Acetaminophen for Altering Body Temperature in Acute Stroke
A Randomized Clinical Trial

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Background and Purpose—Mild alterations in temperature have prominent effects on ischemic cell injury and stroke outcome. Elevated core body temperature (CBT), even if mild, may exacerbate neuronal injury and worsen outcome, whereas hypothermia is potentially neuroprotective. The antipyretic effects of acetaminophen were hypothesized to reduce CBT.

Methods—This was a randomized, controlled clinical trial at 2 university hospitals. Patients were included if they had stroke within 24 hours of onset of symptoms, National Institutes of Health Stroke Scale (NIHSS) score $\geq 5$, initial CBT $<38.5^\circ C$, and white blood cell count $<12,600$ cells/mm$^3$; they were excluded if they had signs of infection, severe medical illness, or contraindication to acetaminophen. CBT was measured every 30 minutes. Patients were randomized to receive acetaminophen 650 mg or placebo every 4 hours for 24 hours. The primary outcome measure was mean CBT during the 24-hour study period; the secondary outcome measure was the change in NIHSS.

Results—Thirty-nine patients were randomized. Baseline CBT was the same: $36.96^\circ C$ for acetaminophen versus $36.95^\circ C$ for placebo ($P=0.96$). During the study period, CBT tended to be lower in the acetaminophen group ($37.13^\circ C$ versus $37.35^\circ C$), a difference of $0.22^\circ C$ (95% CI, $0.08^\circ C$ to $0.51^\circ C$; $P=0.14$). Patients given acetaminophen tended to be more often hypothermic $<36.5^\circ C$ (OR, 3.4; 95% CI, 0.83 to 14.2; $P=0.09$) and less often hyperthermic $>37.5^\circ C$ (OR, 0.52; 95% CI, 0.19 to 1.44; $P=0.22$). The change in NIHSS scores from baseline to 48 hours did not differ between the groups ($P=0.93$).

Conclusions—Early administration of acetaminophen (3900 mg/d) to afebrile patients with acute stroke may result in a small reduction in CBT. Acetaminophen may also modestly promote hypothermia $<36.5^\circ C$ or prevent hyperthermia $>37.5^\circ C$. These effects are unlikely to have robust clinical impact, and alternative or additional methods are needed to achieve effective thermoregulation in stroke patients. (Stroke. 2002;33:130-135.)

Key Words: acetaminophen ■ stroke, acute ■ temperature

Temperature is critically important in influencing outcome of neuronal injury resulting from stroke. Mild to moderate decrements in brain temperature have been shown to decrease postischemic neuronal necrosis.$^{1-2}$ Hypothermia has been proposed as a potential therapy for stroke and head trauma$^{3-5}$ and is routinely used during cardiac bypass surgery and some neurosurgical procedures.$^{6-8}$ However, hypothermia may be difficult to achieve in awake patients, and its use as a therapeutic strategy may be limited by its potential adverse effects, including cardiac arrhythmias, metabolic derangements, and propensity for infections.$^3$ Conversely, hyperthermia appears to exacerbate ischemic injury and is associated with greater morbidity and mortality after stroke.$^5-13$ Relatively small differences in body temperature, particularly in the first 24 hours, appear to have marked effects on outcome.

An unresolved issue is how to induce hypothermia rapidly and safely in stroke patients. In small, anesthetized animals, hypothermia is achieved relatively easily and quickly with external cooling, but in humans, the techniques are time consuming, require general anesthesia, and may not be feasible during the critical period early after stroke onset. Hypothermia was achieved in awake, unanesthetized stroke patients in a small pilot study by use of forced air surface cooling, which reduced body temperature by $1.3^\circ C$ in 6 hours.$^{14}$ This was not purely a nonpharmacological approach,

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because patients were also given meperidine to treat shivering. The use of pharmacological hypothermic agents may offer a method to reduce body temperature in a controlled and reproducible manner. Acetaminophen is a safe, clinically proven antipyretic that is believed to act on the hypothalamic heat-regulating center. It causes few adverse effects except in cases of massive overdosage (>15 g), when it may cause hepatic toxicity. Acetaminophen may also suppress fever in the setting of infection, potentially resulting in delayed diagnosis and treatment of the infection.

