Pilot Dose-Escalation Study of Caffeine Plus Ethanol (Caffeinol) in Acute Ischemic Stroke

Paisith Piriyawat, MD; Lise A. Labiche, MD; W. Scott Burgin, MD; Jaroslaw A. Aronowski, PhD; James C. Grotta, MD

Background and Purpose—In animal models, the combination of caffeine and ethanol (caffeinol) provides robust neuroprotection at blood levels that should be easily and safely achieved in humans. This study was designed to determine the safety and tolerability of ascending doses of this combination in stroke patients.

Methods—This Food and Drug Administration–approved open-label, single-arm, dose-escalation study had 3 original dose groups: group 1, caffeine 6 mg/kg plus ethanol 0.2 g/kg; groups 2 and 3, incremental increases of caffeine and ethanol by 2 mg/kg and 0.2 g/kg, respectively. Intravenous thrombolysis was encouraged if patients qualified. Drug was started within 6 hours of stroke onset, and blood levels of caffeine and ethanol were drawn at baseline and end of infusion. The target blood caffeine and ethanol ranges were 8 to 10 μg/mL and 30 to 50 mg/dL, respectively. Clinical outcome measurements included the National Institutes of Health Stroke Scale at the end of infusion, at 24 hours, and at discharge. Potential complications from caffeine and ethanol were recorded. Cases were reviewed by an independent stroke neurologist for safety.

Results—A total of 23 patients were recruited. Target blood caffeine and ethanol levels were reached in 0 of the 4 patients in the first group. The second dose group (caffeine 8 mg/kg plus ethanol 0.4 g/kg) included 8 patients. The median end-of-infusion caffeine and ethanol levels were within the desired target ranges. Two days after infusion, 1 patient in this group with preexisting cardiac disease and end-of-infusion caffeine and ethanol levels of 10.7 μg/mL and 69 mg/dL developed reversible congestive heart failure and required transfer to an intensive care unit. The original third dose group was canceled given achievement of target blood caffeine and ethanol levels in group 2. However, 3 new dose groups were created in an attempt to minimize the dose of ethanol. Although blood levels were proportional to dose, none of these new dose groups provided optimal blood levels. Congestive heart failure occurred in 1 other patient with previously asymptomatic cardiomyopathy. No other side effects were noted. Concomitant thrombolytic therapy was given in 8 patients, 1 of whom died of intracerebral hemorrhage.

Conclusions—Caffeinol alone or combined with intravenous tissue plasminogen activator can be administered safely. Caffeine 8 mg/kg plus ethanol 0.4 g/kg produces target caffeine and ethanol levels of 8 to 10 μg/mL and 30 to 50 mg/dL, respectively. A randomized, placebo-controlled trial is needed to determine the neuroprotective effect of this combination. (Stroke. 2003;34:1242-1245.)

Key Words: caffeine • ethanol • neuroprotection • stroke, acute

Caffeine and ethanol are frequently consumed substances with high bioavailability in the central nervous system. Caffeine competes with adenosine at its receptors, and ethanol blocks N-methyl-d-aspartate subtype of glutamate receptors and activates γ-aminobutyric acid–mediated neurotransmission.1-4 In rodent stroke models, infarct volume was reduced up to 80% when caffeine and ethanol were coadministered within 180 minutes of ischemia, and optimal neuroprotection was found with blood caffeine and ethanol levels of 8 to 10 μg/mL and 30 to 50 mg/dL, respectively. However, there was no neuroprotection with either caffeine or ethanol administered alone.5

This study aimed to determine the safety and tolerability of ascending doses of the combination of caffeine and ethanol (caffeinol) in acute ischemic stroke patients. We sought to determine the lowest doses of these 2 drugs that produce blood levels in the target range.

Materials and Methods
This study was a pilot open-label, dose-escalation trial. Inclusion criteria were (1) age >18 years, (2) total National Institutes of Health Stroke Score (NIHSS) >4, (3) stroke onset-to-treatment time <6 hours, and (4) clinically suspected cortical ischemia. Exclusion criteria included (1) NIHSS 1a (consciousness) ≥2; (2) a total NIHSS >20 and >25 if right and left hemisphere, respectively; (3)
alcohol intoxication; (4) exogenous caffeine or ethanol use beyond daily consumption of coffee, tea, soft drinks, or several alcoholic beverages; (5) clinically significant cardiac arrhythmia; and (6) coexisting serious or terminal illness. At study inception, candidates were excluded if they received intravenous tissue plasminogen activator (tPA). However, after the first 4 patients were enrolled without serious side effects and after completion of in vivo animal studies and in vitro human blood clotting studies showing no adverse interaction between caffeinol and the lytic property of tPA, the Food and Drug Administration approved concomitant use of intravenous tPA.

