Do Not Substitute: IV Thrombolytic Selection Errors in Acute Stroke

To the Editor:
Activase (alteplase), commonly referred to as tPA, is a tissue-type plasminogen activator approved for treatment of ischemic stroke when given within 3 hours of symptom onset. Of the 6 thrombolytic drugs licensed for any use in the United States, Retaplace (reteplase), and TNKase (tenecteplase) share this mechanism of action.

We have followed all stroke patients treated with intravenous thrombolics in our 4-hospital group since 1996 as part of an investigation into the community use of alteplase. Data are currently available for over 130 patients. We report 2 recent cases in which retevase was documented as substituted, a problem not previously reported in the literature or seen in our database prior to August 2000.

Patient 1 was a 54-year-old man with a sudden left hemiparesis and hemisensory deficit who qualified for intravenous thrombolyis after cranial CT imaging. Following consent, orders were written for “tPA 9 mg IV over 1 to 2 minutes, 81 mg then over 1 hour. Total dose 90 mg.” The patient received a 9-U bolus of reteplase. The patient was notified of the error and admitted to the ICU per protocol. He was discharged 3 days later, ambulatory with 4/5 strength and normal sensation.

Patient 2 was a 74-year-old man who also had an abrupt onset of left hemiparesis with sensory loss and a right gaze preference. CT demonstrated a hyperdense right middle cerebral artery sign. The only thrombolytic stocked in the involved emergency department was retevase. Nursing notes indicated “faex tPA (order) to (inpatient) pharmacy” followed by “retevase 9 mg IVP given, retevase 81 mg to run in 60 minutes.” On review, the patient indeed received reteplase.

Casual usage of the term “tPA” in thrombolytic therapy for acute myocardial infarction may have little consequence in the treatment outcome—each of the 6 drugs are approved for this use—assuming correct patient selection and dosing. Substitution in patients with acute stroke, however, may have serious consequences in terms of safety or efficacy, as only alteplase has approval in this setting. Adding to the confusion is the frequent usage of the terms “tPA,” “TPA,” and “rt-PA” in the stroke literature when referring specifically to treatment with alteplase, including the original efficacy trials published in the New England Journal of Medicine.1

Potential explanations for the sudden development of treatment errors after 4 years of usage include inappropriate utilization of the generic term “tPA” with an expanding number of agents using this mechanism; inadequate physician and staff knowledge of, and experience with, the increasing number of thrombolics; the use of computerized medication dispensing systems (eg, Omnicell, Pixis), which do not recognize the term “tPA” or “rtPA”; similarities in the naming of thrombolytic agents; alterations in hospital formularies on a frequent basis; stacking of a single thrombolytic in the emergency department for cardiac usage; and a lack of understanding of the nonequivalence of cardiac thrombolytic agents and dosing in the treatment of stroke.

Local corrective actions have included the revision of stroke treatment protocols to minimize the chance of substitution, reprogramming of drug dispensing machines, and increased staff education on thrombolytic agent differences. Heightened caution is advised for the proper selection of thrombolytic agents in patients with acute stroke.

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Prediction of Malignant MCA Infarction With DWI: Pitfalls in Hyperacute Stroke

To the Editor:
We read with great interest the excellent article by Oppenheim et al1 regarding the use of diffusion-weighted imaging (DWI) for the prediction of malignant middle cerebral artery (MCA) infarction. The authors report impressive sensitivity and specificity rates of 100% and 94%, respectively, for the parameter “acute DWI lesion volume >145 cm3” predicting subsequent malignant MCA infarction. Thus, in their study only patients with an initial DWI lesion volume exceeding 145 cm3 went on to develop malignant MCA infarction. The mean time between symptom onset and the DWI measurements was 6.5 ± 3.5 hours (range 2 to 14 hours).