This study was designed to determine whether regular administration of acetaminophen could modify core body temperature (CBT) over a period of 24 hours in awake, afibrile patients with acute stroke. Furthermore, because very small differences in temperature may be clinically important, prevention of hyperthermia (>37.5°C) or induction of mild hypothermia (<36.5°C) with acetaminophen was hypothesized to possibly improve stroke outcome.

Subjects and Methods

This was a randomized, controlled clinical trial. Patients were recruited between August 1997 and August 2000 at 2 university hospitals after review and approval of the protocol by each institutional review board. Patients were eligible to participate if they met all of the following inclusion criteria: clinical or radiological evidence of acute ischemic or hemorrhagic stroke, presentation and randomization within 24 hours after onset of symptoms, National Institutes of Health Stroke Scale (NIHSS) score ≤5, admission CBT <38.5°C, admission white blood cell (WBC) count <12.6×10^3 cells/mm^3, and written informed consent obtained from the patient or appropriate representative. Patients were excluded if any of the following were present: clinical or radiological signs suggestive or indicative of infection, severe medical illnesses that would interfere with participation in this study, known contraindication or hypersensitivity to acetaminophen, known contraindication to placement of a urinary catheter, or participation in another interventional clinical trial for acute stroke.

The principal intervention in this randomized trial was treatment with acetaminophen compared with no acetaminophen. Because of logistical issues, randomization and blinding were handled differently at the 2 participating centers. At 1 site (site 1), eligible and consented patients were randomly assigned to receive either acetaminophen 650 mg or a matched placebo every 4 hours for the initial 24 hours after admission (total of 7 doses, 4550 mg), and the study was performed in a fully double-blinded manner. At the other site (site 2), patients were randomly assigned either to receive open-label acetaminophen with the same dosing regimen or to avoid acetaminophen for the initial 24 hours, and investigators were not blinded to treatment allocation. Blinding was not deemed absolutely necessary because the primary outcome measure of CBT was considered unlikely to be biased by the investigator’s or patient’s knowledge of treatment allocation. At both sites, patients were randomized via the opening of a numbered, sealed envelope by a pharmacist or nurse. If patients were not able to take the medication orally, the investigator had the option to place a feeding tube or to give the study medication rectally.

CBT was measured every 30 minutes with a temperature-sensing catheter in the urinary bladder. Neurologic deficit resulting from stroke was measured with the NIHSS. During the 24-hour study period, medications with antipyretic effects, including aspirin and nonsteroidal antiinflammatory agents, were withheld. Patients were monitored for signs of infection or sepsis, as well as any other adverse events. Patients who developed hyperthermia >38.5°C were taken off the study medication and treated accordingly. All patients enrolled in the study had WBC counts and NIHSS performed at admission, at 24 and 48 hours, and at 7 days or discharge. Hospital disposition, the presumed cause of stroke, and other comorbidities during the first week were also recorded. Any adverse events potentially related to the study drug or the study protocol were documented.

The primary outcome measure was the difference in mean CBT between patients treated with acetaminophen and those treated with placebo during the first 24 hours. Because there were repeated measures for each patient, data were analyzed to account for within-subject variability by use of survey methods for linear regression clustered by patient. Additional measures compared between groups were the proportion of time spent hyperthermic >37.5°C and time spent hypothermic <36.5°C. Clinical impairment was analyzed as a secondary outcome comparing the NIHSS in the 2 treatment arms, although the study was not powered to detect a significant difference in this rating scale (see sample size below). The NIHSS is often not normally distributed, so nonparametric comparisons (Wilcoxon ranked sum) were performed. Dichotomous and categorical data were compared by use of Fisher’s exact test.

The study was powered to detect a temperature reduction of at least 0.5°C in a population with an SD of ~0.5°C to 0.6°C, with α=0.05 and β=0.20 (power=80%), requiring about 20 patients in each group. This detectible difference of 0.5°C was deemed to be clinically important on the basis of prior studies.

