Prophylactic use of acetaminophen in children vaccinated with diphtheria-tetanus-pertussis

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Background: **The present randomized non-blind trial was conducted to clarify the effect of analgesics on febrile responses of booster diphtheria-tetanus-whole cell pertussis (DTP) vaccine in 15-20 months old infants.**

Methods: **A total of 270 healthy infants were randomized to receive acetaminophen (10 mg/kg) along with DTP vaccine (group 1), 2 hours after vaccination (group 2), and after the appearance of febrile reactions or irritability following vaccination (group 3, control). In addition to study medication, if the axillary temperature was higher than 38°C or if the infant seemed to be irritable, the parents were told to give acetaminophen (10 mg/kg) and record on a diary card. Vaccinees were monitored for local and systemic reactions.**

Results: **The incidences of local swelling, pain and erythema were not significantly different among the 3 groups. No difference was observed in the incidence of systemic reactions including febrile responses, irritability, anorexia, and vomiting among the 3 groups during the 7 days after vaccination. Of the infants, 45.1%, 46.7% and 51.9% manifested fever (axillary temperature ≥38°C) within 24 hours after the vaccination in groups 1, 2 and 3, respectively (P>0.05). The second dose of acetaminophen was less in the control group than in the prophylactic groups (P=0.009).**

Conclusions: **Administration of acetaminophen along with DTP vaccine or 2 hours after vaccination does not affect the occurrence of febrile responses following booster vaccination. Unnecessary use of analgesics should be prevented.**

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Key words: **acetaminophen; adverse reactions; diphtheria-tetanus-pertussis vaccine; vaccination**

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Introduction

Diphtheria-tetanus-pertussis (DTP) vaccine has both high efficacy and high reactogenicity.[1] One of the main reasons for non-immunization of children was the adverse effect of the previous vaccination.[2] Previous studies revealed that the prophylactic use of acetaminophen in children who have booster DTP vaccination is controversial.[3-5] However, infants vaccinated at 18 months of age have a higher incidence of systemic and local reactions than younger infants. Also children with booster vaccination gave more reactogenicity than those with primary vaccination.[6,7] The Adivisory Committee on Immunization Practices (ACIP) USA has suggested the administration of acetaminophen at the time of immunization and every 4 to 6 hours for 48 to 72 hours in children at a higher risk for seizures than the general population.[7] If the reactogenicity of this vaccine is decreased in the general population, parental anxiety could be relieved and the vaccination coverage could be increased. The present study aimed to evaluate the effect of different protocols of single dose of acetaminophen (along with vaccination, 2 hours after vaccination, and antipyretic use when needed) on the febrile responses of DTP vaccination in 15-20 months old children.

Methods

In a randomized non-blind intervention trial, 15-20 months old healthy infants with booster DTP vaccination were enrolled in the study between May 2001 and April 2002 at Gülveren Health Center in Ankara. Infants with febrile illness, chronic illness or severe reactions to DTP vaccination and family history of seizures were excluded. Those were also ineligible for enrollment in the trial if they had a history of hypersensitivity to acetaminophen, a requirement for ongoing use of anti-inflammatory agent or difficulty in taking liquid medication.

After written informed consent was obtained from their parents, the infants were randomized to receive acetaminophen (10 mg/kg) along with DTP vaccine (group 1), 2 hours after vaccination (group 2), and

after the appearance of febrile reactions or irritability (group 3, control). All the infants also received oral polio vaccine at the first hour of DTP vaccination. DTP vaccine was administered by deep intramuscular injection into the deltoid muscle by the same nurse.

In addition to the prophylactic use of acetaminophen in groups 1 and 2, if the axillary temperature of the infants in all groups was more than 38ºC or if they seemed to be irritable, their mothers were told to give acetaminophen (10 mg/kg, q4-6h)[8] and record on a diary card. The dose of acetaminophen was adjusted for weight and administered by mother.