However, although we strongly agree that acute DWI lesion volume has the potential to become a powerful predictor of subsequent malignant MCA infarction, we would like to point out that the sensitivity of this parameter may be considerably below 100% in the hyperacute phase (<3 hours). We have recently seen 2 patients presenting within 2 hours of symptom onset, 1 with a small (6.3 cm3) and 1 without a diffusion deficit (but with persistent MCA occlusion and extensive perfusion deficits), who both went on to develop complete MCA territory infarction. One of these 2 patients (Figure) developed true malignant MCA infarction with signs of beginning uncal herni-
ation and was treated with hemicraniectomy. In the other, somewhat older, patient (73 versus 64 years), only preexisting cerebral atrophy prevented malignant brain swelling leading to herniation, while the increase in DWI lesion size was similarly dramatic.

The 2 cases presented here, although admittedly extreme examples, highlight a more general problem concerning the use of DWI lesion volume as a parameter for the prediction of malignant MCA infarction. As shown by several groups and as discussed by Oppenheim et al., DWI lesion evolution in acute stroke is a highly dynamic process, particularly in the first hours after symptom onset. DWI lesions can enlarge substantially, and it is easily conceivable that, in a given patient, DWI lesion volume will increase from below 145 cm³ to above that threshold. Thus, in the authors’ opinion it will be necessary to define an optimal time window for the measurement of the DWI lesion volume. Clearly, this “optimal time window” will have to start before the time of the early and often unpredictable changes in DWI lesion volume and will have to end before potential treatment forms, such as hemicraniectomy or hypothermia, become less efficacious.

In the hyperacute phase, other parameters, such as a complete MCA territory perfusion deficit or MCA occlusion shown on MR angiography, may be more predictive of malignant MCA infarction than DWI lesion volume. However, evidence of severe tissue damage more definitive than a perfusion deficit appears desirable before embarking on potentially lifesaving but still experimental changes in DWI lesion volume and will have to end before potential treatment forms, such as hemicraniectomy or hypothermia, become less efficacious.

The antioxidant property of bilirubin, the end product of heme catabolism in mammals, was first demonstrated by Stocker et al. In vitro studies have demonstrated that bilirubin exerts an antioxidant effect in either free or albumin-bound form. Studies in animal models and in humans show that antioxidative agents act against formation of atheromatous lesions, which suggests that reactive oxygen species are involved in the pathogenesis of atherosclerosis. Antithrombogenic effects of bilirubin in vivo have not been well established; however, some previous reports have described the relationship between serum bilirubin levels and coronary artery disease. Schwertner et al. have shown that a 50% decrease in total bilirubin level was associated with a 47% increase in the odds of being in the severe coronary artery category in asymptomatic US Air Force pilots and navigators, and Hopkins et al. have reported that coronary artery disease was less common (60% to 90%) when serum bilirubin was in the upper 2 control quintiles compared with the lowest quintile in subjects with early familial coronary artery disease.

Response

We thank the Frankfurt group for their very nice comments on our paper regarding the use of DWI for the prediction of malignant MCA infarction. This group raises the issue of DWI predictive value at the hyperacute phase (<3 hours), describing 2 patients with initially small DWI abnormalities and persistent MCA occlusion who ultimately develop very large MCA infarcts. One of the 2 patients develops malignant edema. In our nonmalignant group of patients, the final size of the infarct was often much larger than the initial DWI abnormality, but none of the patients had a life-threatening malignant edema. However, few of them were initially studied before 3 hours, and we totally agree that there is a need for defining an “optimal time window” for DWI-based prediction of malignant MCA infarct beyond the first 2 to 3 hours.

