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Comparison of antipyretic effectiveness of equal doses of rectal and oral acetaminophen in children

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Objective: To compare a dose of oral and rectal acetaminophen and to evaluate acceptability of rectal acetaminophen, since oral and rectal acetaminophen is widely used as an antipyretic agent in febrile children and the comparative effectiveness of these two preparations is not well established.

Methods: In this prospective parallel group designed study, 60 children who presented to the emergency department or outpatient pediatric clinic at a tertiary hospital and aged from 6 months to 6 years with rectal temperature over 39 °C were enrolled. Patients were randomly assigned to two equal-sized groups. Group 1 received 15 mg/kg acetaminophen rectally and group 2 received the same dose orally. Temperature was recorded at baseline and 1 and 3 hours after drug administration.

Results: In the first group, mean decrease in temperature, 1 and 3 hours after administration of acetaminophen was 1.07±0.16 ($p < 0.001$) and 1.74±0.25 °C ($p < 0.001$), respectively, and in the second group it was 1.98±0.19 ($p < 0.001$) and 1.70±0.14 °C ($p < 0.001$), respectively ($p > 0.05$).

Conclusion: Rectal and oral acetaminophen preparations have equal antipyretic effectiveness in children. The rectal route proved to be as acceptable as the oral one among parents.

J Pediatr (Rio J). 2010;86(3):228-232: Oral acetaminophen, rectal acetaminophen, fever.

Introduction

Fever is a common symptom in children and is considered as the most prevalent cause of seeking medical treatment.[1-4] Indeed, it is usually a natural reaction to many infections. However, some other factors can raise the body temperature as well.[5]

Parents of febrile children usually suffer from "fever phobia." This could lead to antipyretic overdose,[6-8] although temperatures lower than 39 °C do not need to be treated.[9-12]

Acetaminophen is the most widely used drug for reducing fever in children.[1,2,9,10] It is safe in standard doses of 10-15 mg/kg and could be used either rectally or orally.[1-3,10]

It has been shown that oral acetaminophen is absorbed within 30 to 60 min. In fact, pharmacokinetic properties of single oral dose of acetaminophen are known.[13,14] Nevertheless, pharmacokinetics of its single rectal dose is not well established since its absorption is prolonged and depends on size of suppository, base composition, and rate of dissolutions.[15] Moreover, some evidence revealed that antipyretic serum concentration of 15-20 µg/mL could not be achieved by rectal dose of 10-15 mg/kg and a rectal dose of 30-45 mg/kg was needed.[15-19]

In some circumstances, rectal preparation is used, such as when the patient is vomiting or the physician or parents prefer the rectal route.[20] Although several investigations have been conducted on acetaminophen, it is not known whether equal doses of rectal and oral acetaminophen have similar effectiveness in reducing fever. Actually, in regard to comparative effectiveness of these two preparations,

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contradictory results were reported by different studies. While some investigations showed that oral acetaminophen was more effective than the rectal form[21], others found they had similar effects.[20-23]

Therefore, this study was performed to compare the antipyretic effectiveness of the standard dose of 15 mg/kg acetaminophen administered orally or rectally. We also evaluated the acceptability of rectal acetaminophen among parents of young children.

Materials and methods

This is a randomized clinical trial with parallel group design. This study was conducted at the Shahid Sadoughi Medical Hospital, a tertiary affiliated hospital of the Shahid Sadoughi University of Medical Sciences, Yazd, Iran. The study protocol was approved by the University Ethics Committee and a written consent was obtained from all parents.

Febrile children who presented to the emergency department or outpatient pediatric clinic of the hospital, aged 6 months to 6 years, and had a rectal temperature of ≥ 39 °C were approached for enrolment in the study. Exclusion criteria included the following conditions: diminished level of consciousness, known allergy to acetaminophen, any condition that preclude oral or rectal drug administration, known malignancy, diarrhea or vomiting in the previous 24 hours, or have taken any antipyretics and antibiotics within 24 hours prior to the initiation of the study. Patients were also excluded if they vomited acetaminophen within 20 min, did not retain the suppository for at least 30 min, or required another antipyretic or antibiotic drug.

By a computer-generated random table, subjects were assigned to one of two groups. In the first group, 15 mg/kg acetaminophen was administered rectally and the second group received 15 mg/kg acetaminophen orally.

