Antipyretic Efficacy of an Initial 30-mg/kg Loading Dose of Acetaminophen Versus a 15-mg/kg Maintenance Dose

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ABSTRACT. *Objective.* **To compare the antipyretic efficacy of an initial 30-mg/kg acetaminophen loading dose versus a 15-mg/kg maintenance dose.**

Methods. **A double-blind, parallel-group, randomized clinical trial was conducted. A total of 121 febrile (rectal temperature between 39°C and 40°C) but otherwise healthy outpatients who were 4 months to 9 years of age and weighed 4 to 26 kg were assigned randomly to 1 of the dose groups: 15 mg/kg ($n = 62$) and 30 mg/kg ($n = 59$).**

Results. **In an "intention to treat" analysis, the time to obtain a temperature lower than 38.5°C was significantly shorter in the 30-mg/kg than in the 15-mg/kg group (110 ± 94 minutes vs 139 ± 113 minutes). The maximum temperature decrease was significantly higher in the 30-mg/kg than in the 15-mg/kg group (2.3 ± 0.7°C vs 1.7 ± 0.6°C). Duration of rectal temperature below 38.5°C was significantly longer in the 30-mg/kg than in the 15-mg/kg group (250 ± 92 minutes vs 185 ± 121 minutes, respectively). Adverse events were reported in 6 children in the 30-mg/kg group compared with 5 in the 15-mg/kg group (hyperthermia, hypothermia, vomiting). The difference was not statistically significant.**

Conclusion. **An initial 30-mg/kg acetaminophen loading dose seemed to be more effective in reducing fever than a 15-mg/kg maintenance dose. No difference was observed regarding clinical tolerance. These data suggest that acetaminophen treatment of fever may be more efficient in an initial loading dose.** *Pediatrics* 2001;108(4). URL: http://www.pediatrics.org/cgi/content/full/108/4/e73; *fever, loading dose, acetaminophen, children.*

ABBREVIATIONS. Teff: time to obtain a rectal temperature below 38°C; Rmax, maximum temperature decrease; Tmax, time to maximum temperature decrease.

Fever is a common symptom in children. Although there may be physiologic benefits with elevated temperature, febrile children often are irritable and restless and may experience diffuse, nonspecific pain. Most physicians, therefore, consider it beneficial to try to lower the temperature, because antipyretic agents improve symptoms of discomfort.[1] Among the available antipyretic agents, acetaminophen is one of the most widely used because it has an antipyretic efficacy equivalent to the other antipyretic drugs and a good safety profile.[2–4] Acetaminophen antipyretic efficacy is dose-dependent.[5,6] The recommended dose is 15 mg/kg every 6 hours.[2] Following this dosing schedule, it usually takes several hours after the first acetaminophen administration to obtain the maximal clinical efficacy of the drug.[7] Therefore, Mahar et al[8] suggested a physical "cold therapy" at the initiation of the chemical treatment to decrease the time course to antipyretic effect. However, tepid water sponging or baths may induce shivering and are associated with crying and symptoms of discomfort in children and are not consistent with the aim of the antipyretic treatment.[8–10] As the half-life of acetaminophen in children ranges between 2 and 3 hours, the time to reach acetaminophen steady-state plasma concentrations ranges between 10 and 15 hours. Furthermore, there is a delay in the time course of the antipyretic effect compared with the pharmacokinetic profile.[11,12] We hypothesized that a loading dose of acetaminophen could decrease the time to obtain effective drug concentrations and improve the rate of temperature decrease after the initial dose, as suggested by Wilson et al.[5]

METHODS

Study Design

A single oral dose, double-blind, randomized, parallel-group design was used to compare the antipyretic effect of an initial 30-mg/kg loading dose of acetaminophen with an initial 15-mg/kg maintenance dose. Outpatients who were 4 months to 9 years of age and weighed 4 to 26 kg and who had an initial rectal temperature of 39°C to 40.5°C during a medical consultation with an office-based pediatrician or general practitioner were recruited when the cause of the fever was clinically considered to be of viral or bacterial origin.

