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Comparison of Oral Versus Normal and High-Dose Rectal Acetaminophen in the Treatment of Febrile Children

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ABSTRACT. *Objectives.* To compare the defervescent effect of high-dose rectal suppository acetaminophen with the recommended oral and rectal dosages and to evaluate acceptability of rectal acetaminophen.

Methods. A randomized, controlled trial was performed in 70 patients aged 6 months to 6 years with fever $\geq 39^{\circ}\text{C}$. Group A received rectal acetaminophen 15 mg/kg, group B received rectal acetaminophen 30 mg/kg, and group C received oral acetaminophen 15 mg/kg. Primary outcome was maximal change in temperature during the 3-hour study period after initial treatment.

Results. There were 24 patients in group A, 23 in group B, and 23 in group C. There was no significant difference in temperature change between the groups during the 3 hours or in the maximum drop in temperature or final temperature. Visual analog scores for satisfaction of parents did not reveal any significant differences between the oral and rectal routes.

Conclusions. There was no difference between the temperature decrement in patients treated with 15 mg/kg oral acetaminophen and the same or double dose rectally. Thus, there seems to be no evidence to support the use of higher doses of rectal acetaminophen for the treatment of fever in children. The rectal route proved to be as acceptable as the oral among parents. *Pediatrics* 2002;110:553–556; acetaminophen, fever, rectal, dose.

Acetaminophen is the most commonly used drug in pediatrics.¹ For routine clinical use, it is administered in oral and rectal forms, as a tablet, liquid, or suppository. The rectal route is especially useful in several specific circumstances. Rectal administration of liquid preparations is impractical and has very limited clinical applicability; thus, rectal suppositories occupy an important role in the treatment of fever and pain in children. However, a recent recommendation from the American Academy of Pediatrics² has discouraged the use of rectal acetaminophen by parents unless specific instructions are given by medical personnel, their rationale

being that there is “potential for inadequate therapeutic effect from poor absorption as well as cumulative toxic effects from excessive or too frequently repeated rectal doses.”

In North American clinical texts, the recommended dose for acetaminophen (paracetamol in Europe) is 10 to 15 mg/kg/dose every 4 to 6 hours, regardless of whether the route of administration is oral or rectal.^{3–7} Although some investigators,^{8–12} both in Europe and in North America, have studied and recommended rectal doses as high as 60 mg/kg/dose, these higher doses have not been adopted as standard practice in North America.

The objective of the study was to compare the defervescent effect of high-dose rectal acetaminophen, given as a suppository, with the recommended oral and rectal dosages. We also evaluated the acceptability of rectal acetaminophen in young children.

METHODS

A randomized, controlled trial design was used. Ethical approval was obtained from the research ethics board of the hospital.

Study Population

Children who presented to the emergency department of the Hospital for Sick Children, Toronto, between March 1997 and August 1999, and were between the ages of 6 months and 6 years, had a rectal temperature $\geq 39^{\circ}\text{C}$, and presented between 8 AM and midnight were approached for consent to enroll in the study. Patients who had one of more of the following conditions were excluded from the study: known disorders of temperature control, status epilepticus, diminished level of consciousness, known allergy to acetaminophen, contraindications to the use of rectal drugs such as febrile neutropenia, patients for whom a “nil-by-mouth” order was written, and vomiting or diarrhea in the previous 4 hours. We also excluded children whose parents were unable to provide informed consent because of language difficulties or who had received acetaminophen in the previous 4 hours. Patients who vomited the oral preparation within 20 minutes were excluded as were those who passed the suppository per rectum.

Study Maneuver

Patients were assigned to 1 of 3 treatment groups by use of a computer-generated random-number table. The 3 treatment groups were as follows: group A, rectal acetaminophen, 15 mg/kg, in lipophilic suppository form; group B, rectal acetaminophen, 30 mg/kg, in lipophilic suppository form (both using Acet 120, 160, or 325 suppositories, Pharmascience Inc, Montreal, Quebec, Canada); and group C, liquid oral acetaminophen (Tempra, Mead Johnson, Ottawa, Ontario, Canada), 15 mg/kg.