In a coded questionnaire, weight, gender, and the age of children in months were recorded. Prior to acetaminophen administration, rectal temperature was taken by a general practitioner using a digital thermometer with single-use disposable probe covers (Omron ProTemp) in the pediatric emergency department or pediatric ward. The same thermometer was used for the entire study and only the probe cover was disposed after each use. If the temperature was above 39 °C, then a trained nurse would administer the calculated weight-based dose of acetaminophen either rectally or orally, according to the allocation of patient. The same physician measured and recorded rectal temperatures at 60 and 180 min after drug administration.

Prescribed doses were prepared by the pharmacist in the Pharmacy Department of the hospital. For rectal administration, lipophilic suppositories were employed. Since active ingredient is evenly distributed throughout the suppository, when half of the suppository was needed, it would be cut in half longitudinally using a heated razor blade. In addition, when needed by dosing requirement, some of the suppositories were cut further transversally. Each part was weighed by a sensitive digital scale to make sure they were cut properly. Afterward, they were packaged in aluminum foil and kept in the refrigerator to be used within 30 days. By using whole or part of suppositories, doses within a range of 14 to 16 mg/kg were provided for the children. After proper lubrication, the nurse inserted the suppository beyond the internal sphincter.[23]

For oral route, syrup containing 120 mg/5mL of acetaminophen was used. The dose was calculated in mg and was then converted to mL. The required dose was given by a calibrated sterile syringe.

The physician who controlled the temperature, the pharmacist, and the statistician were blinded to the treatment allocation.

For assessment of parental satisfaction with each of the routes of administration a single 10-cm visual analog scale was completed by either parent after the last temperature measurement.[23]

Statistical analysis

Primary outcome was mean reduction in temperature 60 and 180 min following drug administration. Sample size was calculated to achieve an alpha of 0.05 and power of 80% to detect a difference of 0.5 °C in mean temperature change between groups. Estimated sample size was 22±2 patients per group. However, to allow for dropout of subjects, 30 patients were enrolled in each group.

Statistical analyses were performed using SPSS, version 12.0. To detect any significant difference in temperature among groups, Student's *t* test was applied and changes in temperature within a group were assessed by paired t-test. Intent-to-treat analysis was planned and statistical significance was set at $p < 0.05$.

Level of satisfaction of care was compared between parents of patients who received the medication via an oral route vs. those whose children received rectal acetaminophen using the Wilcoxon rank sum test (or Mann-Whitney statistics). This test was selected because data from a visual analogue were not expected to meet the assumption of normality.

Results

From September 2007 to May 2008, 60 patients were recruited in this study: 30 patients received 15 mg/kg rectal acetaminophen (first group), and 30 subjects received 15 mg/kg oral acetaminophen (second group). Fifty-four patients were treated in the outpatient clinic and left the hospital after 3 hours. Six patients were hospitalized and acetaminophen was part of their treatment regimen.

However, these patients did not receive any antibiotic or temperature-altering drugs during the study period. Three patients in the first group (rectal route) and four individuals in the second group (oral route) did not complete the study, because their parents elected to leave the clinic before the study was over.

Demographic characteristics of the two groups are shown in Table 1. There were no significant differences between them in regard to age, weight, gender, and baseline temperature.

As illustrated in Table 2, in the first group, 1 hour after drug administration, mean temperature dropped from 39.53±0.32 to 38.46±0.30 °C ($p < 0.001$) and after 3 hours it reached 37.80±0.32 °C, which was significantly different from the baseline temperature ($p < 0.001$). In the second group, after 1 hour, mean temperature reduced from 39.55±0.32 to 38.57±0.39 °C ($p < 0.001$) and reached 37.86±0.32 °C after 3 hours ($p < 0.001$) (Table 2). Therefore, both treatments are effective in reducing temperature. It should be mentioned that the drop in temperature between 1 and 3 hours was significantly different in both groups ($p < 0.05$).

Differences in mean reduction in temperature are illustrated in Table 3. There was a significant difference between the two groups with respect to reduction of temperature in the first hour, as assessed by ANOVA ($p = 0.036$). Nonetheless, this difference was not clinically important. In fact, during this period, the difference in the mean decline of temperature between the two groups was 0.09 °C. Also, analysis of variance did not reveal any

Table 1 - Characteristics of study patients

	Group 1 (n = 27) (15 mg/kg rectal)	Group 2 (n = 26) (15 mg/kg oral)	p
Gender (female)	12 (40%)	12 (40%)	
Weight (kg)	12±3.1	13±3.9	0.83
Age (months)	24.5±18.4	27±19.9	0.69
Baseline temperature (°C)	39.5±0.31	39.6±0.32	

Table 2 - Mean temperature 1 and 3 hours after acetaminophen administration

	n	Baseline temperature (°C)	Temperature after 1 hour (°C)	p	Temperature after 3 hours (°C)	p*	p†
Group 1 (15 mg/kg, rectal)	27	39.53±0.32	38.46±0.30	< 0.001	37.80±0.32	< 0.001	< 0.01
Group 2 (15 mg/kg, oral)	26	39.55±0.32	38.57±0.39	< 0.001	37.86±0.32	< 0.001	< 0.01

* Difference between baseline temperature and temperature after 3 hours.
† Difference between temperature at 1 and 3 hours.

