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Effect of Paracetamol (Acetaminophen) on Body Temperature in Acute Ischemic Stroke

A Double-Blind, Randomized Phase II Clinical Trial

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Background and Purpose—Body temperature is a strong predictor of outcome in acute stroke. However, it is unknown whether antipyretic treatment leads to early and clinically worthwhile reduction of body temperature in patients with acute stroke, especially when they have no fever. The main purpose of this trial was to study whether early treatment of acute ischemic stroke patients with acetaminophen (paracetamol) reduces body temperature.

Methods—Seventy-five patients with acute ischemic stroke confined to the anterior circulation were randomized to treatment with either 500 mg (low dose) or 1000 mg (high dose) acetaminophen or with placebo, administered as suppositories 6 times daily during 5 days. Body temperatures were measured with a rectal electronic thermometer at the start of treatment and after 24 hours and with an infrared tympanic thermometer at 2-hour intervals during the first 24 hours and at 6-hour intervals thereafter. The primary outcome measure was rectal temperature at 24 hours after the start of treatment.

Results—Treatment with high-dose acetaminophen resulted in 0.4°C lower body temperatures than placebo treatment at 24 hours (95% CI 0.1°C to 0.7°C). The mean reduction from baseline temperature with high-dose acetaminophen was 0.3°C (95% CI 0°C to 0.6°C) higher than that in placebo-treated patients. Treatment with low-dose acetaminophen did not result in lower body temperatures. After 5 days of treatment, no differences in temperature were found between the placebo and the high- or low-dose acetaminophen groups.

Conclusions—Treatment with a daily dose of 6000 mg acetaminophen may result in a small, but potentially beneficial, decrease in body temperature shortly after ischemic stroke, even in normothermic and subfebrile patients. Further studies should determine whether this effect is reproducible and whether early reduction of body temperature leads to improved outcome. (*Stroke*. 2001;32:1607-1612.)

Key Words: acetaminophen ■ hypothermia ■ randomized controlled trials ■ stroke, acute ■ stroke, ischemic

During the first days after acute stroke, a fever or subfebrile temperature develops in one fifth to almost one half of patients.¹⁻⁴ Increased temperature may have a detrimental effect on the outcome after ischemic stroke. Subfebrile temperatures (37.5°C to 39°C) and fever (>39°C) after a stroke are associated with relatively large infarct volumes, high case fatality, and poor functional outcome, even after adjustment for initial stroke severity.²⁻⁶ The period in which hyperthermia is associated with poor outcome may be limited to the first 12 or 24 hours from stroke onset.^{6,7}

The harmful effects of an early rise in body temperature have been attributed to increased cerebral metabolic demands,⁸ changes in the blood-brain barrier permeability, acidosis, and an increased release of excitatory amino acids.⁹ In animal models of temporary focal cerebral ischemia, mild

intraischemic hyperthermia increased infarct volume,¹⁰ whereas mild hypothermia reduced infarct size.¹¹

A pharmacological reduction of body temperature in patients with acute ischemic stroke may improve functional outcome. To date, however, there are no controlled studies of the effects of antipyretic agents on temperature in these patients or of the effect of temperature reduction on outcome. Moreover, the effect of antipyretic agents on body core temperature in stroke patients with a normal temperature at the onset has not been investigated.

Acetaminophen (paracetamol) has a weak inhibitory effect on peripheral prostaglandin biosynthesis (which accounts for its weak anti-inflammatory activity), but it is a potent inhibitor of prostaglandin production within the central nervous system. This presumably accounts for its analgesic and

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antipyretic properties.¹² Acetaminophen is usually well tolerated, has almost no side effects or drug interactions at therapeutic doses, and has no effect on cardiovascular and respiratory systems.¹² Its use in stroke patients to treat and prevent fever has been advocated, but the effectiveness of such a treatment has never been studied.^{13,14}

There are several arguments against routinely prescribing acetaminophen for patients with stroke. First, there is a safety concern, because treatment with acetaminophen may mask fever, which may lead to later detection of pneumonia, urinary tract infections, and sepsis. Moreover, large doses of acetaminophen may lead to acute liver failure, especially in patients with chronic liver disease. Second, it has not been established whether active reduction of body temperature in patients with acute stroke will lead to an improved clinical outcome.¹⁵ Third, it is equally unknown whether treatment with acetaminophen leads to early and clinically worthwhile reduction of body temperature in stroke patients, especially when they have no initial fever or subfebrile temperature. Therefore, the main purpose of this study was to determine whether early treatment in the acute stage leads to a lower body temperature than when there is no treatment.