Vaccinees were monitored for immediate reactions or early adverse events within at least 2 hours after vaccination. Local reaction (pain, redness and induration at the injection site), axillary temperature, and systemic reactions (drowsiness, loss of appetite, vomiting, diarrhea, and any other adverse events) were recorded by their mothers on the diary card during the 7 days after vaccination. The mothers were instructed to take and record axillary temperature of their infants daily. The reactogenicity was taken as the percentage of local and systemic reactions.

Statistical analysis was performed by SPSS version 9.0 (SPSS Inc., Chicago, IL, USA). Differences in frequencies were analysed by the Chi-square test. Differences in the 3 groups were studied by one-way ANOVA with Dunnett test for post hoc analysis.

Results

A total of 270 healthy infants were recruited in the study, 90 infants in each group. At admission, the age, sex, weight, height, breast feeding status, birth order, birth weight, as well as the parents' age and education were compared between the 3 groups (Table 1). No severe immediate reaction was seen within 2 hours after vaccination. Diary cards were returned from the parents of 229 infants (84.8%), including 73, 75 and 81 infants in groups 1, 2 and 3, respectively.

The incidences of local swelling, pain and erythema were not significantly different among the 3 groups within the first day and on 1-6 days of vaccination. Febrile responses were prominent in the first 24 hours after vaccination. Of the infants, 45.1%, 46.7% and 51.9% manifested febrile responses (axillary temperature ≥38ºC) within 24 hours after vaccination in groups 1, 2 and 3, respectively (P>0.05, Table 2). The frequency of fever on day 1-7 and high febrile responses (axillary temperature ≥39ºC) were similar among the 3 groups. There was no significant difference in the frequency of systemic reactions including irritability, anorexia, vomiting during the 7 days after vaccination (Table 2). Convulsion, hypotonic hyporesponsive episode, encephalopathy, or temperature higher than 40.5ºC were not observed.

In the control group, 14 infants (17.3%) did not take acetaminophen (Table 3). There was less use of the second dose of acetaminophen in the control group than in the prophylactic groups (P=0.009). The frequencies of infants receiving ≥3 doses of acetaminophen were similar among the 3 groups. The mean number of doses of acetaminophen in the first day of vaccination was higher in the prophylactic groups than in the control group (P<0.001, Table 3).

In infants whose parents did not return the diary card at the 7th day of vaccination, we phoned the parents between 8-10 days of vaccination. Eighteen parents were reached and they reported that no systemic adverse events (high fever, febrile convulsion and drowsiness) occurred in their infants; however, they still did not fill in the diary card.

Discussion

Acetaminophen given with DTP vaccine did not affect the incidence of any adverse events after vaccination. The incidence of systemic and local reactions in the

Table 1. General characteristics of infants enrolled*

Characteristics	Group 1 (n=90)	Group 2 (n=90)	Group 3 (n=90)
Age (mon)†	16.9±1.3	16.7±1.2	16.6±1.4
Male‡	48 (53.3)	44 (48.9)	46 (51.1)
Birth order: 1st child‡	28 (31.1)	31 (34.4)	33 (36.7)
Breast feeding‡	24 (26.7)	29 (32.2)	29 (32.2)
Body weight (kg)†	11.5±2.0	11.3±1.9	11.3±1.6
Length (cm)†	76.4±3.8	76.9±3.5	77.5±3.9
Birth weight (kg)†	3.30±0.43	3.34±0.40	3.29±0.36
Mother's age (y)†	28.7±6.1	27.6±5.9	28.3±5.6
Father's age (y)†	31.9±5.9	31.7±6.0	32.4±6.3
Mother's education level ≥8 y‡	36 (40.0)	40 (44.4)	39 (43.3)
Father's education level ≥8 y‡	53 (58.9)	46 (51.1)	49 (54.4)

*: P>0.05 for all comparisons among the 3 groups; †: means ± SD; ‡: n (%).