On the basis of our animal data, the intended target ranges of blood caffeine and ethanol were 8 to 10 μg/mL and 30 to 50 mg/dL, respectively. Three dose groups were originally created, the beginning dose being caffeine 6 mg/kg plus ethanol 0.2 g/kg, followed by dose escalation in increments of 2 mg/kg caffeine and 0.2 g/kg ethanol.

Preenrollment investigations included chest x-ray, 12-lead ECG, liver function tests, and preinfusion blood caffeine and ethanol levels. After informed consent was obtained, caffeinol was delivered intravenously over 2 hours. Intravenous tPA was administered without delay to all thrombolysis-eligible patients. Vital signs, cardiac rhythm, and neurological status were monitored during the infusion period and subsequent 24 hours with special attention given to level of consciousness, ataxia, and agitation. Neurological status was assessed by serial NIHSS assessments at baseline, end of infusion, 24 hours, and discharge (or day 5). All adverse events were also noted.

**Caffeine and Ethanol Levels**

Blood levels of caffeine and ethanol were obtained at the end of infusion. Caffeine and ethanol levels were measured in the hospital laboratory by spectrophotometry and immunoassay, respectively. For quality control, blood levels were also randomly checked by our own research laboratory.

**Safety**

In addition to internal review, the case report forms for each patient were reviewed by an independent stroke neurologist (ISN) at another institution.

**End Points**

Enrollment in a dose group was terminated if 1 of the following end points occurred: (1) end-of-infusion blood levels of caffeine or ethanol outside the target range in 2 consecutive patients, (2) consistent achievement of target blood caffeine and ethanol levels of 8 to 10 μg/mL and 30 to 50 mg/dL, or (3) serious complications related to caffeinol (sedation requiring intubation, resultant ataxia, significant cardiac arrhythmia, or pneumonia) occurring in 2 patients.

This study was reviewed and approved by the Committee for the Protection of Human Subjects, the University of Texas at Houston, and the Memorial Hermann Hospital (Houston, Tex).

**Results**

Between March 2001 and September 2002, 23 patients (16 female) were enrolled. Nine were black, 9 were white, 4 were Hispanic, and 1 was Asian. Mean and median ages were 68.5 and 71.0 years, respectively. Serial NIHSS scores, radiographic findings, and blood caffeine and ethanol levels are presented in the Table.

Four patients were recruited into the first dose group (caffeine 6 mg/kg plus ethanol 0.2 g/kg). The average caffeine and ethanol levels at this dose were 6.2 μg/mL and <13 mg/dL, respectively, both below the target range. In 2 patients, the end-of-infusion blood levels were unreliable (drawn substantially after the end of infusion). No neurological deterioration was observed in this group. One patient had full recovery with no infarct on follow-up MRI.

There were 8 patients enrolled into group 2 (caffeine 8 mg/kg plus ethanol 0.4 g/kg). Blood caffeine levels at the end of infusion were within the target range (mean, 9.0 μg/mL; median, 8.1 μg/mL). Ethanol levels ranged from <13 to 69 mg/dL (median, 45 mg/dL) and were within the target range in 5 patients. In 2 patients, ethanol levels were undetectable, and in 1 patient, the value was unreliable (drawn too late). These ethanol levels correlated well with simultaneous analyses conducted in our research laboratory. Three patients in this group received concomitant intravenous tPA: 2 with significant improvement and 1 with herniation from tPA-related intracerebral hemorrhage. In the latter case, blood caffeine and ethanol levels could not be drawn as scheduled. One patient developed transient drowsiness, which completely resolved within 12 hours. Congestive heart failure (CHF) requiring intensive care unit monitoring was noted 2 days after the caffeinol infusion in 1 patient with a history of coronary artery disease and CHF and cardiomegaly on baseline chest x-ray. The CHF resolved with treatment. In this patient, end-of-infusion caffeine and ethanol levels were 10.7 μg/mL and 69 mg/dL. Despite this adverse event, the NIHSS score improved 4 points by day 5, and the blinded ISN judged that the CHF was unrelated to the caffeinol infusion.