By using half or whole suppositories containing 120 mg and 160 mg, doses were accurate within a range of 29 to 32 mg/kg for the 30 mg/kg group and 12.3 to 17.1 for the 15 mg/kg group. The 120-mg and 160-mg suppositories were cut in half longitudinally, when necessitated by dosing requirements, because the active

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drug is evenly distributed throughout the suppository (manufacturer's information). The manufacturing service of the Department of Pharmacy at our hospital cut the suppositories in half using standard procedures with a razor blade heated for sterility. The suppositories were subsequently packaged in aluminum foil and used within 60 days. After appropriate lubrication, the study worker inserted the suppository beyond the internal sphincter.

Temperatures were assessed before the acetaminophen was given, and at times 10, 30, 60, 90, 120, and 180 minutes after administration, using a rectal temperature probe (Medtronic 2103, Parker, CO) and temperature monitor (TM21, Englewood, CO) specifically dedicated to the study. The thermometer was calibrated according to National Institute of Standards Technology standards using a water bath at 37°C. Patients were followed for 180 minutes because most were ready to leave the emergency department by this time.

Parents were advised to reduce the amount and thickness of clothing the child was wearing. A single 10-cm visual analog scale was completed by either parent to assess parental satisfaction with each of the routes of administration after the last temperature measurement.

Analysis Plan

The primary outcome was maximal change in temperature during the 3-hour period after enrollment. We also examined several secondary endpoints: proportion of patients with a drop of at least 1°C and 2°C in temperature, mean temperature at the end of the study (3 hours), the decrement in fever at each time point, and the area under the temperature (versus time) curve for each group, calculated using the trapezoidal method. Continuous outcomes were first plotted to assess normality. The groups were compared using analysis of variance initially for change in temperature during 3 hours, then for the secondary continuous outcomes. Differences in the proportion in each group that experienced a drop of 1°C or 2°C were assessed by χ^2 statistics (2×3 contingency tables). Finally, the level of satisfaction with care was compared between those who were receiving medication via an oral route versus rectal route using the Wilcoxon rank sum test (or Mann-Whitney statistic). This test was selected because data from a visual analog scale were not expected to meet the assumption of normality.

The sample size was estimated on the basis of a clinically important difference of 0.5°C in mean temperature change between groups. Using a standard deviation of 0.43°C,¹² we estimated that 22 patients per group were necessary to obtain a power of 80% with an α of 0.05. To allow for dropout of patients, 30 patients were recruited per group.

RESULTS

Twenty-nine patients received 15 mg/kg rectal acetaminophen (group A), 31 received 30 mg/kg rectal acetaminophen (group B), and 29 received 15 mg/kg oral acetaminophen (group C). Five patients in group A, 8 in group B, and 6 in group C did not complete the study because >3 measurements were missing in their data, usually because their parents elected to leave the emergency department before the conclusion of the study. Thus, 24 patients in group A, 23 in group B, and 23 in group C were

available for the final analysis. Table 1 shows the demographic features of these study groups. There were no significant differences in age, weight, or temperature at time 0 among the 3 groups.

The maximum drop in temperature for each of the 3 groups is summarized in Table 2. There was no statistically significant difference among groups on this outcome as assessed by 1-way analysis of variance. Analysis of the distribution of the dependent variable, equality of variances, and post hoc assessment of residuals all confirmed the appropriateness of this analysis. Likewise, the assessment of secondary outcomes did not identify differences among the 3 groups. The proportion of patients with drops in temperature of at least 1°C and at least 2°C and the mean temperature at the end of the study are also shown in Table 2. Figure 1 shows the average temperatures at each time point for the 3 groups.