Methods

Setting

Paracetamol (Acetaminophen) in Patients with Acute Stroke (PAPAS) was a 3-center, randomized, double-blind, placebo-controlled, parallel-group study of high- and medium-dose acetaminophen in patients with acute ischemic stroke. The study was carried out in 3 hospitals: 2 university hospitals with a regional patient care function, and 1 large regional hospital.

Patients

Patients with a clinical diagnosis of acute ischemic anterior circulation stroke were included in the study. A cranial CT scan was obligatory before randomization and had to be compatible with acute ischemic stroke. All patients were required to have a stable focal deficit without rapid improvement and the possibility of starting treatment within 24 hours to be included in the study.

Patients were excluded if their body temperature at admission was $<36.0^{\circ}\text{C}$ or $>39.0^{\circ}\text{C}$ or if they had already been treated with steroids or nonsteroidal anti-inflammatory drugs within 3 days before the stroke, because this could confound a possible treatment effect. We also excluded patients with a severe illness of a different nature, which could affect the assessment of the effect of the study medication on temperature, and patients with residual neurological impairment resulting from a previous stroke, which could influence the assessment of functional outcome.

Because of safety considerations, we excluded patients with chronic liver failure or cirrhosis, chronic renal failure, or a history of alcohol abuse and those who were allergic to acetaminophen or aspirin. Furthermore, patients who were moribund and those for whom no informed consent was given were not included in the study.

Ethical Aspects

All patients were given verbal and written information about the potential risks and benefits of participation in the study. Written consent was required before randomization. The medical ethics committee of each participating center approved the study protocol.

Treatment Allocation and Blinding

Treatment consisted of suppositories containing 500 mg (low dose) acetaminophen, 1000 mg (high dose) acetaminophen, or placebo, given 6 times daily for 5 days. We used suppositories because we anticipated a high incidence of swallowing difficulties early after

stroke. The study medication was provided in white paper boxes, numbered consecutively with a medication number. The treatment allocation schedule was based on computer-generated random numbers. The treatment codes resided with the hospital pharmacist in each center. One copy of the treatment codes was kept by the secretary (A.K.) of the Safety Monitoring Committee, whose members were not involved in execution of the study. The Executive Committee and the local investigators were not aware of treatment assignments. No treatment code was broken before the last follow-up visit was completed. The treatment allocation was stratified for early (within 12 hours) and late (12 to 24 hours) treatment, and the study medication was blocked in lots of 6 (each by center).

Study Activities

All patients were admitted to an acute stroke care unit. The National Institutes of Health Stroke Scale (NIHSS) was used to assess the severity of the stroke.¹⁶ After 1 month, stroke type was classified according to the TOAST criteria.¹⁷ Body temperature was measured by means of a standard rectal electronic thermometer at the start of treatment and 24 hours later. Tympanic temperatures were taken at 2-hour intervals during the first day and at 6-hour intervals during the next 6 days. Because the acetaminophen dose in the high-dose group exceeded the usually recommended maximal dosage of 4 g/d, we assessed potential effects on liver enzymes at baseline and after 5 days.

