Combined Neuroprotective Modalities Coupled with Thrombolysis in Acute Ischemic Stroke: A Pilot Study of Caffeinol and Mild Hypothermia

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Background: Both caffeinol and hypothermia are neuroprotective in preclinical models of transient middle cerebral artery occlusion. We tested whether combining caffeinol and hypothermia with tissue plasminogen activator (t-PA) in patients with acute stroke is safe and feasible. *Methods:* Twenty patients with acute ischemic stroke were treated with caffeinol (caffeine 8-9 mg/kg + ethanol 0.4 g/kg intravenously [IV] × 2 hours, started by 4 hours after symptom onset) and hypothermia (started by 5 hours and continued for 24 hours [target temperature 33-35°C] followed by 12 hours of rewarming). IV t-PA was given to eligible patients. Meperidine and buspirone were used to suppress shivering. *Results:* All patients received caffeinol, and most reached target blood levels. Cooling was attempted in 18 patients via endovascular (n = 8) or surface (n = 10) approaches. Two patients were not cooled due to catheter or machine failure. Thirteen patients reached target temperature; average time from symptom onset was 9 hours and 43 minutes. The last 5 hypothermia patients received surface cooling with iced saline induction and larger doses of meperidine; all patients reached target temperature, on average within 2 hours and 30 minutes from induction and 6 hours and 21 minutes from symptom onset. Three patients died: one from symptomatic hemorrhage, one from malignant cerebral edema, and one from unrelated medical complications. No adverse events were attributed to caffeinol. One patient had reduced respiratory drive due to meperidine, requiring BiPAP. *Discussion:* Combining caffeinol with hypothermia in patients with acute stroke given IV t-PA is feasible. A prospective placebo-controlled randomized study is needed to further assess safety and to test the efficacy of caffeinol, hypothermia, or both. **Key Words:** Acute ischemic stroke—neuroprotection—hypothermia—safety—feasibility.

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Neuroprotective trials in human beings with ischemic stroke have yielded disappointing results.[1,2] There are a number of reasons postulated to explain why positive results in animal models of stroke fail to translate to human beings with spontaneous ischemic stroke. Among these is failure to initiate treatment in the appropriate time frame,[3] doses too low to allow for effective brain penetration of the drug,[4] and targeting only a single step in the complex ischemic cascade.[2] Most drugs that have shown efficacy in animals used a model of temporary vessel occlusion. Recanalization, and more importantly, reperfusion may be essential for drug delivery in

concentrations that would be effective and has not been typically addressed in human trials. Lastly, the majority of neuroprotective drugs have greatest benefit on cortical penumbra in animal models,[3] yet strokes in human beings have variable locations and severity of ischemia.

We designed this study to address each of these concerns. Our neuroprotective strategy was to administer the neuroprotective treatment soon after symptom onset in combination with intravenous (IV) tissue plasminogen activator (t-PA) to achieve reperfusion and improve delivery of neuroprotection to target tissue in as many patients as possible. We limited enrollment to patients most likely to have cortical injury and used a combination of agents (caffeine and ethanol = caffeinol, + hypothermia) that have rapid brain penetration and target multiple aspects of the ischemic cascade.

We chose caffeinol for the following reasons. Caffeinol consists of caffeine and ethanol, and exerts its biological effect through central adenosine, gamma-aminobutyric acid $(GABA)_A$, and N-methyl-D-aspartate receptors.[5] Caffeine and ethanol are among the most widely consumed substances in most societies. Consequently, there are substantial data and human experience regarding the speed of their effects on the brain, blood levels, and side effects in human beings that can guide their therapeutic use. As an adenosine receptor antagonist, caffeine speeds up neural activity, stimulates the pituitary-adrenal axis promoting adrenaline release, increases the cerebral metabolic rate, and can actually reduce cerebral blood flow.[5] In rats, the areas of reduced blood flow are the same as those that demonstrate increased metabolic rate. Caffeine may allow a higher metabolic rate for a given rate of cerebral blood flow, which could allow critical metabolic pathways to continue functioning despite reduced perfusion in the setting of ischemic stroke.[5] Caffeine has differential activity at low and high doses. At subtoxic doses, caffeine acts primarily as an antagonist to adenosine receptors, including the A2a subtype of the receptor that has inhibitory effects on synaptic glutamate release and excitotoxicity in context of ischemic stroke.[6] At toxic doses, caffeine inhibits phosphodiesterase, blocks $GABA_A$ receptors, and stimulates the release of intracellular calcium.[5] A survey published in 1996 reported that the estimated mean daily intake of caffeine was in the range of 4 mg/kg,[7] and one cup of coffee contains up to 100 mg of caffeine.