The originally planned third dose group (caffeine 10 mg/kg plus ethanol 0.6 g/kg) was canceled because target blood levels were consistently achieved in the second group. Because 1 of the 2 patients in the second group with end-of-infusion ethanol levels >50 mg/dL had an adverse cardiac event, a new dose group was created using caffeine 8 mg/kg plus ethanol 0.3 g/kg (group 1A). Five patients were recruited. Although the target end-of-infusion caffeine level was achieved (mean 10.6 μg/mL; median, 8.0 μg/mL), the target ethanol level was reached in only 1 patient. This patient, with preexisting atrial fibrillation and dilated cardiomyopathy, developed CHF and required intubation 2 days after the caffeinol infusion. The CHF responded to treatment, and 30 days after stroke, only minimal left hemiparesis (modified Rankin score 1) remained. Again, the blinded review by the ISN suggested no direct cause-effect relationship between caffeinol and this cardiac event.

The fourth and fifth dose groups (groups 1B and 1C) were devised by minimally increasing the ethanol dose to 0.35 and 0.375 g/kg, respectively, maintaining a constant caffeine dose (8 mg/kg). Two patients were recruited into group 1B and 4 into group 1C. Target end-of-infusion ethanol levels were achieved in 0 patients in group 1B and 3 of 4 patients in group 1C.

A total of 19 patients received caffeine 8 mg/kg. The mean and median end-of-infusion caffeine levels among these patients were 9.5 and 9.0 μg/mL.

Of the 8 patients receiving concomitant intravenous tPA, neurological improvement of >4 on NIHSS was achieved in 5 patients (63%) at 24 hours and 6 patients (75%) at discharge or day 5. Protocol violations occurred in 2 patients who received caffeinol slightly beyond the 6-hour window.
Discussion

Thrombolysis is the only approved therapy for acute ischemic stroke. Fifteen to 20% of acute ischemic stroke patients receive thrombolysis in our center as a result of tremendous efforts to educate the public and organize emergency response.6 Neuroprotective therapy may increase the number of patients who benefit from acute stroke therapy by providing an alternative for patients ineligible for thrombolysis or may be used to augment the benefit of tPA.

Despite impressive efficacy in animal models, neuroprotective drugs have not demonstrated robust effects in clinical trials. Several explanations exist for this disparity, including delayed treatment time, lack of residual flow, impaired delivery of drugs to jeopardized tissue, and multiple simultaneous pathways, triggered by the ischemic process, leading to cellular death. This protocol was designed to address these deficiencies. Although its precise mechanism is unknown and is under active study in our laboratory, caffeinol likely affects multiple pathways of the ischemic cascade, especially when coupled with reperfusion with tPA. Although the protocol allowed enrollment up to 6 hours, early administration of caffeinol was strongly encouraged.

The primary objective of this study was to determine the doses of combined caffeine and ethanol that produced therapeutic-range blood levels in animals. It is not certain, of course, that blood levels in rats and humans are analogous and provide similar central nervous system bioavailability. However, given the efficient brain penetration of both drugs, we propose that rodent blood levels represent a reasonable guide to those that should be targeted in humans. What is less certain is the interspecies receptor kinetics of those compounds; therefore, we cannot conclude with certainty that the “target” blood levels in rats will have the same clinical effect in human stroke patients.

### Patient Baseline Characteristics and Outcomes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Caff, mg/kg</th>
<th>ETOH, g/kg</th>
<th>tPA Onset to Infusion, h</th>
<th>NIHSS Baseline</th>
<th>Caff</th>
<th>ETOH</th>
<th>NIHSS at 24 h</th>
<th>Follow-Up CT/MRI</th>
<th>TOAST</th>
<th>NIHSS at D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>88</td>
<td>F</td>
<td>6</td>
<td>0.2</td>
<td>N</td>
<td>4:30</td>
<td>7</td>
<td>2.4</td>
<td>&lt;13</td>
<td>9</td>
<td>5.2</td>
<td>&lt;13</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>F</td>
<td>6</td>
<td>0.2</td>
<td>N</td>
<td>3:30</td>
<td>17</td>
<td>1.9</td>
<td>&lt;13</td>
<td>15</td>
<td>4.0</td>
<td>&lt;13</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>F</td>
<td>6</td>
<td>0.2</td>
<td>N</td>
<td>6:00</td>
<td>15</td>
<td>5.4</td>
<td>&lt;13</td>
<td>7</td>
<td>12.0</td>
<td>&lt;13</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>F</td>
<td>6</td>
<td>0.2</td>
<td>N</td>
<td>3:15</td>
<td>9</td>
<td>&lt;1.0</td>
<td>&lt;13</td>
<td>8</td>
<td>3.6</td>
<td>&lt;13</td>
</tr>
</tbody>
</table>