Children were not included in the study if they either had taken any temperature-altering drug or antibiotics within 24 hours before the study or would require antibiotic treatment during the first 4 hours after the administration of the studied treatment. Patients with hepatic, renal, or neurologic diseases were not included; neither were those who had a history of hypersensitivity to acetaminophen or of febrile seizures or who had vomited during the medical consultation.

After parental informed consent was obtained, children were assigned randomly to the loading-dose or to the maintenance-dose group. Children who were older than 6 years gave consent, and no procedure was performed if the child objected.

During the postdosing period of 6 hours, patients were not allowed to receive any temperature-altering drug. However, when the rectal temperature remained at least as high as 39.5°C 1 hour after acetaminophen administration, a tepid water bath was allowed. When the temperature did not decline by at least 0.5°C

within 4 hours of acetaminophen administration, another administration of acetaminophen (15 mg/kg) was permitted at least 4 hours after the first. In these 2 cases, the last temperature measured just before the bath or the second acetaminophen administration was carried forward to the sixth hour (last observation carried forward method). Antibiotics were not allowed for 4 hours postdosing.

Acetaminophen Administration

The drug under study was supplied by Theraplix as a solution containing either 30 mg/mL or 15 mg/mL of acetaminophen. The two preparations were identical in appearance and taste. Acetaminophen (1 mL/kg) was given with an oral syringe that was graduated per milliliter. The investigators were unaware of the dose of acetaminophen given to the children.

Weight, height, and significant clinical history were recorded at the initial visit. Rectal temperature was measured electronically with a digital display temperature probe (Philips [Eindhoven, The Netherlands] HP5316; precision ± 0.01°C) just before and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, and 6 hours after the initiation of the treatment and carefully recorded. Any event considered an adverse effect by the investigator was recorded at the end of the study.

The primary endpoint for antipyretic efficacy was the time to obtain a rectal temperature below 38.5°C (Teff). When the temperature did not decrease below 38.5°C during the 6-hour study period, Teff was considered equal to 6 hours. The following secondary endpoints also were studied: maximum temperature decrease (Rmax), time to maximum temperature decrease (Tmax), time interval with temperature maintained below 38.5°C, rate of temperature decrease (Rmax/Tmax), and number of patients administered "temperature-altering treatment" during the 6-hour postdosing period (physical or drug treatment).

Number of Patients

The sample size was calculated to achieve a statistical power of 90% to detect a 1-hour difference in Teff between the 2 study groups. With a Teff estimated at 3.84 ± 1.22 hours in the control group (data obtained from a previously unpublished preliminary study with different children not included in the present study) and a type I error of 5%, the calculated sample size was 31 patients per group. It was preferable, however, to include 60 patients per group.

Statistical Analysis

Statistical analysis was performed on an intention-to-treat basis. All randomized patients with at least 1 temperature recorded were included in the analysis. A second "per protocol" analysis was performed without patients who spit out the medication or vomited during the first 2 hours of the observation period. Qualitative data were analyzed using Fisher's exact test. Quantitative data were expressed as mean (standard deviation) and compared by an analysis of variance after the homoscedasticity was evaluated using the Bartlett test. Results of the analysis of variance were verified using the Mann-Whitney U test. For the analysis of the simultaneous influence of dose and time on temperature, an analysis of variance was performed and completed by a Student's t test using the error variance to compare the 2 dose groups at each observation time. Multiple linear regression was used to test simultaneously the influence of age and initial temperature on the primary endpoint and completed with an analysis of covariance to take into account the 2 different doses. The study was approved by the Ethics Committee of Cochin Hospital (Paris).