Table 3 - Mean decrease in temperature 1 and 3 hours after acetaminophen administration in two groups

	Temperature decrease after 1 hour (°C)	p	Temperature decrease after 3 hours (°C)	p
Group 1 (15mg/kg, rectal)	1.07±0.16 (0.8-1.4)		1.7±0.25 (1.4-2.8)	
Group 2 (15mg/kg, oral)	0.9±0.19 (0.6-1.4)	0.036	1.7±0.14 (1.4-2.0)	0.393

Values expressed as mean ± standard deviation (minimum-maximum).

significant difference in the mean temperature decrease between both groups 3 hours after drug administration (p = 0.393)

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 = 0.43, median for rectal 93 of 100 and for oral 86 of 100).

Discussion

Acetaminophen has been widely used as antipyretic in children. Although both rectal and oral forms have been shown to be effective as fever-reducing agents, controversy regarding the comparative antipyretic effectiveness of equal doses of both preparations still exists.

Consequently, we decided to compare the effectiveness of 15 mg/kg of rectal and oral acetaminophen. It should be emphasized that since there is a weak relationship between acetaminophen concentration and decline in temperature, we did not measure its level.[4,23]

In this study, the antipyretic effects of equal doses of rectal and oral acetaminophen (15 mg/kg) were statistically significant in 60 min after receiving the drug (p = 0.036). Nevertheless, the difference in mean temperature decrement between both groups was 0.09 °C, which was not clinically important. Therefore, it could be deduced that both preparations have similar effectiveness in reducing temperature after 1 hour. Also, effects of both therapies were analogous after 180 min (p = 0.39). Hence, the antipyretic effects of rectal and oral forms of 15 mg/kg acetaminophen are similar in 1 and 3 hours after drug administration.

Previous studies on the comparison of the antipyretic effects of rectal and oral acetaminophen had conflicting results. Leary et al. showed that oral acetaminophen was more effective than rectal preparation in reducing temperature in febrile children.[21] However, they employed axillary temperature, which is not reliable.[24] In a study conducted by Keinanen et al., oral acetaminophen was reported to be more effective and its effect was observed faster.[25] Nonetheless, this study was not randomized and a low dose of 10 mg/kg acetaminophen was administered. In addition, they used the polyethylene glycol base suppository that has been shown to be inferior to the lipophilic suppository in children.[23]

In another study, 15 mg/kg acetaminophen was administered either via gastric tube or rectally to febrile patients following cardiac surgery. Temperature reductions were similar in both groups.[26] Likewise, in a randomized study, Vernon et al. reported no difference between rectal and oral acetaminophen in a dose of 15 to 20 mg/kg.[22]

Scolnik et al. found similar antipyretic effects with 15 mg/kg rectal and oral acetaminophen. Moreover, they noticed that doubling the dose of rectal acetaminophen to 30 mg/kg did not produce any additional benefit over 15 mg/kg given rectally.[23] However, this study was not blinded and each group included only 23 to 24 patients. Talebian et al. found no difference between 10-15 mg/kg rectal and oral acetaminophen.[27]

Results of a study conducted by Nabulis et al. revealed no difference in the defervescent effects of 15 mg/kg oral and rectal acetaminophen, and rectal dose of 35 mg/kg.[20] However, this study was performed among hospitalized patients, many of whom received antibiotics. Furthermore, it comprised a wide age range between 6 months and 13 years and there were only 16 to 18 subjects in each group.

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. Moreover, a recommendation from the American Academy of Pediatrics[6] has discouraged the use of rectal acetaminophen by parents unless specific instructions are given by medical personnel. Thus, this route can be considered especially in conditions in which the oral route poses difficulties, such as when the child is vomiting or spitting up oral medications.

Conclusion

Rectal and oral acetaminophen preparations have equal antipyretic effectiveness in children. The rectal route proved to be as acceptable as the oral among parents.

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