**Group 1A**

| 5       | 30     | F   | 8           | 0.3         | N                       | 6:00           | 15   | NA   | NA          | 14              | 22.6   | 54         | Right MCA infarct | 2    | 20          |
| 6       | 58     | M   | 8           | 0.3         | N                       | 6:00           | 18   | 3.5  | <13         | 18              | 8.1    | 27         | Right MCA infarct | 2    | 11          |
| 7       | 60     | F   | 8           | 0.3         | Y                       | 2:30           | 10   | 0    | <13         | 9               | 7.2    | 17         | Right MCA infarct | 1    | 7           |
| 8       | 78     | M   | 8           | 0.3         | N                       | 4:25           | 17   | 1.2  | <13         | 16              | 8.0    | 28         | Right MCA infarct | 2    | 15          |
| 9       | 74     | F   | 8           | 0.3         | N                       | 6:45           | 10   | NA   | NA          | 10              | 7.1    | <13        | Left MCA infarct  | 2    | 10          |

**Group 1B**

| 10      | 26     | M   | 8           | 0.35        | Y                       | 3:15           | 24   | 2.1  | <13         | 8               | 10.0   | 23         | Left MCA infarct  | 2    | 5           |
| 11      | 90     | F   | 8           | 0.35        | Y                       | 5:25           | 11   | NA   | <13        | 7               | 6.8    | 16         | Right MCA infarct | 1    | 3           |

**Group 1C**

| 12      | 72     | F   | 8           | 0.375       | N                       | 6:08           | 22   | 3.3  | <13         | 21              | 13.4   | 37         | Left MCA infarct  | NA   | 23          |
| 13      | 55     | F   | 8           | 0.375       | Y                       | 2:40           | 11   | 2.0  | <13         | 4               | 6.2    | 25         | Right MCA infarct | 5    | 0           |
| 14      | 80     | M   | 8           | 0.375       | N                       | 5:30           | 7    | 1.8  | <13         | 3               | 8.5    | 50         | Right pontine infarct | 3    | 2           |
| 15      | 61     | F   | 8           | 0.375       | Y                       | 2:14           | 7    | 2.7  | <13         | 7               | 11.7   | 42         | No new infarct, ICH | NA   | 0           |

**Group 2**

| 16      | 71     | M   | 8           | 0.4         | N                       | 4:00           | 16   | NA   | NA          | 3.5             | <13    | 2           | No acute ischemia | NA   | 2           |
| 17      | 62     | F   | 8           | 0.4         | Y                       | 4:20           | 23   | <1.0 | <13         | 29              | 7.4    | <13        | Expired ICH with herniation | 1    | Expired     |
| 18      | 84     | F   | 8           | 0.4         | N                       | 5:55           | 23   | <1.0 | <13         | 4               | 9.8    | 50         | Left MCA infarct  | 2    | 0           |
| 19      | 84     | F   | 8           | 0.4         | N                       | 4:45           | 17   | 4.9  | <13         | 24              | 10.0   | 40         | No acute ischemia | NA   | 4           |
| 20      | 68     | M   | 8           | 0.4         | N                       | 5:57           | 15   | 3.7  | <13         | 16              | 10.7   | 69         | Left MCA infarct  | 2    | 11          |
| 21      | 57     | M   | 8           | 0.4         | Y                       | 2:59           | 17   | 5.9  | <13         | 11              | 9.1    | <13        | Left MCA infarct  | 1    | 10          |
| 22      | 87     | F   | 8           | 0.4         | N                       | 4:29           | 20   | <1.0 | <13         | 6               | 9.0    | 63         | Left MCA infarct  | 2    | 0           |
| 23      | 87     | F   | 8           | 0.4         | Y                       | 3:25           | 24   | 3.0  | <13         | 27              | 12.3   | 50         | Left MCA infarct  | 2    | 12          |