RESULTS

Demographic Characteristics of the Patients

The study comprised 121 patients: 62 in the 15-mg/kg group and 59 in the 30-mg/kg group. For 1 patient in the second group, no data were available (temperature was not measured) and this patient was not included in the statistical analysis. The remaining 120 patients were eligible for the intention-to-treat analysis. Demographic characteristics of the children were not statistically different between the 2

treatment groups (Table 1). Five children in the 30-mg/kg group and 6 children in the 15-mg/kg group who spit out or vomited during the first 2 hours of the observation period were dropped from the per-protocol analysis. Sixteen patients (7 children in the 30-mg/kg group and 9 children in the 15-mg/kg group) received antibiotics after the dose of study medication. Demographic characteristics and initial temperature in these subgroups were not statistically different from the groups used for the intention-to-treat analysis. Diagnoses associated with fever were as follows: respiratory tract infection (11%) and otitis and acute tonsillo-pharyngitis (74%). The cause of the fever was not identified in 15% of the patients.

Efficacy

Rectal temperature at each evaluation time is presented in Fig 1. The Teff was significantly shorter in the 30-mg/kg group than in the 15-mg/kg group both in the intention-to-treat and per-protocol analyses (110.7 ± 94.3 vs 139.4 ± 112.6 minutes and 87.1 ± 56.6 vs 115.8 ± 90.6 minutes, respectively; $P <$ .05). The mean difference between the 2 groups was 29 minutes (95% confidence interval: −66.5; −8.9; Table 2). Rmax and time interval with temperature maintained below 38.5°C were significantly higher in the 30-mg/kg group ($P <$ .05; Table 2). The Rmax/Tmax and the time to Tmax were not significantly different between the 2 groups.

Six patients (3 in each group) had received cold therapy (bath) during the study, and 12 received a second administration of acetaminophen (2 in the 30-mg/kg group and 10 in the 15-mg/kg group). Four children received another antipyretic agent (aspirin or ibuprofen) not allowed in the protocol (1 in the 30-mg/kg group and 3 in the 15-mg/kg group). The number of patients who received a temperature-altering treatment during the observation period was significantly different between the 30-mg/kg and the 15-mg/kg groups (6 and 16, respectively; $P <$ .05).

A multiple linear regression analysis of covariance revealed a statistically direct relationship between the initial rectal temperature and the Teff: the higher

TABLE 1. Clinical Data From the Patients Included in the Intention-to-Treat Analysis*

	30-mg/kg Loading Dose	15-mg/kg Maintenance Dose
Age (y)		
Mean (SD)	3.22 (2.10)	2.89 (1.78)
Mean	3.05	2.31
Range	0.42; 8.39	0.38; 6.66
Weight (kg)		
Mean (SD)	14.59 (4.87)	13.95 (4.16)
Mean	13.3	13.6
Range	6.4; 25	6.8; 25.5
Sex		
Female	27	24
Male	31	38
Baseline temperature (°C)		
Mean (SD)	39.35 (0.24)	39.35 (0.28)
Median	39.30	39.25
Range	39; 40	39; 40