Yet, we believe that “brain-time” will become increasingly more important than “clock-time”; that patients with a high NIH score, large perfusion defect, small DWI abnormality with moderate ADC decrease, and persistent MCA occlusion should first be considered excellent candidates for intravenous or intraarterial thrombolysis; and that hemicraniectomy should only be considered several hours later if reperfusion has not been achieved and if the DWI abnormality has been rapidly growing (>145 cm³). Finally, our clinical experience is that “slowly growing” infarctions (>24 hours) may achieve very large volume without occurrence of malignant edema. This, again, points to the importance of defining a precise time window for DWI prediction of malignant edema. Future studies are likely to show that the optimal time window is somewhere between 0 to 3 hours and 24 to 48 hours after stroke.

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High Serum Bilirubin Level Is Inversely Associated With the Presence of Carotid Plaque

To the Editor:

The antioxidant property of bilirubin, the end product of heme catabolism in mammals, was first demonstrated by Stocker et al. In vitro studies have demonstrated that bilirubin exerts an antioxidant effect in either free or albumin-bound form. Studies in animal models and in humans show that antioxidative agents act against formation of atheromatous lesions, which suggests that reactive oxygen species are involved in the pathogenesis of atherosclerosis. Antithrombogenic effects of bilirubin in vivo have not been well established; however, some previous reports have described the relationship between serum bilirubin levels and coronary artery disease. Schwertner et al. have shown that a 50% decrease in total bilirubin level was associated with a 47% increase in the odds of being in the severe coronary artery category in asymptomatic US Air Force pilots and navigators, and Hopkins et al. have reported that coronary artery disease was less common (60% to 90%) when serum bilirubin was in the upper 2 control quintiles compared with the lowest quintile in subjects with early familial coronary artery disease.

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To assess the possible association between serum bilirubin level and lower risk of atherosclerotic disease in a larger population, we analyzed 1741 subjects between April 1994 and February 1997 who underwent general health screening tests and high-resolution B-mode ultrasonography (Sonolayer SSA270A, Toshiba) equipped with a 7.5-MHz transducer (PLF-703ST, Toshiba) at Multiphasic Health Testing and Services, Mitsui Memorial Hospital. Carotid arteries were examined bilaterally at the levels of the common carotid, bifurcation, and internal carotid arteries from transverse and longitudinal orientations by trained sonographers. Results of carotid ultrasound studies were interpreted by an observer who was blinded to the results of laboratory tests. Plaque was defined as focal thickening of the intimal-medial layer with an intimal-medial thickness (IMT) of ≥1.3 mm at the common or internal carotid arteries or the carotid bulb.10

Of 1741 subjects enrolled in the present study, 330 subjects (19%) were found to have carotid plaque in either or both of the carotid arteries. The distributions of serum bilirubin concentration in the subjects with or without carotid plaque are shown in the Figure, panel A. An unpaired t test showed that the subjects with carotid plaque had significantly lower serum bilirubin level than those without carotid plaque (14.4±3.8 versus 15.4±5.13 μmol/L; P<0.05). By univariate logistic regression analysis, the following variables were found to have statistically significant odds ratios for carotid plaque (odds ratio; 95% CI): male sex (2.1: 1.8 to 2.5), age >50 years (7.8: 6.0 to 10.0), systolic blood pressure ≥140 mm Hg (2.1: 1.8 to 2.4), HDL cholesterol ≥1.03 mmol/L (0.65; 0.56 to 0.74), triglyceride >1.69 mmol/L (1.8; 1.6 to 2.0), HbA1c ≥5.9% (2.1: 1.8 to 2.5), total bilirubin ≥17.1 μmol/L (0.7; 0.6 to 0.8), uric acid ≥416 μmol/L (1.5; 1.3 to 1.7), alanine transaminase >40 U/L (1.9; 1.6 to 2.4), and alkaline phosphatase (1.4; 1.2 to 1.6).

After adjustment for sex and age, odds ratios compared with the lowest quartile were calculated (Figure, panel B). A 32% and 41% reduction in risk was seen at the highest and the second highest quartiles, respectively.