Results

Thirty-nine patients were enrolled, with 20 randomized to receive acetaminophen and 19 randomized to receive placebo. Characteristics of the patient population are summarized in the Table. The 2 groups (acetaminophen versus placebo) were similar with regard to age (70±13 versus 67±18 years, P=0.53), sex (45% versus 37% male, P=0.61), and stroke type (80% versus 89% ischemic, P=0.66). Although stroke types were not available at baseline, they were ultimately found to be comparable in the 2 groups. Three patients in each group received open-label intravenous tissue plasminogen activator (tPA) before participation in the study. Patients in the acetaminophen group tended to have slightly more severe deficits according to the NIHSS score (mean, 14 versus 11; median, 15.5 versus 9; P=0.09). However, the range of NIHSS scores was 5 to 23 in both groups. There were no significant differences in baseline characteristics between the 2 study sites.

Initial CBT was almost identical: 36.96±0.64°C in the acetaminophen group and 36.95±0.45°C (P=0.96) in the placebo group. The categorical distribution of initial CBTs was also very similar and is summarized in the Table. Although no febrile (CBT >38.5°C) patients were included in the study, 3 patients—2 in the acetaminophen group and 1 in the placebo group—had initial CBTs between 38.0°C and 38.4°C (P=0.52).

During the 24-hour study period, the mean CBT was 37.13±0.11°C in the acetaminophen group and 37.35±0.10°C in the placebo group, with a net difference of 0.22°C (95% CI, −0.08°C to 0.51°C; P=0.14, accounting for clustering by patient) cooler in the acetaminophen group. Age, sex, baseline NIHSS, treatment with tPA, and site of participation were not significantly associated with CBT during the study period, and adjustment for these potential confounders had no significant effect on the CBT difference between groups. Among the ischemic stroke patients, acetaminophen nonsignificantly changed body
temperature by $-0.16^\circ C$ (95% CI, $-0.50$ to $0.17$; $P=0.33$), whereas in the intracerebral hemorrhage patients, acetaminophen nonsignificantly changed CBT by $-0.5^\circ C$ (95% CI, $-1.2$ to $0.11$; $P=0.09$). Although these point estimates appear to be somewhat different, there was no significant effect relative to placebo in either group, nor was there a difference in the effect of acetaminophen between these stroke types ($P=0.74$). The distribution of CBTs in the 2 treatment arms is depicted in the Figure. In both groups, 13 patients had $\geq 1$ CBTs $>37.5^\circ C$ during the study period ($P=1.00$). However, patients treated with acetaminophen tended to be more often hypo-thermic $<36.5^\circ C$ (14% of the study period) compared with placebo patients (5% of the study period) (OR, 3.4; 95% CI, 0.83 to 14.2; $P=0.09$). Conversely, acetaminophen tended to reduce the amount of time in which patients were hyper-thermic $>37.5^\circ C$ (27% of the study period) compared with placebo (41% of the study period) (OR, 0.52; 95% CI, 0.19 to 1.44; $P=0.22$). However, neither of these associations was statistically significant.

The change in NIHSS did not differ between the 2 groups from baseline to 24 hours (1 point versus 1 point, $P=0.99$), to 48 hours (2 points versus 2 points, $P=0.71$), or to discharge or day 7 (5 points versus 5 points, $P=0.40$).

Clinical events and outcomes are summarized in the Table. There was no difference in the incidence of infection during the study period, diagnosed in 2 of 20 patients (10%) treated with acetaminophen (1 pneumonia and 1 urinary tract infection) and in 1 of 19 patients (5%) given placebo (1 urinary tract infection). Study medication was discontinued because CBT was $>38.5^\circ C$ in 1 of 20 patients (5%) treated with acetaminophen and 2 of 19 patients given placebo (11%). There was no clinical or laboratory evidence of hepatotoxicity in any patient in this study. One patient in each group (5%) died during hospitalization for stroke: 1 because of symptomatic hemorrhagic conversion of the infarction and 1 because of cerebral herniation. Other than these infections and deaths, there were no other comorbid events in any patients in this study. The posthospitalization dispositions of patients were similar in the 2 arms of the study and are summarized in the Table. No patients were lost to follow-up before study completion.