SD indicates standard deviation.
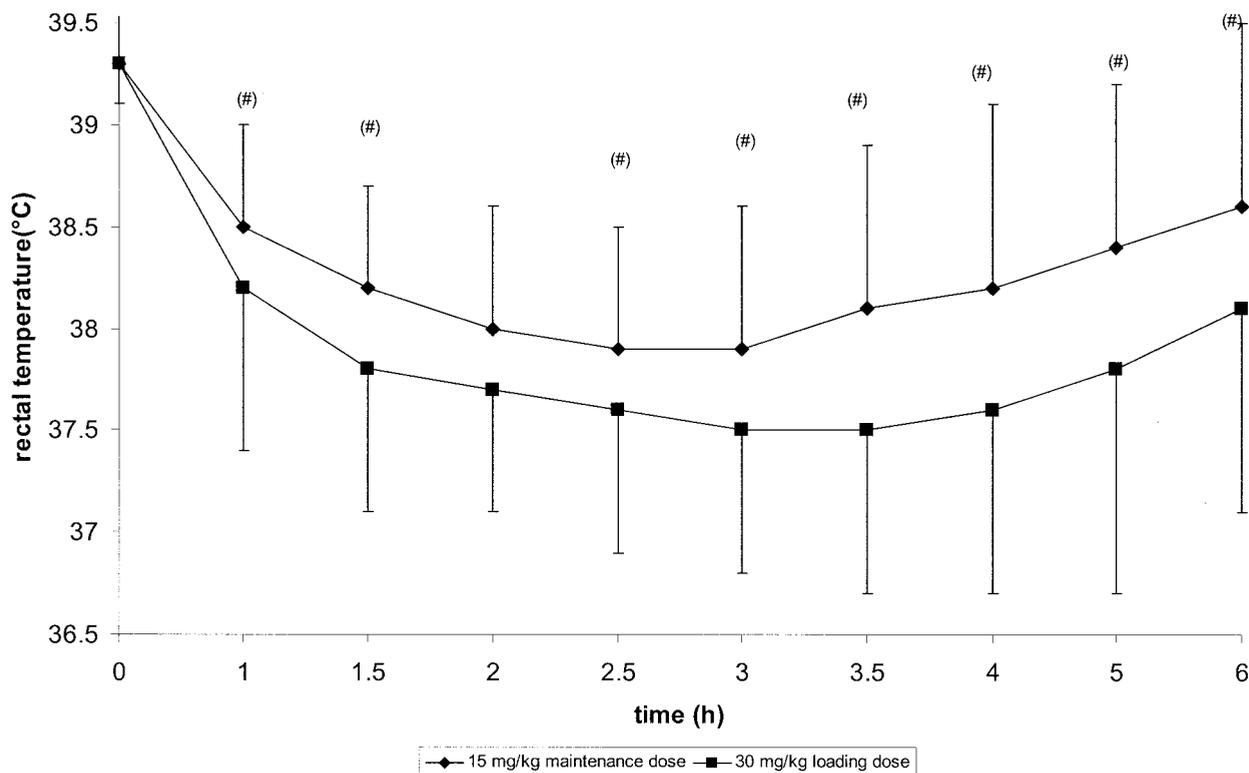* Patient characteristics were not significantly different between the 2 treatment groups.

Fig 1. Mean (± standard deviation) temperature time curve in the 2 groups of febrile children who were treated randomly with either an initial 30-mg/kg paracetamol loading dose or an initial 15-mg/kg maintenance dose. # indicates a significant difference between the 2 groups ($P < .05$).

TABLE 2. Antipyretic Efficacy of an Initial 30-mg/kg Paracetamol Loading Dose

	Time to Obtain Temperature <38.5°C (Min)	Minimum Temperature (°C)	Maximum Decrease of Temperature (°C)	Time to Maximum Decrease of Temperature (MIN)	Rate of Temperature Decrease (°C/Min)	Time Interval With Temperature Below 38.5°C (Min)	Number of "Temperature-Altering Treatment"
15-mg/kg group	139.48 ± 112.68	37.6 ± 0.6	1.76 ± 0.59	161.0 ± 63.08	0.012 ± 0.006	200.76 ± 117.62	16
30-mg/kg group	110.71 ± 94.32	37.1 ± 0.8	2.27 ± 0.72	190.10 ± 80.64	0.014 ± 0.009	255.23 ± 87.86	6
Statistical significance	$P < .05$	$P < .05$	$P < .05$	$P < .05$	$P < .05$	$P < .05$	$P < .05$
95% Confidence interval of the difference	(−66.5; −8.9)	(−0.74; −0.2)	(0.25; 0.75)	(0.0; 55.91)	(−0.0061; 0.00513)	(14.74; 94.20)	(4.74%; 32.73%)

the temperature, the higher the time delay ($P < .05$). This relationship was not significantly affected by the dose of paracetamol. No influence of age was shown. The results of the per-protocol analysis were consistent with those of the intention-to-treat analysis.

Adverse Events

No serious adverse event was reported during the study. The rate of reported adverse events was not significantly different between the 2 groups (5 and 6 in the 15-mg/kg and 30-mg/kg groups, respectively). The reported adverse events were fever (7), vomiting (3), and hypothermia (1). Hypothermia occurred in a patient in the 30-mg/kg group: the temperature was 35.4°C 4 hours after administration of paracetamol and returned spontaneously to 37.6°C 6 hours after dosing. In another patient, a 34.9°C temperature was recorded 3.5 hours after a 30-mg/kg acetaminophen dose but was not reported by the investigator as an adverse event.

