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

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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.

ADDENDUM

Since the preparation of this manuscript, a patient at our Veteran's Hospital with no prior neurological history (similar to our previous patient) unexpectedly suffered amaurosis fugax following dipyridamole administration despite the above precautions. This brings our overall incidence to 2 of 735 studies. Our recognition and response to the incident was facilitated by the concepts discussed above. This second event may suggest that the actual incidence of CVA or TIA is higher than previously suspected and that physician recognition and reporting of such may increase with education and closer patient monitoring.

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The Technetium-99m-DTPA Renal Uptake-Plasma Volume Product: A Quantitative Estimation of Glomerular Filtration Rate

TO THE EDITOR: In their recent description of the renal uptake-plasma volume product (RUPV) as a measurement of individual kidney glomerular filtration rate (IKGFR), Zubal and Caride (*1*) assumed that the plasma concentration of ^{99m}Tc-DTPA remained constant for the first 3 min after injection, so that the activity accumulated by the kidneys in this time could be compared with the injected dose, thereby giving IKGFR as a fraction per unit time of the plasma volume. They quoted a paper by Peters et al. (*2*) in support of this assumption. On the contrary, in their paper, Peters et al. (*2*) emphasized the marked fall in the plasma concentration that occurs during this time and quantified its effect, as a background signal, in terms of its "GFR equivalent." This group has also emphasized the high extraction efficiency of small hydrophilic solutes such as ^{99m}Tc-DTPA (MW 492 Daltons) in the capillaries of skin and muscle (*3,4*), which results in the rapidly declining early plasma concentration of ^{99m}Tc-DTPA.

It is very easy to appreciate the substantial early loss of ^{99m}Tc-DTPA from the plasma compartment from any routine multiple sample ^{99m}Tc-DTPA or ^{51}Cr EDTA plasma clearance study by dividing the sum of the zero-time intercepts, A + B, of the conventional bi-exponential clearance curve with the injected dose, which should give the plasma volume. In fact, it gives a value of almost 6 liters, twice the expected value, implying the presence of a fast early exponential which is completed shortly after about 5 min, and which has a zero-time intercept approximately equal to A + B. This early exponential can also be inferred by careful inspection of the relationship of a 5-min sample, in such a multiple sample clearance curve, to the conventional first exponential based on samples from 10 min, which always passes under the 5 min point. By simultaneously measuring plasma volume with radio-iodinated albumin, Neilsen (*5*) was able to identify and quantify an early rapid exponential for the plasma clearance of polyfructosan (a larger molecule than ^{99m}Tc-DTPA), which had an intercept of about 25% of the total zero-time plasma concentration and a rate constant of about 0.5 min^{-1}.

From data derived as part of a previously published study (*6*), I have measured the decrease in left ventricular count rate of ^{99m}Tc-DTPA in comparison with an intravascular reference marker, ^{99m}Tc human serum albumin (HSA). Data were available in nine patients who had relatively normal renal function and who were undergoing routine ^{99m}Tc-DTPA renography for suspected outflow tract obstruction. About 40 MBq of HSA were given 5 min before the DTPA (300 MBq) and dynamic data recorded at a frame rate of 20 sec for HSA and 10 sec for DTPA. The count rate from HSA at 5 min was subtracted from the subsequent count rate to generate the DTPA count rate. Examples of the time-activity curves recorded over the left ventricle are shown in Figure 1. The zero-time count rates were determined by fitting exponential functions to the data recorded between 0 and 4 min. HSA and DTPA count rates both fell between injection and 3 min, the HSA to 0.86 (s.d. 0.037) and the DTPA to 0.63 (s.d. 0.054) of their corresponding zero time values. The mean ratio of these two values at 3 min was 0.74 (s.d. 0.054; range 0.65–0.81), implying a loss of DTPA from the vascular compartment of 26%. This is an underestimation of DTPA lost since, first, a small amount of ^{99m}Tc-HSA may also be lost, and second, even at 3 min, as much as 20% of the count rate over the left ventricle after DTPA may arise from extravascular tracer in the overlying chest wall (*6*). On average, at least 30% of DTPA will have left the vascular compartment by 3 min. This would effectively result in an overestimation of 30% of the dose in Equation 7 of Zubal and Caride's paper (*1*), and a corresponding underestimation of RUPV.

This would explain the regression slopes recorded by Zubal and Caride (*1*) of about 0.7 in their correlations against blood clearance GFR of RUPV based on two of the three conversion equations used for estimating plasma volume from height and weight. Their third conversion equation, which gave a slope close to unity for the regression of RUPV on blood sample GFR, gives estimates of plasma volume some 30% higher than the other two, and clearly higher than the 3 liters for standard man that would be expected from the literature.

The error in RUPV resulting from intravascular loss of DTPA may be systematic, since, unless there is an abnormality of microvascular permeability which might affect the rate of transfer of ^{99m}Tc-DTPA between the intravascular and extravascular compartments in the first few minutes, the early rate of decrease of plasma concentration should be relatively constant (note the range in the nine patients above). Brochner-Mortensen (*7*), when describing the first equation for correcting GFR measurements based on the terminal exponential of the clearance curve (in reality the *third*), pointed out that the area under the *conventional first* exponential (in reality, the *second*) was relatively constant from patient to patient and could therefore be assumed.

Precisely what physiological processes these exponentials represent is by no means clearly understood. Bell et al. (*3*) have shown that the net extraction efficiency of ^{99m}Tc-DTPA from