Because it is possible that temperatures dropped more rapidly in 1 particular patient or group and this would not be reflected in the calculations described so far, the area under the curve for temperature versus time was individually calculated for all patients in the 3 groups. This comparison did not reveal any significance among the 3 groups ($P = .18$). Analysis of visual analog scores for satisfaction of parents with the route of administration of acetaminophen did not reveal any significant differences between the oral and rectal routes ($P = .31$, median for rectal 91 of 100 and for oral 83 of 100).

DISCUSSION

We have shown that, in febrile children who presented to a pediatric emergency department, the antipyretic effect of single-dose rectal and oral acetaminophen 15 mg/kg is similar and that doubling the dose of rectal acetaminophen did not produce additional benefit. Moreover, the rectal route was as satisfactory to the parents as the oral.

The use of high-dose rectal acetaminophen has recently been studied extensively.^{11,13-15} Although this literature suggests that higher doses of rectal acetaminophen may be needed to achieve therapeutic levels, 40 mg/kg rectal acetaminophen was not superior to normal doses of the drug in postoperative pain management.^{13,15}

Rumack,¹⁶ in an unreferenced review, quoted acetaminophen serum levels of 10 to 20 mg/L as being therapeutic. Walson et al¹⁷ found that even concentrations as low as 6.8 mg/L reduce temperature to a

TABLE 1. Characteristics of Study Patients

	Group			P Value
	A (n = 24)	B (n = 23)	C (n = 23)	
Dosage and route of administration	15 mg/kg Rectal	30 mg/kg Rectal	15 mg/kg Oral	
Gender-male (%)	13 (54%)	13 (57%)	14 (61%)	
Weight (kg, \pm SD)	12.0 (\pm 2.6)	12.4 (\pm 3.4)	13.7 (\pm 4.8)	.26
Age (mo, \pm SD)	21.5 (\pm 9.9)	24.6 (\pm 15.7)	30.8 (\pm 18.4)	.11
Baseline temperature in °C (\pm SD)	39.6 (\pm 0.4)	39.7 (\pm 0.6)	39.7 (\pm 0.5)	.60

SD indicates standard deviation.

TABLE 2. Comparison of Changes in Temperature in Study Patients

	Group			P Value
	A 15 mg/kg Rectal (n = 24)	B 30 mg/kg Rectal (n = 23)	C 15 mg/kg Oral (n = 23)	
Maximum drop in temperature °C (±SD)	1.6 (±1.0)	2.0 (±0.7)	1.7 (±0.7)	.32
Number (%; 95% CI) of patients with drop of ≥1°C in temperature	18 (75%, 50.8%–89.7%)	20 (87%, 64.5%–96.1%)	20 (87%, 64.5%–96.1%)	.45
Number (%; 95% CI) of patients with drop of ≥2°C in temperature	9 (38%, 13.8%–70.2%)	13 (43%, 26.7%–81.6%)	10 (56%, 20.1%–69.3%)	.41
Temperature at time 180 min in °C (±SD)	38.0 (±1.0)	37.7 (±0.6)	38.0 (±0.6)	.22
Area under the temperature time curve in °C × min (±SD)	6820 (±412)	7005 (±196)	6936 (±375)	.18

CI indicates confidence interval; SD, standard deviation.

significantly greater extent than placebo. Others did not find a correlation between maximal serum concentration and fall in temperature.¹⁸ Moreover, the shape of the acetaminophen serum concentration versus time graph is different from that of the temperature versus time curve.¹⁹ The weak correlation between serum concentrations and clinical outcome, and the availability of temperature as a reliable and objective outcome measure were the reasons we chose to study the effect of different doses and routes of acetaminophen without assessing serum levels. This approach is limited, however, because it cannot assess the systemic absorption of the drug.