DISCUSSION

The time interval after dosing to reach a temperature equal to 38.5°C in the control group was similar to the findings of previously reported studies.[2,5,11] The time lag is consistent with the sequence of events that mediate temperature decrease after the administration of an antipyretic drug. These events include the pharmacokinetic processes for the drug to be absorbed and to reach the hypothalamus and the pharmacodynamic ones that alter temperature regulation leading to a decrease in heat production and an increase in heat loss.[13] The pharmacokinetic processes may be a limiting factor in rapidly obtaining the expected antipyretic efficacy. It has been shown that the plasma half-life of acetaminophen ranges between 2 and 10 hours in febrile children[5,11,14]; con-

sequently, acetaminophen steady-state plasma concentrations can be reached only approximately between 10 and 50 hours after the first administration.

It can be assumed that to circumvent this inconvenience, the use of an initial loading dose to attain therapeutic plasma concentrations more rapidly may provide a faster antipyretic effect. Using computer simulation, Wilson et al[5] suggested a 22.4-mg/kg acetaminophen loading dose followed by a 13.3-mg/kg maintenance dose every 6 hours for children 2 to 8 years of age. We chose to test a 30-mg/kg loading dose, as it may be easier and more accurate to administer a loading dose that is twice the maintenance dose. The present study showed that a 30-mg/kg loading dose produces the target 38.5°C rectal temperature an average of 30 minutes earlier than the usual 15-mg/kg dose.

Transient hypothermia possibly related to acetaminophen intake was alleged by Walson et al[2] in a group of 16 patients who received 15 mg/kg every 6 hours. However, it is very difficult to differentiate the causal role of viral infection and acetaminophen administration. Mild transient hypothermia has no known clinical consequences.

No biological data were available in our study. However, it is unlikely that a 30-mg/kg loading dose could be responsible for hepatic toxicity, as the maximum plasma concentrations reported after administration of doses ranging between 25 and 27 mg/kg/8 hours[15] were always below 40 mg/L, ie, below the threshold concentration (120 mg/L) reported as being associated with toxicity in adults and adolescents after a single ingestion.[16] No specific data are available in febrile children on the relationship between acetaminophen plasma concentration and hepatotoxicity. Nevertheless, in a prospective observational study that included 1039 children who were younger than 7 years, no sign of hepatotoxicity was reported after an acute acetaminophen exposure of up to 200 mg/kg.[17] The use of high single rectal doses after surgery also supported the safety of a loading dose approach.[18,19] Heubi et al[20] compiled 47 reports of acetaminophen hepatotoxicity in children who received 60 to 420 mg/kg/day for 1 to 42 days. However, in many of these cases of toxicity after "therapeutic doses," initial acetaminophen blood concentrations were not compatible with the doses reported to have been given by the parents. Indeed, because the volume of distribution is approximately 1 L/kg,[5] a child with an acetaminophen concentration of >100 mg/L cannot have ingested a therapeutic dose. Anyway, tolerability observed after a single dose cannot be used to predict safety after repeated doses, and a repeated-dose study with pharmacokinetic and biological safety data would be necessary to determine whether the results of the present single-dose study can be of clinical relevance when a 30-mg/kg loading dose is followed by several repeated 15-mg/kg maintenance doses. If a loading dose of acetaminophen provides a more effective initial antipyretic therapy, then the irrational, untested use of combined, alternating antipyretic drug administration (ibuprofen or aspirin with acetaminophen) could be decreased.

CONCLUSION

Our results suggest that a 30-mg/kg loading dose of acetaminophen could be an efficient way to obtain a faster (0.5 hour earlier) significant temperature decrease (0.5°C more) that lasts longer (1 hour more) after the first dosing in febrile children who may benefit from antipyretic medication. Tolerance should be evaluated in a repeated-dose study, initiated with a 30-mg/kg acetaminophen loading dose.

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