Outcome Measures

The primary outcome measure in this study was body temperature at 24 hours from the start of treatment, measured with a rectal thermometer. Secondary outcome measures were reduction in body temperature after 1 and 5 days from the start of treatment and the area under the 1- and 5-day temperature curves. As a tertiary outcome measure, we deter-

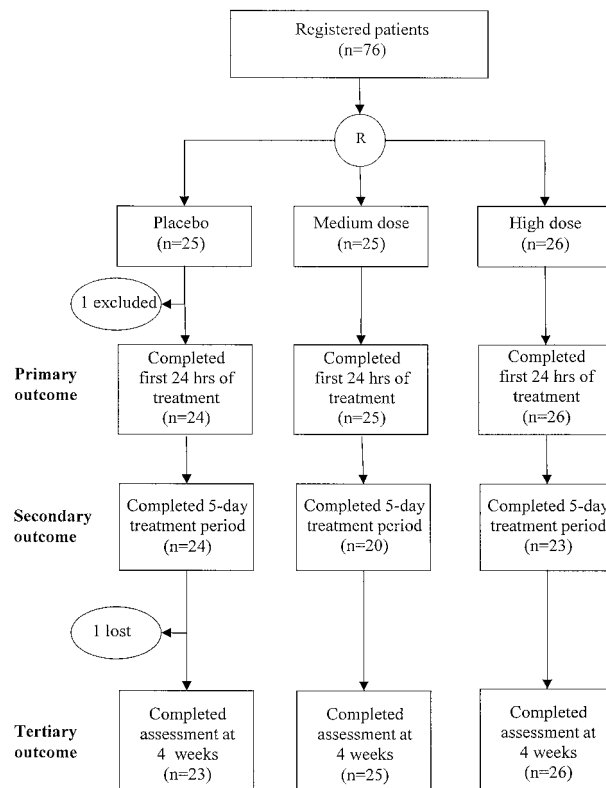


Figure 1. Treatment allocation and participant flow. The number of patients who completed assessment at 4 weeks could be larger than the number who completed the 5-day treatment period, because some patients were discharged early and discontinued the study medication.

TABLE 1. Baseline Characteristics

	High Dose (n=26)	Medium Dose (n=25)	Placebo (n=24)
Demographics			
Age, y, mean (SD)	69 (13)	74 (14)	68 (15)
Male sex, n (%)	12 (46)	14 (56)	16 (67)
Risk factor for stroke, n (%)			
Hypertension	12 (46)	12 (48)	13 (54)
Cardiac disease	10 (38)	9 (36)	6 (25)
Peripheral vascular disease	3 (12)	2 (8)	2 (8)
Diabetes mellitus	4 (15)	4 (16)	3 (13)
Hypercholesterolemia	6 (23)	5 (20)	8 (33)
Previous transient ischemic attack	5 (19)	5 (20)	5 (21)
Previous stroke	4 (15)	3 (12)	4 (17)
Cigarette smoking	10 (42)	12 (48)	17 (71)
Neurological characteristic, n (%)			
Lowered consciousness level	6 (23)	6 (24)	3 (13)
Aphasia, n (%)	5 (19)	11 (44)	7 (29)
NIHSS, mean (SD)	8.8 (5.6)	10.0 (8.2)	6.8 (5.4)
Lacunar stroke, n (%)	10 (38)	5 (20)	11 (46)
Other clinical characteristic			
Treatment within 0–12 h, n (%)	11 (42)	11 (44)	11 (44)
Temperature at admission, mean °C (SD)	36.9 (0.65)	36.9 (0.76)	36.9 (0.64)
Temperature at start of treatment, mean °C (SD)	37.1 (0.47)	37.2 (0.41)	37.2 (0.51)

Medium dose indicates 500 mg acetaminophen 6 times daily; high dose, 1000 mg, 6 times daily. Values are absolute numbers with percentages of totals in treatment strata, unless stated otherwise.

mined stroke severity at 1 month, as defined by the score on the modified Rankin scale,¹⁸ although this study was not designed to detect a significant effect on clinical outcome.

Safety

Serious adverse events were defined as any potentially life-threatening deterioration in health status within the study monitoring period (day 0 to day 7). Adverse events included any infection, such as pneumonia, sepsis, or urinary tract infection that requires antibiotic treatment according to the judgment of the treating physician; any liver function disturbance (ASAT, ALAT, AF, or total bilirubin levels that exceed twice the local upper limit of normal); and any neurological deterioration (ie, decrease in level of consciousness of >1 point on the Glasgow Coma Scale or an increase of ≥ 2 points on the NIHSS). Then independent, unblinded Safety and Data Monitoring Committee reviewed all serious adverse events on a weekly basis.