Table 2. Effect of prophylactic acetaminophen on adverse events of booster DTP vaccination, n (%)*

Side effects	Group 1 (n=73)	Group 2 (n=75)	Group 3 (n=81)
Local			
Pain	32 (43.8)	33 (44.0)	41 (50.6)
Induration	16 (21.9)	16 (21.3)	19 (23.5)
Erythema	18 (24.7)	19 (25.3)	22 (27.2)
General			
Axillary temperature ≥38ºC	33 (45.1)	35 (46.7)	42 (51.9)
Axillary temperature ≥39ºC	6 (8.2)	7 (9.3)	9 (11.1)
Irritability	38 (52.1)	41 (54.7)	46 (56.8)
Drowsiness	24 (32.9)	25 (33.3)	30 (37.0)
Anorexia	14 (19.2)	14 (18.7)	17 (21.0)
Vomiting	5 (6.9)	4 (5.3)	5 (6.2)
Persistent cry	0 (0.0)	0 (0.0)	0 (0.0)

*: P>0.05 for all comparisons among the 3 groups.

Table 3. The frequency of acetaminophen use, *n* (%)

Doses	Group 1 (*n*=73)	Group 2 (*n*=75)	Group 3 (*n*=81)
Acetaminophen use			
Along with vaccination	73 (100.0)	0 (0.0)	0 (0.0)
2 hours after vaccination	0 (0.0)	75 (100.0)	18 (22.2)
3-23 hours after vaccination	52 (71.2)	54 (72.0)	65 (80.2)
Day 1	28 (38.4)	29 (38.7)	32 (39.5)
Day 2	11 (15.1)	9 (12.0)	12 (14.8)
Mean number (range) of doses at day 0*	2.09 (1-4)‡	1.98 (1-3)‡	1.10 (0-3)§
Acetaminophen given for indication	58 (79.5)	61 (81.3)	67 (82.7)
Second dose of acetaminophen, including prophylaxis†	58 (79.5)‡	61 (81.3)‡	50 (61.7)§
≥3 doses of acetaminophen, including prophylaxis	35 (48.0)	38 (50.7)	29 (35.8)
No acetaminophen	0 (0.0)	0 (0.0)	14 (17.3)

*: $P<0.001$ for comparison among the 3 groups; †: $P=0.009$ for comparison among the 3 groups. ‡, §: values with different superscript in the same row were significantly different.

control group in this study was similar to that reported elsewhere.[1,6]

The efficacy of prophylactic acetaminophen in infants with primary DTP vaccination was marked but in infants with booster vaccination it was controversial or absent.[3-5] Lewis et al[4] reported no difference in the incidence of local reactions between the acetaminophen and placebo groups, whereas Ipp et al[3] found a significantly low incidence of local reactions with an area of redness of 2 cm in the acetaminophen groups, compared with the placebo group, among infants at the age of 2-6 months. Jackson et al[9] reported that prophylaxis with either acetaminophen or ibuprofen (three dose, given at 6-hour intervals) was not associated with a clinically significant reduction in risk of local reactions among children receiving the fifth DTaP (diphtheria-tetanus-acellular pertussis) vaccination. Similarly, in the present study, no improvement was observed in either local or systemic adverse events. Prophylaxis with acetaminophen did not decrease the need for analgesic use. It might be partially due to the time for analgesic use. The early use of acetaminophen might demolish the effects of the agent. For infants and children the recommended dose of acetaminophen was 10-15 mg/kg, q4-6h.[8] The lowest dose (10 mg/kg) of acetaminophen we used might be a limitation.

The non-blind nature of the trial is one of the limitations for the present study. Another limitation is that the sample size is not enough to detect difference in the incidences of severe side effects. However, this is not the aim of the trial; the trial aimed to show the effect of prophylactic antipyretics on fever and the need for antipyretic use. In this study, 61.7% of subjects in the control group received the second dose of acetaminophen and 79.5% and 81.3% in the other groups also received the same dose of prophylactic acetaminophen.

In conclusion, prophylaxis with one dose of acetaminophen is not associated with a clinically significant reduction in the incidence of fever in children receiving the fourth booster DTP vaccination. Unnecessary use of analgesics should be prevented.

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