was diagnosed based on the sudden onset of a focal neurological deficit lasting for more than 24 hours. Computed tomography (CT) scan excluded hemorrhage and tuma in all patients, and we observed no major differences on CT, echocardiography, and 24-hour cardiac Holter among the stroke subgroups. Groups 1 and 2 were studied 2.9±2.1 and 3.0±1.8 days after the onset of stroke, respectively. In group 2, five patients had been taking aspirin as a primary preventative for vascular disease, five for pain/arthralgias, four following myocardial infarction, and three following previous ischemic stroke. Group 3 patients were all participants in the Canadian American Ticlopidine Study (CATS) in thromboembolic stroke and had been on prophylactic treatment with ticlopidine following onset of stroke. Platelet [Ca^{2+}] was measured in aequorin-loaded, gel-filtered washed platelets as previously described. Final concentrations of collagen (Chrono-Log Corp., Haverton, Pa.) (2 and 4 μg/ml), thrombin (Parke Davis) (0.5 and 1.0 unit/ml), and platelet activating factor (Calbiochem Corp., La Jolla, Calif.) (5 and 10 μM) were the stimulating agents applied. Student's t test was used to test for differences in baseline and activated platelet [Ca^{2+}].

Compared with levels in untreated patients, platelet levels of [Ca^{2+}] decreased only in patients taking aspirin (Table 1). Although collagen- and thrombin-induced increases in platelets [Ca^{2+}] were inhibited in both the aspirin- and ticlopidine-treated patients, neither treatment inhibited platelet activating factor-induced responses. Compared with the aspirin-treated group, the ticlopidine-treated patients had a higher baseline [Ca^{2+}] and less inhibition of collagen- and platelet activating factor-induced responses. Taken together, our results suggest that while ticlopidine inhibits some measurements of platelet [Ca^{2+}], the effects are less pronounced than with aspirin. Therefore, mechanisms other than platelet inhibition may need to be considered as contributing to the relatively greater clinical benefit of ticlopidine over aspirin.

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kopenia is associated with reduced volume of infarction raise the possibility that ticlopidine-induced leukopenia seen in some pa-
tients may have therapeutic benefit. Ticlopidine reduces blood fibrinogen and decreases blood viscosity, which may also con-
tribute to its beneficial effect. In conclusion, we have shown that ticlopidine, compared with aspirin, has a less pronounced effect in reducing platelet [Ca^{2+}]. Besides platelet inhibition, other mechanisms may contribute to the greater clinical efficacy of ticlopidine over aspirin.

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namic and pharmacokinetic properties, and therapeutic efficacy in platelet dependent disease states. Drugs 1987;34:222-262
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TABLE 1. Baseline Values of, and Collagen-, Thrombin-, and Platelet Activating Factor-Induced Changes in, Platelet Ionized Calcium Concentration ([Ca^{2+}]) in Control, Aspirin-Treated, and Ticlopidine-Treated Ischemic Stroke Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline [Ca^{2+}]</th>
<th>Collagen-induced</th>
<th>Thrombin-induced</th>
<th>PAF-induced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control n=22</td>
<td>Aspirin n=17</td>
<td>Ticlopidine n=12</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.2±0.5</td>
<td>1.9±0.4</td>
<td>2.3±0.4</td>
<td></td>
</tr>
<tr>
<td>4 μg/ml</td>
<td>3.8±1.3</td>
<td>2.4±0.9</td>
<td>3.0±0.5</td>
<td></td>
</tr>
<tr>
<td>2 μg/ml</td>
<td>3.3±1.2</td>
<td>2.1±0.8</td>
<td>2.8±0.5</td>
<td></td>
</tr>
<tr>
<td>1.0 unit/ml</td>
<td>4.8±1.7</td>
<td>3.5±1.3</td>
<td>3.4±0.4</td>
<td></td>
</tr>
<tr>
<td>0.5 unit/ml</td>
<td>4.2±1.3</td>
<td>3.1±1.2</td>
<td>3.0±0.4</td>
<td></td>
</tr>
<tr>
<td>10 μM</td>
<td>15.8±3.8</td>
<td>15.5±5.3</td>
<td>20.7±3.7</td>
<td></td>
</tr>
<tr>
<td>5 μM</td>
<td>13.7±2.3</td>
<td>14.0±3.3</td>
<td>16.3±3.4</td>
<td></td>
</tr>
<tr>
<td>PAF-induced</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 μM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 μM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD.
PAF, platelet activating factor.
*Compared to control group.
†Compared to aspirin group.
Letters to the Editor 533

Effect of Emitted Power on Waveform Intensity in Transcranial Doppler

To the Editor:

The problem of obtaining usable signals in the transcranial Doppler examination of elderly females due to hyperostosis of the temporal bone has been evident since the early days of this technology. That this phenomenon is more pronounced in blacks and Orientals is a particular source of frustration to those, such as Dr. James Halsey, working in areas with a high population of these stroke-prone groups. His attempt to quantify the role of increased ultrasonic emission in overcoming this problem may cast more confusion than light on an area that is already unfamiliar to most clinical neurologists, unfortunately detracting from what is an important contribution to this subject.

The main fault is the failure to define adequately the units of ultrasonic emission being applied. This in turn calls into question the calibration of the transcranial Doppler system on which they are stated to be based and suggests that Halsey may have relied too heavily on the data provided by the manufacturers of the system used.

Our measurements on 14 such systems, which have been confirmed by other centers in Europe and the United States, show that even in a 9-year-old girl, only 6% of the emitted ultrasonic emission being applied. This in turn calls into question the amplifying the backscattered rather than the emitted ultrasound. For this reason, we take the approach of using less acoustic power in the examination of these problem patients, while seeking to increase the sensitivity of the transducer, for instance, by amplifying the backscattered rather than the emitted ultrasound. This approach is not only producing significantly improved Doppler signals, but reduces the risk of possible bioeffects due to unnecessarily high ultrasonic intensities. This consideration is of special importance now that transcranial Doppler is increasingly used as a monitoring method over longer periods of time.

Our failure rate of less than 2%, with a patient population consisting almost entirely of females 50 years old or older, is confirmed by other centers using probes of increased sensitivity. However, we have very few black patients in central Europe, and I am therefore particularly pleased that Dr. Halsey has agreed to collaborate with us in a study to evaluate very carefully our approach in this stroke-prone group of patients.

Alec Eden, PhD
Eden Medical Electronics Group
Überlingen, FRG

References


The following is in response:

To the Editor:

The unit of intensity used by me in my article was a modification of the Food and Drug Administration—defined "estimated in situ intensity," using an attenuation coefficient of 0.59 dBCm−1 MHz−1 for brain tissue rather than lower values, which are applicable to fetal examination. With this attenuation coefficient, a calibrated water-
Effect of ticlopidine and aspirin on platelet ionized calcium in ischemic stroke.
R Joseph, E Han, S Grunfeld and W Robertson

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