Dipyridamole Testing in Cerebrovascular Patients

TO THE EDITOR: Whiting et al. should be complimented for their excellent description of a case of stroke following dipyridamole infusion (*1*). The Multicenter Dipyridamole Safety Study was designed to determine the risk of serious complications during dipyridamole testing. Preliminary results in 64,130 patients (0.56 mg/kg in 55,489 patients, 0.74 mg/kg in 6189 patients and 0.84 mg/kg in 2452 patients) collected by 73 co-investigators in 50 hospitals in 13 countries show an extremely low risk of cerebrovascular events: there were nine transient cerebral ischemic attacks (with reversible speech and/or motor defects) (1/5000) and only one stroke.

Although we do not know how many of the patients studied had cerebrovascular disease, we can assume that there was a significant number since the test is frequently carried out in multilevel vascular patients. Conversely, what is the risk of NOT performing dipyridamole testing in suspected and known coronary patients with carotid artery disease and a low exercise tolerance? In how many cerebrovascular patients will dipyridamole testing undercover severe life-threatening coronary artery disease? Indeed, it is well known that peripheral vascular disease is associated with a high prevalence of underlying coronary artery disease.

A study is presently under way at our institution to perform a risk/benefit analysis of dipyridamole imaging in cerebrovascular patients with suspected or known underlying coronary artery disease and a low exercise tolerance. Preliminary results suggest that the potential benefits of the test far outweigh its risks.

REFERENCE

1. Whiting JH Jr, Datz FL, Gabor FV, Jones SR, Morton KA. Cerebrovascular accident associated with dipyridamole thallium-201 myocardial imaging: case report. *J Nucl Med* 1993;34:128–130.

Jean Lette
Maisonneuve Hospital and
the Montreal Heart Institute
Montreal, Quebec, Canada

REPLY: We read with great interest Dr. Lette's comments about our case report on a cerebrovascular accident (CVA) that occurred following the intravenous administration of dipyridamole (*1*). Such information was not available when we contacted the DuPont Merck Pharmaceutical Company during manuscript preparation. The statistics from the Multicenter Dipyridamole Safety study confirm our impression that CVA and transient ischemic attacks (TIAs) following intravenous dipyridamole administration are rare. Our clinical experience over the last 2 yr demonstrates that there was only one CVA in 728 patients studied with intravenous dipyridamole over a 2-yr period. This figure correlates well to the findings of Pounds et al. who reported one TIA in 600 patients studied (*2*). We anticipate that the risk/benefit analysis study for CVA with dipyridamole administration now being conducted will confirm our general clinical suspicion that the ratio is low and that dipyridamole will continue to be used in the vast majority of patients at risk for CVA or TIA.

Although we agree that the consequences of not performing dipyridamole testing may fail to uncover life-threatening coronary artery disease, a CVA, no matter how infrequent, is a devastating "side effect" with potential long-term debilitating and permanent life altering consequences. Therefore, every effort should be made to avoid or mitigate the event. After the CVA at our institution, we discussed the following considerations.

A brief review of the patient's relevant risk-related history should be performed. If the review discloses multiple risk factors for CVA, discussion with the patient's physician may be warranted to further evaluate how or if the dipyridamole scintigraphy results will alter the patients care, and what alternative methods for evaluating cardiac function and myocardial perfusion are available. If scintigraphy remains warranted, the physician should proceed with the exam.

A simple brief neurological exam with written documentation of abnormalities prior to dipyridamole administration may facilitate CVA recognition and provide a baseline for those responding to an untoward event, should one occur.

If CVA or TIA is suspected, dipyridamole infusion should be terminated immediately. Aminophylline should be ready for prompt infusion in high-risk patients so that time is not wasted in instituting reversal. The onset of reversibility with aminophylline is variable and may be prolonged, absent or incomplete depending on pharmacological and biochemical factors that may interfere with its ability to antagonize dipyridamole. The effective half-life of aminophylline is shorter than that for dipyridamole (*3–5*), therefore, repeat aminophylline infusions may be necessary to maintain the patients' initial improvement and prevent relapse. Patients suspected of having TIA or CVA should be monitored for an extended period of time in an appropriate environment equipped to respond to further events should they arise.

In the future, a risk/benefit analysis may favor the use of adenosine or dobutamine over dipyridamole in high-CVA-risk individuals. The vasodilatory effect of adenosine on coronary arteries is a maximum of 1–2 min following the start of intravenous infusion; the half-life is between 2–10 sec (*3*). Reversibility is almost instantaneous with the simple termination of the infusion. In contrast, maximum vasodilatation with dipyridamole, while reported as 7–9 min, is variable between patients (*3,4*). Dipyridamole's half-life in blood is 1–2 hr, considerably longer than adenosine's (*3–5*). Reversibility is antagonist dependent and requires the rapid infusion of aminophylline. The short effective half-life of aminophylline and the relatively long half-life of dipyridamole may create a situation of symptom occurrence or recurrence in patients who have left the imaging department.

Dobutamine increases myocardial contractility and myocardial oxygen demands, producing regional coronary artery vasodilatation; systemic vasodilatation is generally avoided (*5*). In addition, blood pressure is maintained, prohibiting generalized hypotension from contributing to stroke. The onset of action of dobutamine occurs at about 2 min and its half-life is about 2.4 min. Like adenosine, dobutamine reversal is not antagonist dependent; terminating the infusion reverses its effect.