Tissue Plasminogen Activator Overdose in Acute Ischemic Stroke Patients Linked to Poorer Functional Outcomes

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Background: The dose of intravenous tissue plasminogen activator (tPA) administered in acute ischemic stroke patients is calculated using the patient's weight (0.9 mg/kg). Patients are rarely weighed before treatment in actual practice, although overestimating patient weights leads to higher doses of tPA, which may adversely influence outcome. *Methods:* We investigated the weight used to calculate the dose of tPA compared to the actual measured weight in consecutive acute ischemic stroke patients treated over a 4-year period at our center. The rate of intracranial hemorrhage (ICH), discharge modified Rankin Scale (mRS) score, and mortality at 3 months were compared between groups, according to accuracy of the dose of tPA. *Results:* We found that 140 of 164 (85%) acute ischemic stroke patients treated with tPA had a measured weight documented in the chart after treatment. Of these, 13 patients received ≥1.0 mg/kg and 16 patients received ≤0.8 mg/kg, based on a comparison of the weight used for the tPA dose calculation and the subsequent measured weight. Four of 13 (31%) patients treated with ≥1.0 mg/kg of tPA developed ICH. Patients who inadvertently received higher doses of tPA had a lower likelihood of a good functional outcome at discharge (mRS score 0-2; 0% v 34%; P = .009). No difference in 3-month mortality was observed, although patients who were not weighed in hospital had a threefold increase in discharge mortality (21% *v* 7%; P = .019). *Conclusions:* Our findings provide support for the practice of accurately weighing all acute ischemic stroke patients before thrombolysis. **Key Words:** Acute stroke—medical errors—thrombolytic therapy—tissue plasminogen activator.

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Thrombolysis using intravenously administered tissue plasminogen activator (IV tPA) represents the standard of care for treatment of acute ischemic stroke. The National Institute of Neurological Disorders and Stroke (NINDS) tPA stroke study established the efficacy of IV tPA at a dose of 0.9 mg/kg within 3 hours of symptom onset,[1] although patients were not actually weighed before administration of the drug.[2] The European Cooperative Acute Stroke Study III (ECASS III) further established efficacy between 3 and 4.5 hours of symptom onset.[3] The use of IV tPA in acute ischemic stroke is associated with an increased risk of symptomatic intracranial hemorrhage (ICH; 4-6%), and an even greater likelihood of asymptomatic ICH (~10%).[1,4,5] Initial dose-finding trials suggested increased risks of ICH with doses >0.95 mg/kg[6,7] and

greater rates of ICH using higher doses of IV tPA have been reported in the cardiac literature.[8,9] Even small amounts of ICH may have unforeseen clinical sequelae.[10,11] The benefits of IV tPA at a higher dose in the original ECASS trial (1.1 mg/kg) were offset by greater rates of hemorrhagic complications, although an additional contributing factor may have been the prolonged treatment window of 6 hours in this trial.[12]

The dose of IV tPA administered for the treatment of acute ischemic stroke is calculated using the patient's weight, up to a maximum of 90 mg for those who weigh ≥100 kg, although a reported or estimated weight is often used in actual practice, given time restrictions and other perceived limitations involved in weighing the patient. Patients weighing >100 kg receive the maximum dose of tPA and are therefore routinely administered <0.9 mg/kg. These patients often have worse outcomes and are more likely to deteriorate after treatment.[13,14] Underestimating a patient's weight might likewise result in an insufficient or ineffective dose of tPA.[13] Conversely, overestimating a patient's weight results in overcalculating the dose of tPA, which has previously been linked to an increased risk of any ICH and for symptomatic ICH after adjusting for possible confounders, such as age, baseline National Institutes of Health Stroke Scale (NIHSS), and major early computed tomographic (CT) findings.[15]

We set out to determine: (1) the proportion of acute ischemic stroke patients who actually had their weight measured in the acute phase of their presentation to our center; (2) whether estimated or reported weights were accurate, and whether errors were more frequently errors in underestimation (resulting in a dose of ≤0.8 mg/kg) or overestimation (resulting in a dose of ≥1.0 mg/kg); (3) whether an increase in ICH on brain imaging was noted in the proportion of patients who received a dose of tPA ≥1.0 mg/kg; and (4) whether outcomes were worse (discharge modified Rankin Scale [mRS] and mortality) in the proportion of patients who received a dose of tPA ≥1.0 mg/kg.

Methods

Approval for an observational study, based on retrospective chart review, was obtained from the Research Ethics Board at Hamilton Health Sciences. Data over a 4-year period (May 1, 2005 to April 30, 2009) were retrieved on all patients treated with tPA for acute ischemic stroke at the Hamilton General Hospital, Regional Stroke Centre for Central South Ontario, Canada.

The population characteristics (age and sex) and initial stroke severity according to the NIHSS scores was tabulated, as were clinical factors known to be related to the risk of ICH, such as blood pressure, blood glucose, platelet count, and international normalized ratio (INR). Outcome measures included mRS score at discharge and discharge mortality. Brain imaging was independently reviewed in all cases to confirm the presence or absence of ICH.

Patients admitted to our stroke unit are routinely weighed if they are medically stable. The weight used to calculate the dose of tPA was compared to the measured weight in all patients subsequently weighed, and patients were then divided into groups according to whether an accurate dose of tPA was administered (0.9 ± 10%, or 0.81-0.99 mg/kg), patients were underdosed (≤0.8 mg/kg), or patients were overdosed (≥1.0 mg/kg). Patients who were underdosed were further subdivided into those who were inadvertently underdosed and those weighing >100 kg who received the maximum dose of tPA (90 mg) and were therefore underdosed according to protocol.

Statistical analyses were performed using commercially available SPSS software (version 14; SPSS, Inc, Chicago, IL). For example, the Mann–Whitney *U* test (2-tailed) was used for comparing mean NIHSS scores and the Pearson Chi-square test (2-tailed) for comparing discharge mortality rates between weighed and unweighed patients.

Results

The 164 patients ranged from 23 to 96 years of age (mean 70.0 ± 14.6 years). Seventy-five of 164 (45.7%) study participants were women. One hundred forty of 164 (85%) patients had a measured weight documented in the chart after treatment. Patients who were not weighed during hospitalization had greater mean NIHSS scores on admission (15 *v* 11; $P = .014$) and a threefold increase in discharge mortality (21% *v* 7%; $P = .019$; Table 1).

Eight of 140 patients received the maximum dose of 90 mg of tPA, based on a weight >100 kg. Twenty-one of 132 (15.9%) of the remaining patients (in whom documentation of a dose miscalculation was possible) received a dose of tPA in excess of ±10% of the proper dose. Eight additional patients (6.1%) received ≤0.8 mg/kg of tPA, while 13 (9.8%) patients received ≥1.0 mg/kg of tPA (Table 2). Patients receiving ≥1.0 mg/kg tPA had a lower likelihood of a good functional outcome at discharge (mRS score 0-2; 0% v 34%; $P = .009$), in addition to a trend for increased mortality (15% *v* 6%; not significant; Table 2).

Twenty-five (17.9%) of the 140 patients developed any hemorrhagic transformation of their ischemic stroke (Table 3). Four of 13 (31%) of the patients treated with ≥1.0 mg/kg of tPA developed some hemorrhagic transformation of their ischemic stroke, compared to 21 of 129 (16.3%) of the patients who received <1.0 mg/kg of tPA ($P = .16$; not significant).

Discussion

Up to half of all patients admitted to hospital are never weighed.[16] In emergency department (ED) and intensive