Then the multivariate logistic regression analysis was performed with the following variables: sex, age, status of cigarette smoking, hypertension, serum levels of total cholesterol, HDL cholesterol, triglyceride, HbA1c, total bilirubin, and uric acid. An increase of 17.1 μmol/L in serum bilirubin concentration was associated with an odds ratio of 0.37 (95% CI, 0.28 to 0.49). The odds ratio associated with a bilirubin of ≥17.1 μmol/L was 0.64 (95% CI, 0.56 to 0.75) when bilirubin was entered into the model as a continuous variable.

In the present study we demonstrated that serum bilirubin level was inversely correlated with carotid plaque. Nieto et al11 have reported that the level of serum uric acid, but not serum bilirubin, was significantly higher in cases with atherosclerotic carotid artery lesions than in normal counterparts. Different findings between their study and ours may be explained by differences in positive criteria of carotid atherosclerosis (Nieto et al defined their cases by the top decile of mean IMT in a series of 1410 participants; in the present study, focal thickening of the intimal-medial layer with IMT of ≥1.3 mm was considered to be carotid plaque) or differences in race or age range.

In summary, we showed an odds ratio of 0.37 for carotid plaque associated with an increase of 17.1 μmol/L (ie, 1.0 mg/dL) in serum bilirubin concentration. We do not know the mechanism linking serum bilirubin to a decreased risk of carotid plaque, although it may possibly be that bilirubin exerts an antiatherogenic effect through its antioxidant property. Whether lower serum bilirubin is a cause or a result of carotid plaque formation, and thus atheromatous disease, awaits further investigation.

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5. Crawford RS, Kirk EA, Rosenfeld ME, LeBoeuf RC, Chait A. Dietary antioxidants inhibit development of fatty streak lesions in the LDL.
HIV-Associated Stroke

To the Editor:

We read with particular interest the article by Connor et al1 in view of our approximately concurrent publication on the same topic2 that was not cited. Our study population was very different, the most pertinent aspects being black race, heterosexual HIV infection, and the fact that our series was relatively devoid of opportunistic infection. Our conclusions were similar, however, in that no evidence of a vasculitic process was found on the available angiographic investigations, which included 10 HIV stroke patients. Rather, large-vessel occlusive patterns were noted on catheter and MR angiography in the middle and posterior cerebral and internal carotid arteries. Our repertoire of prothrombotic tests was not extensive enough to permit diagnostic accuracy for a hypercoagulable state. We suggested a vascular bed-specific hemostasis as the most likely pathomechanism. The postmortem study by Connor et al also suggested a hypercoagulable state or as-yet undefined microemboli or covert HIV-induced vasculopathy. We think the similar conclusions in these 2 diverse HIV populations, 1 antemortem heterosexual HIV infection with a paucity of superinfection and 1 postmortem bed–specific hemostasis as the most likely pathomechanism. The exact mechanism of cerebral infarction remains unclear, and we agree with Hoffmann et al that altered vasoreactivity or altered vascular bed–specific hemostasis as well as microemboli, a hypercoagulable state, or covert HIV-induced vasculopathy are all possible—but unproven—pathological mechanisms.

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Response

We appreciate the interest and comments of Hoffmann and colleagues regarding our recent article1 and have read with interest their recently published findings2 in a heterosexual South African population. Our study was designed to specifically exclude opportunistic infection, lymphoma, or embolic sources, and described patients with pathological evidence of cerebral infarction unrelated to these conditions. Both studies1,2 therefore included patients without opportunistic infection. The absence of vasculitis in both a clinical series2 and an autopsy series with clinical correlation1 highlights our suspicion that cerebral vasculitis unrelated to opportunistic infections or lymphoma is rare in HIV-infected individuals. The exact mechanism of cerebral infarction remains unclear, and we agree with Hoffmann et al that altered vasoreactivity or altered vascular bed–specific hemostasis as well as microemboli, a hypercoagulable state, or covert HIV-induced vasculopathy are all possible—but unproven—pathological mechanisms.

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HIV-Associated Stroke
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