Statistical Analysis

The study results were analyzed on an intention-to-treat basis. No interim analysis was carried out. The main results of the study are presented as the mean absolute difference in temperature between the 2 treatment groups and the control group, with 95% CIs. Multiple linear regression was performed to study a possible dose-effect relationship between treatment and body temperature and to adjust for possible confounding factors, such as age, ischemic stroke subtype, stroke severity, and body temperature at admission and at the start of treatment.

Sample Size

It was determined beforehand that a 0.5°C difference in body temperature after 24 hours would be clinically significant. Such a difference could be equivalent to a 5% to 10% absolute lower risk of poor outcome in patients with a moderately severe stroke.⁶ To be able to detect a

difference in body temperature at 24 hours of 0.5°C, with a significance level of 0.05 and power of 0.80, assuming an SD of 0.6°C, we would need ≥ 23 patients in each treatment group. This number was rounded to 25. No formal statistical stopping rule was used.

Results

Participant Flow and Follow-Up

Seventy-six patients were randomized and included in the study. Twenty-six patients were allocated to treatment with high-dose acetaminophen, 25 to medium-dose acetaminophen, and 25 to placebo.

One patient, who awoke with a right-sided hemiparesis and aphasia, was diagnosed as having a low-grade glioma, 2 days after inclusion in the study. This patient was excluded from the analysis. Another patient, a 51-year-old man with a pure sensory stroke, was lost to follow-up after having been

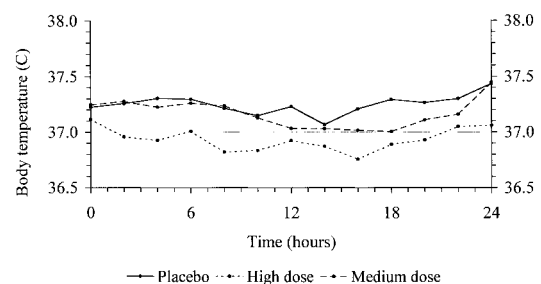


Figure 2. Mean body temperatures during the first 24 hours after the start of treatment according to treatment.

TABLE 2. Average Body Temperatures at 24 Hours and 5 Days After Start of Treatment and Area Under the Curve for High-Dose, Medium-Dose, and Placebo Groups

	High Dose	Medium Dose	Placebo	High Dose Minus Placebo (95% CI)
Temperature at 24 h, °C (SD)	37.0 (0.37)	37.5 (0.47)	37.4 (0.64)	-0.4 (-0.7 to -0.1)
Reduction in temperature at 24 h, °C (SD)	0.1 (0.5)	-0.2 (0.5)	-0.2 (0.6)	0.3 (0 to 0.6)
Reduction in temperature at 5 d, °C (SD)	0.2 (0.5)	0.1 (0.5)	0.2 (0.5)	0 (-0.2 to 0.3)
AUC first treatment day, °C×h (SD)	886 (13)	891 (10)	894 (15)	-8 (-17 to 0)
AUC total treatment period, °C×h (SD)	4423 (52)	4445 (56)	4454 (64)	-31 (-67 to 5)

discharged 6 days after the onset of symptoms (Figure 1). In this patient, the last observation of functional outcome was carried forward. Both these patients were receiving placebo. Nine patients discontinued the study medication because they were discharged early after a speedy recovery; these patients did complete the 1-month follow-up assessment. Six patients died after the treatment was completed but before the scheduled 1-month follow-up.

No crossovers occurred, and all patients were treated according to the allocated protocol at least during the first 24 hours, until the primary outcome assessment. For all patients in the study, the blinding was maintained, and no applications for unblinding were made by the local investigators. No safety concerns were raised by the Data Monitoring and Safety Committee.