Previous studies on the antipyretic effects of rectal acetaminophen in children yielded conflicting results. Keinanen et al²⁰ showed that both oral and rectal acetaminophen were effective in reducing temperature in febrile children: the maximal temperature decrement was significantly greater in the oral group, and the effect was seen earlier. However, this study was not randomized, used the relatively low dose of 10 mg/kg acetaminophen, and used the polyethylene glycol base suppository, which, in children, has been shown to be inferior to the lipophilic formulation.²¹ In contrast, Gotte and Liedtke²² in a nonrandomized study, using dosages based on age rather than on weight, found no difference between oral and rectal acetaminophen in 144 febrile children. In a nonrandomized trial,¹⁸ administering 15 mg/kg acetaminophen to the same febrile patients rectally the first day after cardiac surgery or via nasogastric tube the next day produced no difference in temper-

ature reduction. In a randomized study, Vernon et al²³ showed no difference in the decrement in fever among 37 children who were treated with either oral or rectal acetaminophen in a dose of 15 to 20 mg/kg. However, the effect of high-dose rectal acetaminophen was not investigated.

Although a recent article²⁴ showed that 30 mg/kg oral acetaminophen caused a swifter and greater decrement in fever than conventional doses of 15 mg/kg, the clinical significance of these findings can be questioned because the mean difference in temperature was only 0.5°C. That our study did not show a significant difference in the performance of 30 mg/kg acetaminophen may be related to the different routes of administration of this higher dose of acetaminophen.

In the past few years, there has been an increased number of reports of liver failure associated with prolonged and excessive acetaminophen administration given for therapeutic reasons.^{25–29} In the largest series quoted, which describes liver failure associated with acetaminophen ingestion, the details are not given regarding dosage, route, or duration for all of the patients. Thus, caution must be exercised in widespread adoption of any repeated dosing recommendations that use higher doses of acetaminophen.

Parents were as satisfied with the rectal as with the oral routes of administration of acetaminophen, although these results may have been different if they had had to insert the suppository themselves. Thus, this route can be considered especially in conditions in which the oral route poses difficulties, such as with the child who is vomiting or spitting up oral medications.

Our study had several limitations. It was randomized but not blinded or placebo controlled. Because the primary outcome measure was an objective measure (body temperature), which is not subject to observer bias, blinding was not considered necessary. Furthermore, the additional interventions required to maintain blindness, such as placebo suppositories, were not considered ethically justifiable. The Research Ethics Board of the Hospital for Sick Children recommended that a placebo arm not be included (ie, using a double dummy design) because of the invasiveness of administering rectal drug. Therefore, the 3-group randomized design was chosen for this study. Usage of ibuprofen was not an exclusion cri-

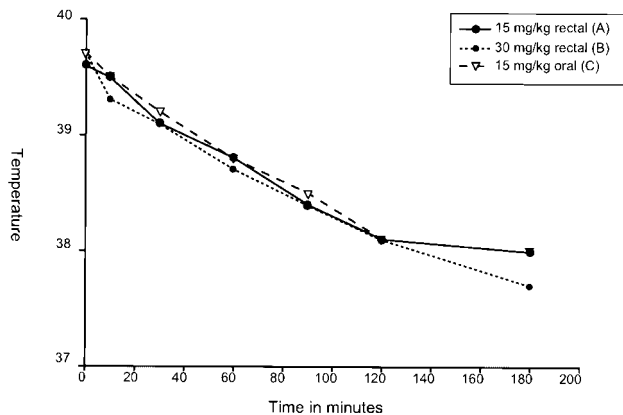


Fig 1. Mean temperature of the 3 treatment groups.

terion for the study; however, this drug became available in Canada in the liquid formulation only after the commencement of the research. Its use became widespread only in the ensuing few years. Furthermore, because patients were randomized, an equal number of patients in each study arm should have been exposed to the drug if its use were more widespread than anticipated.

We found no difference between the temperature decrement brought about by regular doses of oral versus rectal acetaminophen, and there was no additional advantage to doubling the dose of rectal acetaminophen. Thus, there does not seem to be any evidence to support the use of higher doses of acetaminophen in the treatment of fever in children. Normal doses (15 mg/kg) of rectal acetaminophen may be used in the treatment of fever in children.

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