Caff indicates caffeine; ETOH, ethanol; Onset to Infusion, time from onset to caffeinol administration; D/C, discharge or day 5; MCA, middle cerebral artery; TOAST, stroke subtype: 1 = large vessel disease, 2 = cardioembolism, 3 = small vessel disease, 5 = undetermined; and ICH, intracerebral hemorrhage.
Unlike caffeine, ethanol produced more variable postinfusion blood levels, probably because of patients’ baseline hepatic function before exposure to ethanol and the timing of postinfusion blood draw.\textsuperscript{7,8} Despite these limitations, caffeine 8 mg/kg plus ethanol 0.4 g/kg produced reasonably consistent target blood levels of both caffeine and ethanol that were associated with a robust neuroprotective effect in animal stroke models. Excluding 1 case with improper handling of blood samples, ethanol 0.4 g/kg was associated with target end-of-infusion levels in 5 of 7 patients. In 2 patients in this group and in 1 patient in the group receiving 0.3 g/kg, the end-of-infusion ethanol level was undetectable. As expected, blood levels with ethanol 0.375 g/kg were slightly lower than in the 0.4 g/kg group but below the target range in only 1 of the patients treated. Only 1 patient in the entire series (patient 5) had blood ethanol levels markedly above what was expected, but even in this patient, the level (54 mg/dL) was within the target range. Future studies could use serum markers of chronic alcohol use (elevated mean corpuscular volume of red blood cells and γ-glutamyltransferase) as additional exclusion criteria to possibly identify patients in whom ethanol might produce unpredictable levels and in whom previous ethanol exposure might reduce benefit.

Safety and feasibility were other primary objectives of this study. The target blood ethanol range is below the legal intoxication levels (50 to 100 mg/dL). The death of 1 patient, who also received intravenous tPA, was most likely attributable to the initial severity of stroke. Our preclinical studies showed no interaction of caffeinol and tPA with regard to rate of intracerebral hemorrhage in vivo or recanalization or clot lysis in vitro.\textsuperscript{9} Therefore, we conclude that it is safe to administer caffeinol concomitantly with intravenous tPA. Cardiac complications, particularly CHF, were noted in 2 patients with preexisting advanced subclinical cardiac conditions. Both occurred 2 days after the infusion was completed and resolved with treatment. No cardiac events occurred in any of the patients whose pretreatment cardiac evaluation was normal, and the ISN judged that the 2 cardiac events were unrelated to caffeinol. Therefore, we conclude that caffeinol is not likely to directly cause cardiac complications but may exacerbate underlying abnormalities of cardiac rhythm and function. Caffeine can be arrhythmogenic if a predisposing cardiac condition is present, whereas ethanol depresses myocardium in animals in a dose-dependent fashion.\textsuperscript{10–12} Caution should be exercised to exclude patients with significant underlying cardiac disease in future studies. Although altered mental status was anticipated, this short-lived reversible side effect was observed in only 1 patient. No other clinical symptoms or signs of acute alcoholic intoxication such as ataxia or metabolic acidosis were noted.

Neurological improvement by >4 on the NIHSS was seen in 13 patients (57%), 6 who also received intravenous tPA. However, a randomized, placebo-controlled trial will be necessary to determine the efficacy of caffeinol in stroke.

In summary, we have established a safe and well-tolerated dose of combined caffeine and ethanol that produces blood levels in humans that are highly protective in animal stroke models.\textsuperscript{13}

Acknowledgments

This study was supported by NINDS fellowship training grant T32NS07412 to the University of Texas—Houston Stroke Program and by NINDS grant 1R01NS040974-01A1. We would like to thank David Sherman, MD, who served as safety monitor for this study.

References

Pilot Dose-Escalation Study of Caffeine Plus Ethanol (Caffeinol) in Acute Ischemic Stroke
Paisith Piriyawat, Lise A. Labiche, W. Scott Burgin, Jaroslaw A. Aronowski and James C. Grotta

Stroke. 2003;34:1242-1245; originally published online April 10, 2003;
doi: 10.1161/01.STR.0000067706.23777.04

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/34/5/1242

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/