Ethanol acts on the brain mainly through $GABA_A$ receptor stimulation and inhibition of N-methyl-D-aspartate receptors,[8,9] thereby helping to promote inhibitory and antiexcitotoxic synaptic pathways. Ethanol has antiplatelet function that may impact postischemic cerebral perfusion.[10] In low doses, ethanol alone had no effect on infarct volume.[11] In combination with caffeine, even at very low doses (0.2 g/kg), ethanol showed a neuroprotective effect, both on infarct volume and in neurologic outcome.[11] The mechanism of this neuroprotective effect in combination with caffeine, but not when given alone, is unknown.

Caffeinol delivered as an IV infusion over 2 hours starting 120 minutes after common carotid artery/middle cerebral artery (CCA/MCA) occlusion in a rat model was effective in reducing the severity of neurologic function and the final cortical infarct volume (by 45%) at doses as low as 6 mg/kg of caffeine and 0.2 g/kg of ethanol.[11] Another group confirmed that the same doses of caffeinol were effective in reducing infarct volume in a rodent model, and that this effect was restricted primarily to the cerebral cortex.[12] One neutral study has been reported with caffeinol + t-PA, but used a largely subcortical injury model and different doses of caffeinol and t-PA than effective studies.[13] In our animal studies, caffeinol did not increase the incidence of hemorrhagic transformation after t-PA,[11] nor did it affect the thrombolytic effect of t-PA in an ex vivo bioassay (data on file). The effect of caffeinol on stroke volume and neurologic outcome in a permanent model of ischemic stroke has not been performed. Because our animal model showing a beneficial effect of caffeinol-involved reversal of the occlusion, the potential benefit to the ischemic brain in the absence of recanalization is unknown. Pilot clinical trials of caffeinol have shown that blood levels effective in rodents are easily achieved and well tolerated in patients with stroke.[14] These blood levels (caffeine $>$ 8 μg/mL and ethanol 30-50 mg/dL) are within the usual limits achieved by social consumption of these substances (legal ethanol blood level in most states is 50-80 mg/dL). More recently, we found that caffeinol may improve clinical outcome in patients receiving t-PA.[15] Finally, our preclinical studies have demonstrated that the robust neuroprotective effect of caffeinol can be augmented by mild hypothermia (35°C).[11]

We chose hypothermia for the following reasons. Several studies have shown that patients presenting with ischemic stroke and hyperthermia have worse outcomes and larger infarcts than patients who are normothermic at presentation.[16] The ischemic cascade is susceptible to blunting by hypothermia by multiple mechanisms. In addition to reduced cerebral metabolism, reduced blood-brain barrier disruption, and blunted inflammatory response, hypothermia also inhibits maladaptive processes in ischemic brain cells that lead to apoptosis. Hypothermia has been effective in reducing ischemic damage in multiple experimental models of stroke.[17]

Improved outcomes have been achieved with therapeutic hypothermia in patients with global brain ischemia after cardiac arrest, but these studies were performed on intubated and paralyzed patients.[18,19] The COOL AID (Cooling for Acute Ischemic Brain Damage) study combined thrombolysis with mild hypothermia. Although few patients were treated (10 in the hypothermia group), adverse events were low and there was a trend toward improved outcome. Small safety and feasibility studies of hypothermia in awake, nonintubated patients with