Collagen-induced
4 μg/ml  3.8±1.3  2.4±0.9  3.0±0.5 *p<0.001 *p<0.05

Collagen-induced
2 μg/ml  3.3±1.2  2.1±0.8  2.8±0.5 *p<0.005 *p=NS

Thrombin-induced
1.0 unit/ml  4.8±1.7  3.5±1.3  3.4±0.4 *p<0.02 *p<0.01

PAF-induced
10 μM  15.8±3.8  15.5±5.3  20.7±3.7 *p=NS *p<0.005

5 μM  13.7±2.3  14.0±3.3  16.3±3.4 *p=NS *p<0.05

Values are mean±SD.
*Compared to control group.
†Compared to aspirin group.

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.1 The exact mechanism by which ticlopidine exerts its antiplatelet effect is unknown.2 Changes in platelet ionized calcium concentration ([Ca<sup>2+</sup>]) are believed to be involved,3 but this possibility has not been studied in stroke. Accordingly, we compared the effects of aspirin and ticlopidine on baseline and activated platelet [Ca<sup>2+</sup>] in patients with ischemic stroke. Fifty-one ischemic stroke patients were studied; 22 had not taken antplatelet 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 tumor 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 stroke1 and had been on prophylactic treatment with ticlopidine following onset of stroke. Platelet [Ca<sup>2+</sup>] was measured in aequorin-loaded, gel-filtered washed platelets as previously described.4 Final concentrations of collagen (Chrono-Log Corp., Havertown, 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<sup>2+</sup>].

Compared with levels in untreated patients, platelet levels of baseline [Ca<sup>2+</sup>] decreased only in patients taking aspirin (Table 1). Although collagen- and thrombin-induced increases in platelet [Ca<sup>2+</sup>] 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<sup>2+</sup>] 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<sup>2+</sup>], 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.6 Therefore, the experimental observations that ticlopidine reduces platelet-dependent neutrophil activation7 and increases the stability of erythrocyte membranes8 may be clinically important. Recent observations that experimentally induced leukopenia is associated with reduced volume of infarction9 raise the possibility that ticlopidine-induced leukopenia seen in some patients1 may have therapeutic benefit. Ticlopidine reduces blood fibrinogen10 and decreases blood viscosity,8 which may also contribute to its beneficial effect. In conclusion, we have shown that ticlopidine, compared with aspirin, has a less pronounced effect in reducing platelet [Ca<sup>2+</sup>]. Besides platelet inhibition, other mechanisms may contribute to the greater clinical efficacy of ticlopidine over aspirin.

References

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**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 acoustic output of ultrasound devices is, however, only an estimate, based on the very low attenuation coefficients of amniotic fluid and urine, which are efficient vectors of ultrasound when driving in fog is improved by dimming the headlights to avoid the glaring reflections of the full beam. This self-defeating disadvantage of using higher acoustic intensities is not mentioned in Halsey’s study.

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.

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**References**


The following is in response: To the Editor:

The unit of intensity used 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 · MHz 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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