Clinical–Diffusion Mismatch and Benefit From Thrombolysis 3 to 6 Hours After Acute Stroke

Martin Ebinger, MD, PhD; Takeshi Iwanaga, MD; Jane F. Prosser, FRACP; Deidre A. De Silva, MD; Soren Christensen, MMSc; Marnie Collins, BCom, BSc; Mark W. Parsons, PhD, FRACP; Christopher R. Levi, FRACP; Christopher F. Bladin, PhD, FRACP; P. Alan Barber, PhD, FRACP; Geoffrey A. Donnan, MD, FRACP; Stephen M. Davis, MD, FRACP; for the EPITHET Investigators

Background and Purpose—The clinical-diffusion mismatch (CDM) model has been proposed as a simpler tool than perfusion-diffusion mismatch (PDM) to select acute ischemic stroke patients for thrombolytic therapy. We hypothesized that in the 3- to 6-hour time window, the effect of tPA was significantly greater in patients with CDM than in patients without CDM.

Methods—This is a substudy of EPITHET, a double-blind multi-center study of 100 patients randomized to tPA or placebo 3 to 6 hours after stroke onset. MRI was obtained before treatment, and at 3 to 5 days and 90 days after treatment. Presence of PDM (perfusion deficit/DWI \( \text{volume} > 1.2 \) and perfusion deficit at least 10 mL/DWI \( \text{volume} \) ) and CDM (NIHSS \( \geq 8 \) and DWI \( \text{volume} \leq 25 \) mL) was determined for each patient. We assessed lesion growth and neurological improvement (decrease in NIHSS \( \geq 8 \) points between baseline and 90 days, or a 90-day NIHSS \( \leq 1 \)).

Results—86% of the patients had PDM, but only 41% had CDM. CDM detected PDM with a sensitivity of 46% and a specificity of 86%. We found statistically significant effects of reperfusion on the rate of neurological improvement (OR 9.92, 95% CI 1.91 to 51.64; \( P < 0.01 \) ) and on absolute growth (difference: \(-59.60 \) mL, 95% CI \(-95.40 \) mL to \(-23.81 \) mL; \( P < 0.01 \)). Neither treatment with tPA nor reperfusion had a significantly different impact on lesion growth or clinical course in CDM patients compared to patients without CDM.

Conclusions—There was no increased benefit from tPA in patients with CDM. The beneficial effects of reperfusion were similar in patients with and without CDM. (Stroke. 2009;40:2572-2574.)

Key Words: MRI ■ stroke ■ tPA ■ clinical-diffusion mismatch

Clinical-diffusion mismatch (CDM) has been suggested as a useful alternative to perfusion-diffusion mismatch (PDM).1 Originally, CDM was defined as NIHSS \( \geq 8 \) and diffusion-weighted imaging (DWI) lesion \( \leq 25 \) mL.1 CDM has a high specificity but a low sensitivity for predicting PDM.2 In the DEFUSE-study, no agreement was shown beyond chance between CDM and PDM; moreover, no association between good clinical outcome and reperfusion was found in patients with CDM.3 However, this analysis of tPA-effects was limited because of the lack of a control group.

We hypothesized that in the 3- to 6-hour time window, the effect of tPA compared to placebo was significantly greater in patients with CDM than in patients without CDM.

Methods

This is a substudy of EPITHET, a prospective, multicenter, randomized, double-blind, placebo-controlled trial using MRI parameters to test the efficacy of tPA in ischemic stroke 3 to 6 hours after symptom onset. Patients were eligible if they had a premorbid mRS \( < 3 \), NIHSS \( \geq 4 \), no evidence of hemorrhage or major early ischemic changes on CT, and if they were able to undergo MRI. Detailed methods have been published.4

Perfusion deficit volumes were determined on Tmax-maps. Hypoperfused tissue was defined by a Tmax-value \( > 2 \) seconds. Reperfusion was defined as a reduction in perfusion deficit volume between the baseline and the day 3 to 5 MRI of at least 90%.

PDM was defined as perfusion deficit volume/DWI lesion volume \( > 1.2 \) and exceeding DWI lesion volume by at least 10 mL.4 CDM was defined as DWI lesion volume \( \leq 25 \) mL and NIHSS \( \geq 8 \).1,2 A secondary analysis was performed using mismatch criteria with potentially superior discriminating power.3 Modified CDM was defined as NIHSS \( \geq 8 \) and DWI lesion volume \( < 15 \) mL and modified PDM as a perfusion deficit volume exceeding DWI lesion volume by at least 10 mL and DWI lesion volume \( < 15 \) mL.3

Received January 18, 2009; accepted February 26, 2009.

From the Department of Neurology (M.E., J.F.P., D.A.D.S., S.C., S.M.D.), The Royal Melbourne Hospital, Parkville, Australia; the Statistical Consulting Centre (M.C.), University of Melbourne, Parkville, Australia; the Department of Neurology (M.W.P., C.R.L.), Hunter Medical Research Institute, John Hunter Hospital, University of Newcastle, Australia; the Department of Neurology (C.F.B.), Box Hill Hospital, Melbourne, Australia; the Department of Neurology (P.A.B.), Auckland Hospital, New Zealand; and the Department of Neurology (T.I., G.A.D.), Austin Hospital, Melbourne, Australia.