**Discussion**

Mild alterations in CBT have prominent effects on ischemic cell damage. In a retrospective study, fever and modest elevations in CBT (between $37.5^\circ C$ and $38.0^\circ C$) were found to worsen residual symptoms of stroke.\(^{14}\) In a prospective study, it was found that among all other variables, temperature was the only factor that significantly influenced morbidity.\(^{10}\) Another study showed that patients with fever in the first 7 days after stroke had 3.4-fold higher odds of poor outcome than those without fever.\(^9\) Finally, a prospective consecutive study of stroke patients demonstrated an association between CBT and initial stroke severity, infarct size, mortality, and outcome.\(^{12}\) Mortality was lower and outcome was better in patients with lower CBTs on admission. For each $1^\circ C$ increase in CBT, the odds of death or severe disability more than doubled. These studies suggest that small
early increases in CBT may be critically important with regard to outcome.

This study aimed to determine whether acetaminophen could reduce CBT in stroke patients by at least 0.5°C. The study failed to support this hypothesis, although temperature in the acetaminophen group tended to be slightly lower by 0.22°C. The CI surrounding this estimated effect included 0.5°C, suggesting that it is still possible that acetaminophen could have an effect of this size, but such a result seems less likely. There was also a modest tendency toward less hyperthermia and more hypothermia among patients treated with acetaminophen but no difference in the proportion of patients who ever developed hyperthermia during the study period. The results of this randomized, clinical trial suggest that acetaminophen alone is unlikely to promote a robust reduction in CBT in normothermic patients with acute stroke. However, acetaminophen appears to be safe, and perhaps the small effect on CBT warrants its adjunctive prophylactic use in stroke patients.

The role of acetaminophen as a potential therapy or adjunct to the management of patients with cerebrovascular events has scarcely been evaluated in the past. A few recent studies have examined this issue by using a variety of settings and methods. Kalafut and colleagues compared 16 stroke patients treated with acetaminophen with 16 historical control patients. In this observational study, they obtained results similar to ours, finding no difference in CBT between the groups at 24 hours but a trend toward a small difference of about 0.2°C during the first 72 hours. In a study of 60 patients undergoing cardiopulmonary bypass, acetaminophen failed to alter peak CBT or prevent hyperthermia after rewarming. In contrast, Dippel and colleagues randomized 75 patients with acute ischemic stroke within 24 hours of onset to high-dose acetaminophen (1000 mg), low-dose acetaminophen (500 mg), or placebo every 4 hours (6000, 3000, or 0 mg/d). Temperature was lowered significantly in the high-dose group by 0.4°C (95% CI, 0.1 to 0.7) compared with the placebo group, but low-dose acetaminophen had no effect. Interestingly, they did not demonstrate a difference in CBT with any dose of acetaminophen after 5 days of treatment. Similarly, Koennecke and Leistner reported their study of 42 patients who were randomly assigned to receive either acetaminophen 1000 mg or placebo every 6 hours (4000 mg/d) for 5 days. This regimen prevented CBTs from exceeding 37.5°C, which occurred in only 1 of 20 acetaminophen-treated patients (5%) compared with 8 of 22 patients given placebo (36%). Our study used an intermediate dose (3900 mg/d), and it is possible that a dose-response relationship exists that requires further study. Finally, a few cases of significant hypothermia have been reported as an adverse effect of acetaminophen, predominantly in children, suggesting that some populations may be differentially affected by this medication.

Although this study was small, a clinically relevant difference in CBT between the 2 groups seems unlikely on the basis of the prespecified sample size and CIs. Thus, the risk of failing to observe such a difference as a result of chance should have been relatively small. Furthermore, CBT is an objective parameter that should be minimally affected by potential bias, such as differential selection of patients into the 2 arms of the study, differential measurement of CBT, or loss to follow-up during the brief duration of the study. However, because the study was not double blinded at both sites, there is potential for bias with regard to clinical outcomes that may be more subjective. Other patient characteristics, such as age or stroke type, may have an effect on CBT, although these associations have not been described. We did not identify any such differences, and the randomization of patients into this study and the resulting balance between the groups should have minimized potential association between treatment assignment and these characteristics, thus limiting sources of confounding. This study was not powered for the secondary end point of neurological deficit as measured by the NIHSS. However, because acetaminophen has no known direct neuroprotective effects, it is also unlikely to have a clinically important effect on outcome without a significant reduction in CBT. Finally, it remains possible that a different dose of acetaminophen could have yielded different results.