The clinical characteristics of the study population are summarized in Table 1. The treatment groups were balanced with regard to potential determinants of body temperature, except for a slight excess of patients with nonlacunar infarction and with aphasia in the medium-dose group. The score on the NIHSS was on average 3.2 points higher in the medium-dose group than in the placebo group and 2.0 points higher in the high-dose group than in the placebo group, suggesting more severe strokes in the patients receiving active treatment.

Main Results

The mean body temperature at 24 hours after the start of treatment was 0.4°C lower in the high-dose group than in the placebo group (95% CI 0.1°C to 0.7°C) (Figure 2 and Table 2). The mean reduction in body temperature during the first 24 hours of treatment differed by 0.3°C between the high-dose and placebo groups (95% CI 0°C to 0.6°C). The area under the curve was significantly smaller in the high-dose group, at least during the first 24 hours of treatment, which implies that the total time with elevated temperature in that period decreased with the use of acetaminophen. Adjustment for stroke severity (NIHSS at baseline), stroke type (lacunar or nonlacunar), or start of treatment (within 12 hours or between 12 to 24 hours) by multiple linear regression did not change the effect estimate of 0.4°C in the high-dose treatment group.

On day 5, no statistically significant difference in body temperature was observed between the placebo and medium- or high-dose group (Table 2).

In an "on-treatment" analysis, we excluded data from patients who did not actually take their study medication. This did not change the effect estimates; most likely because all patients

completed the 24-hour treatment period and 67 (89%) completed the 5-day treatment period.

Functional outcome at 1 month did not differ significantly among the 3 treatment groups. Twelve patients in the placebo group (48%), 13 (52%) in the medium-dose group, and 17 (65%) in the high-dose group had a poor outcome (modified Rankin scale >2). The relative risk (OR) of poor outcome due to high-dose acetaminophen compared with placebo was 1.9 (95% CI 0.6 to 5.9), but after adjustment for baseline NIHSS in a multiple logistic regression model, this relative risk was reduced to 1.1 (95% CI 0.2 to 5.7). Thus, an apparent adverse effect of high-dose acetaminophen on functional outcome could be attributed to a slight imbalance in the distribution of stroke severity at baseline in this study.

Serious Adverse Events

Six patients died during the study: 1 from pneumonia leading to sepsis, 2 from myocardial infarction, and 3 from progressive stroke. The patient with pneumonia had been allocated to the placebo group. Serious adverse events did not occur more often in the patients on active treatment than in the patients receiving placebo (Table 3).

Discussion

After 24 hours of treatment, we found a small, but statistically significant, difference in body temperature in favor of treatment with high-dose acetaminophen. A difference of 0.4°C may not seem impressive. However, keeping in mind the results of the Copenhagen Stroke Study, which suggested a 2-fold increase in mortality risk for every 1°C increase in body temperature and an average 3.9-point increase in Scandinavian Stroke Score,⁶ this effect on temperature may be worthwhile, given the low cost and safety of acetaminophen. These results should also provide a stimulus to continue the search for a more effective medical regimen for decreasing body temperature and, perhaps, improving outcome after acute ischemic stroke.

TABLE 3. Serious Adverse Events

Serious Adverse Events, n (%)	High Dose	Medium Dose	Placebo
Pneumonia/sepsis	3 (12)	4 (16)	1 (4)
Neurological deterioration	0 (0)	1 (4)	3 (13)
Liver function disturbance*	6 (23)	6 (24)	8 (33)
Death	1 (4)	4 (16)	1 (4)
Other	0 (0)	2 (8)	0 (0)

*AF, ALAT, or bilirubin 2× upper limit of normal.

The concern that treatment with an antipyretic drug may mask emerging infections, and thus lead to treatment delay, sepsis, and poor outcome, was not substantiated in this study.

We measured body temperature with a standard rectal thermometer. The relationship between body temperature (measured with a rectal thermometer) and brain temperature is controversial.¹⁹ The results of the Copenhagen Stroke Study, in which only rectal temperature was measured, should have made this discussion unnecessary.⁶ Moreover, in a study of moderate hypothermia in patients with traumatic brain injury, rectal temperatures remained very close to actual brain temperatures, as measured intracranially.²⁰

We did not measure plasma concentrations of acetaminophen in this study. Such information would have been helpful in explaining the lack of effect in the medium-dose group, in further exploring a dose-response relationship, and in designing further pragmatic studies that make use of oral acetaminophen.