Correspondence to Prof Stephen M. Davis, Department of Neurology, Royal Melbourne Hospital, Grattan Street, 3050 Parkville, Australia. E-mail Stephen.Davis@mh.org.au

© 2009 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.109.548073
Table 1. Agreement Between PDM and CDM Models

<table>
<thead>
<tr>
<th></th>
<th>Present (n)</th>
<th>Absent (n)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>39</td>
<td>46</td>
<td>85</td>
</tr>
<tr>
<td>Absent</td>
<td>02</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>58</td>
<td>99</td>
</tr>
</tbody>
</table>

PDM indicates perfusion-diffusion mismatch; CDM, clinical-diffusion mismatch.

We assessed whether the presence of CDM predicted response to treatment or reperfusion in terms of the following end points:

1. Expansion of the initial lesion size expressed as absolute growth (mL);
2. Neurological improvement (NI) defined as a decrease in NIHSS ≥8 points between baseline and 90 days, or a 90-day NIHSS ≤1.

Sensitivity and specificity for detection of a PDM using CDM criteria were calculated. General linear models were fitted for the continuous growth outcome, and logistic regression was used for the binary clinical outcome. The main effects of either treatment or reperfusion and CDM as well as their interaction (ICT and ICR, respectively) were assessed for statistical significance while controlling for baseline DWI volume, baseline NIHSS score, premorbid mRS, and time to treatment. In addition, we repeated the same analyses as described above, but replaced the variable CDM with the variable modified CDM. Data were analyzed using SPSS15.0 and Minitab15.0; \( P<0.05 \) was deemed statistically significant.

In an exploratory analysis, we derived CDM from a regression line (CDMlr). We limited the analysis using this new CDM definition to the effect of reperfusion on NI.

Results

Baseline characteristics were well matched between the tPA and the placebo groups,\(^1\) between patients with CDM (n=41) and without CDM (n=59; except for parameters differing because of the definition of CDM; Supplemental Table I, available online at http://stroke.ahajournals.org), and between CDM patients treated with tPA (n=21) or placebo (n=20).

PDM was present in 86% (85/99) and CDM was present in 41% (41/100). Agreement between the 2 models was present in 52% of patients (51/99) (Table 1). There was a moderate correlation between acute perfusion deficit volume and acute NIHSS score (Spearman rho 0.48, \( P<0.01 \)). The CDM model detected PDM with 46% sensitivity and 86% specificity, positive predictive value 95%, and negative predictive value 21%. There were 2 patients with CDM and without PDM (false-positive), and 46 with PDM but no CDM (false-negative). The majority of the false-negatives (35/46) consisted of patients with moderate to large DWI lesions, ie, volumes >25 mL.

Treatment, CDM, ICT, and ICR had no statistically significant impact on the rate of NI or absolute growth. Reperfusion had an effect on the rate of NI and absolute growth for patients with and without CDM depending on tPA-treatment or reperfusion.

Using modified mismatch criteria\(^3\) we found 30% of the patient population had CDM and 36% had PDM. Sensitivity of the modified CDM for predicting the modified PDM was 78%, specificity was 97%. Treatment, modified CDM, ICT, and ICR had no statistically significant impact on the rate of NI or on absolute growth. Reperfusion had an effect on the rate of NI with an odds ratio of 9.32 (95% CI 2.22 to 39.24; \( P<0.01 \)) and on absolute growth (mean difference \(-26.99 \text{mL} \) to \(26.35 \text{mL} \) to \(43.22 \text{mL} \), \( P<0.01 \)). Table 2 shows the distribution of NI and absolute growth for patients with and without CDM.

Discussion

In EPITHET, the previously published CDM model did not predict the potential for infarct growth attenuation and clinical improvement after tPA or reperfusion. In contrast to other studies,\(^1\)\(^2\)\(^3\) the beneficial effects of reperfusion on clinical outcome or lesion growth attenuation were similar in patients with and without CDM. Thus, it would be inappropriate to...
exclude patients based on the lack of CDM. In accordance with previous results, the specificity of CDM for PDM was high and sensitivity was low. Recently proposed mismatch criteria did not appear to be superior to the conventional mismatch definitions. Using a CDM definition derived from a logistic regression, CDM was an excellent predictor of NI. This approach needs further validation.

Sources of Funding
This work was supported by the Royal Melbourne Hospital Neuroscience Foundation.

Disclosures
S.M.D. has served on advisory boards for Servier and Sanofi-Aventis and has given invited lectures at meetings sponsored by Boehringer Ingelheim. G.A.D. is a member of the Boehringer Ingelheim, PAION, Servier, and Sanofi Aventis Advisory Boards.

References
Clinical–Diffusion Mismatch and Benefit From Thrombolysis 3 to 6 Hours After Acute Stroke

Martin Ebinger, Takeshi Iwanaga, Jane F. Prosser, Deidre A. De Silva, Soren Christensen, Marnie Collins, Mark W. Parsons, Christopher R. Levi, Christopher F. Bladin, P. Alan Barber, Geoffrey A. Donnan and Stephen M. Davis

for the EPITHET Investigators

Stroke. 2009;40:2572-2574; originally published online April 30, 2009;
doi: 10.1161/STROKEAHA.109.548073

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/7/2572

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/