We conclude that early administration of acetaminophen at a dose of 650 mg every 4 hours to afebrile patients with acute stroke may result in a very modest reduction in CBT. This effect is unlikely to have robust clinical impact, and alternative methods are needed to achieve effective thermoregulation after acute stroke. However, future investigations with larger study populations and longer follow-up periods may be warranted to determine whether the small effect on temperature translates into a measurable effect on clinical outcome.

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References
The significance of elevated body temperature (BT) in cerebral infarction was first suggested a quarter of a century ago by Hindfelt in a retrospective series of patients.1 Meanwhile, fever has emerged as an independent predictor of unfavorable outcome in acute ischemic stroke.2–5 As a consequence, interest grew on the issue of lowering BT in acute stroke patients. Several pilot studies, which were focused mainly on patients with severe strokes, applied physical methods (cooling blankets, endovascular cooling catheters) in order to decrease BT to 32°C to 33°C during the days after the ictus.6–9 In all these studies, patients were sedated and intubated for several days, and the results of these attempts were hampered by high complication rates including thrombocytopenia, cardiac arrhythmia, hypotension, and pneumonia. Nevertheless, one study group was able to demonstrate that hypothermia markedly lowers elevated intracranial pressure as long as the patients remain hypothermic; however, in spite the rather high dose of acetaminophen, no significant side effects were reported; however, the BT decrease was not sustained over the study period of 5 days, and whether such a small temperature decrease will improve outcome remains questionable.

The present study by Kasner et al adds to our knowledge of pharmacologically modifying BT in acute stroke. Over 3 years, this 2-center study randomized 39 patients with a baseline temperature of up to 38.4°C to receive either a total dose of 3900 mg acetaminophen or placebo for 24 hours after admission. The hypothesis was tested whether acetaminophen can significantly lower BT in order to improve clinical outcome at discharge (secondary hypothesis). Both hypotheses were rejected. In addition, the proportion of patients with fever >37.5°C did not differ between verum and placebo. In contrast to other studies, patients with intracerebral hemorrhage (ICH; n=6), equally distributed among groups, were included. To date, only 1 report systematically investigating the incidence and prognostic impact of fever in ICH has been published.10–12 It remains debatable whether ischemic and hemorrhagic strokes should be lumped together in therapeutic studies of stroke.

The significance of the present study and the one by Dippel et al13 persists in the strong suggestion that treatment with acetaminophen is safe but may not efficiently induce hypothermia in patients with acute stroke. Given that hypothermia as an adverse effect of acetaminophen has merely been reported in children, this truly is not surprising. The question arises whether future attempts to induce hypothermia with acetaminophen in acute stroke patients are worthwhile, or whether future studies should rather aim at fever prevention. According to Azzimondi et al,3 fever (ie, a BT >37.5°C) complicates the course of up to 40% of patients with acute stroke, with 15% developing fever on the first day poststroke, while another 49% become febrile on day 2, and the remainder even later in the course. Currently, even moderate hypothermia (32°C to 33°C) can be achieved only by rather
invasive and potentially harmful means, while pharmacological attempts are not capable to effectively cool patients. Furthermore, a recent study demonstrated that hypothermia after severe brain injury, being a routine treatment for years, lacks a beneficial effect on clinical outcome. \(^{13}\) Although traumatic brain injury and stroke differ pathophysiologically, this is not encouraging for those believing hypothermia might relate to stroke outcome.

Doubtlessly, there is compelling evidence that even mild hyperthermia has a deleterious effect in acute stroke. \(^{5}\) Given the 30% to 40% incidence of fever during the acute and subacute phases, another and probably more feasible concept for treatment might be the consequent prevention of hyperthermia by prophylactic administration of antipyretics. Why not routinely administer a well-tolerated drug like acetaminophen during the first days after stroke? Preventing fever in more than one third of patients might improve outcome without imposing significant risks in acute stroke. A multi-centered, randomized, controlled trial seems worthwhile in order to prove this concept.

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