One may argue that increased body temperature does not accelerate the ischemic cascade but is merely an epiphenomenon. In the Copenhagen study, however, the relationship between body temperature and outcome remained statistically significant after adjustment for initial stroke severity.⁶ This makes it less likely that body temperature only reflects the amount of brain tissue damage. Early body temperature measurements (within the first 6 hours) seem to be more strongly related to outcome than later measurements. This suggests that the relationship with poor outcome is not confounded by the occurrence of secondary infections, such as pneumonia or urinary tract infection, because these usually appear later in the course of the disease. Moreover, animal studies of acute middle cerebral artery territory ischemia suggest a protective effect of early hypothermia and a detrimental effect of induced hyperthermia.¹⁰ In a recent study of 725 consecutive patients admitted within 6 hours from the onset of acute ischemic stroke, no relation was found between initial body temperature and outcome.¹⁸ The authors did use a rather insensitive method of statistical analysis (Spearman correlation and comparison of median modified Rankin scale scores with a nonparametric test). All patients with a body temperature of $>37.0^{\circ}\text{C}$ were treated with acetaminophen. Consequently, the results of this study should be interpreted with care.

To the best of our knowledge, no other randomized, controlled study of medical treatment that aimed at decreasing body or brain temperature in patients with ischemic stroke has been published. In a randomized clinical trial of moderate hypothermia ($\pm 33^{\circ}\text{C}$) in patients with severe head injury, a beneficial effect on speed of recovery and on the rate of good outcome was noted in the subgroup with a Glasgow Coma Scale score of 5 to 7,²⁰ although in a more recent and larger study, no effect of moderate hypothermia was found.²¹

The induction of moderate hypothermia was studied in a small study of patients with severe ischemic stroke in the territory of the middle cerebral artery. Temperatures of 34°C were reached, but a drawback of this approach was that patients had to be heavily sedated and artificially ventilated.²² Recently, Kammergaard et al²³ reported that hypothermic therapy with a forced air method for a period of 6 hours in unanesthetized stroke patients was sufficient to lower body temperature by 1.3°C on average. This procedure was well tolerated, but

intravenous meperidine (pethidine) had to be used to control shivering. A similar approach with low-dose midazolam to control shivering resulting in a mean reduction of 1.25°C was used by our group.²⁴ An important drawback of mechanical cooling is the need for some kind of analgesia and sedation, as well as the necessity of constant monitoring.

Conclusions

Treatment with high-dose acetaminophen results in a small, but potentially worthwhile, decrease in body temperature early in the acute phase of stroke, even in normothermic patients. Further studies should determine whether this effect of acetaminophen can be reproduced and whether an early reduction in body temperature leads to improved outcome.

Appendix

Study Organization

Executive Committee: D.W.J. Dippel, H. Visser, E. van Breda, R.J. Meijer, H.B. van de Worp, H.M.A. van Gemert. *Data Management:* H. Visser, E. van Breda, H. Hilkemeijer. *Statistical Analysis:* D.W.J. Dippel. *Data Monitoring and Safety Committee:* A. Algra (chairman), J. van Gijn, F.G.A. van der Meché, A. Koudstaal. *Advisory Committee:* P.J. Koudstaal, L.J. Kappelle. *Writing Committee:* D.W.J. Dippel, R.J. Meijer, E. van Breda, H.B. van der Worp, H.M.A. van Gemert, L.J. Kappelle, P.J. Koudstaal. Participating centers were Eemland Hospital Amersfoort, the Netherlands (25 patients): H.M.A. van Gemert, A. Hovestad, M.B.M. Vermeulen; University Hospital Rotterdam (46 patients): D.W.J. Dippel, M.P.J. van Goor, R.J. Meijer, D. Siepman; and University Hospital Utrecht (5 patients): L.J. Kappelle, H.B. van der Worp.

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