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Abstract

Accumulating evidence suggests that the use of acetaminophen increases the risk of developing asthma and that its widespread use has contributed to the increasing prevalence of asthma. *Study design.* To investigate the immediate effect of a single dose of acetaminophen on airways reactivity and inflammation in asthmatic and controls. A double blind placebo-controlled study was conducted on 42 asthmatic children and 21 healthy age-matched controls. Each participant received one oral dose of acetaminophen (15 mg/kg [160 mg/mL]) and one dose of a volume-matched placebo. Physical examination, spirometry results, and fractional exhaled nitric oxide levels were assessed before and 60 minutes following acetaminophen or placebo ingestion. *Results.* None of the studied variables showed any significant change after acetaminophen or placebo ingestion in either the asthmatic or the control groups. *Conclusions.* One single dose of acetaminophen neither evokes a bronchoconstriction response nor an increase in airway inflammation in children with asthma.

Keywords

paracetamol, asthma, FeNO, spirometry

Introduction

The use of acetaminophen (paracetamol) has increased over the past decades with the reduced utilization of aspirin. The prevalence of asthma has also increased, leading to the hypothesis that there is a link between the 2 trends.¹ Accumulating data suggest that the early use of acetaminophen increases the risk of asthma and other allergic disorders.^{2–4} This is supported by convincing epidemiological studies that showed that the risk of asthma increases significantly with intrauterine exposure to acetaminophen^{5,6} as well as with the use of acetaminophen more than once in the first 6 to 12 months of life.^{7,8} One randomized controlled study showed that children who took ibuprofen had lower rates of hospitalization and fewer outpatient visits for asthma compared with children who used acetaminophen.⁹ There was, however, a dose–response effect, with a higher cumulative incidence of asthma being associated with higher acetaminophen doses.⁹ Acute exacerbations of asthma in infancy and childhood are frequently triggered by viral

respiratory tract infections.¹⁰ Acetaminophen is the most commonly prescribed antipyretic medication during these infections.¹ Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human alveolar macrophages and type II pneumocytes.¹¹ Since glutathione is a major nonenzymatic antioxidant found in the respiratory tract lining fluid of the lungs,¹² its depletion may impair the protection against the injurious effects of oxygen radicals during respiratory infections, resulting in airways hyperresponsiveness, inflammation, and asthmatic exacerbation.^{13–15} We hypothesized that treatment with acetaminophen may contribute to the acute exacerbation of asthma. The aim of the current study was to investigate

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whether the consumption of a single dose of acetaminophen by asthmatic children induces or increases airways inflammation and bronchoconstriction expressed as elevation of fractional exhaled nitric oxide (FeNO) levels and deterioration of spirometric indices. This is a pilot study that may stimulate further research.

Method

Participants

This is a cross-over double blind study. Forty-two asthmatic children were recruited from the pediatric pulmonary outpatient clinic. Inclusion criteria were (a) follow-up in the pulmonary clinic due to asthma for at least 2 years; (b) clinically stable (ie, no exacerbation or rescue treatment for the preceding 1 month); (c) cooperative and successful completion of FeNO measurements and either adenosine challenge rest and/or spirometry; and (d) positive bronchial hyper-responsiveness documented by positive adenosine challenge test (ie, a provocation concentration causing 20% reduction in forced expiratory volume in 1 second [$PC_{20}FEV_1$] <104 mg/mL adenosine or positive reversibility of airway narrowing by a significant bronchodilation response [$\Delta FEV_1 \geq 12\%$] to short-acting bronchodilators). Exclusion criteria were (a) any acute or chronic disease during the study period except for asthma; (b) any regular use of medications except those that were given as asthma regulators; and (c) any treatment with systemic corticosteroids within 1 month prior to entering the study. None of the participants had a medical past history of hypersensitivity to acetaminophen.

Twenty-one healthy age- and gender-matched controls were recruited from the families of the hospital employees. The following information was collected for each participant: age, gender, weight, height, diagnosis of asthma among parents and siblings, exposure to smoking, smoking during pregnancy, pets at home, a known food allergy, a history of viral bronchiolitis, exposure to acetaminophen during pregnancy, and any regular treatment.

Each of the 63 participants was tested twice with an interval of 5 to 10 days between tests. Each test session started with a physical examination, an FeNO measurement, and spirometry (0 minutes, time 0') followed by ingestion of either 15 mg/kg acetaminophen (Paramol Kat for children, bubble gum flavor, 160 mg/5 mL, manufactured by Perrigo Company, Allegan, MI) or an equivalent volume of placebo (a sweet soft drink of similar taste and color). A repeat physical examination and spirometry were performed 30 minutes after ingestion of acetaminophen (time 30') and at 60 minutes post ingestion when the FeNO measurement was also repeated

(time 60'). The order in which acetaminophen or placebo was given to the participant was randomized by an assistant who was not a part of the study. Acetaminophen was assigned the letter "A" and placebo was assigned the letter "B," and both were prepared by a research assistant who was not a part of the research team and who was the only one aware of the solution composition. The participants, their parents and the researchers were not aware of the solution provided to the participant. The key for identifying "A" and "B" solutions was opened only after the results had been analyzed.

Spirometry was performed using a handheld spirometer (Micro-Lab ML3500/S, Micro-Medical Ltd, Kent, UK) according to the American Thoracic Society guidelines¹⁶ using Polgar Ref. FeNO was measured online using a chemiluminescence analyzer (Eco Physics CLD88, NO chemiluminescence analyzer, EcoMedics AG, Duernten, Switzerland) and the Denox 88 NO free supplier module with online recording during a single breath exhalation, according to the American Thoracic Society/European Respiratory Society guidelines, and expressed as parts per billion (ppb).^{17,18} Breaths for which FeNO was more than 10% off were discarded. The maneuver was repeated with 30-second intervals of relaxed breathing between the measurements until three reproducible NO values were obtained, and the average was recorded. All the children were instructed to avoid the following prior to the test: eating or drinking for 1 hour, any exercise for 3 hours, exposure to cigarette smoke for 24 hours, medications, alcoholic beverages, and Coca-Cola and lettuce on the morning of the test.

The study was approved by the local institutional review board (Helsinki Committee). The parents of all the participants signed a written informed consent.

Statistical Analysis

Comparison between asthmatic and healthy children for demographic and clinical parameters was performed using the Student's 2-sample *t* test for continuous variables and χ^2 or Fisher's exact test, as applicable, for categorical variables. The mean values before acetaminophen and before placebo for each study group were used to compare the baseline (time 0') spirometric and FeNO values between groups. Lung function indices: FEV_1 , forced vital capacity (FVC), and the forced expiratory flow between 25% and 75% of expired vital capacity (FEF_{25-75}) were compared between solutions and between time points using a repeated measures analysis of variance within each group. In addition, a one-way analysis of variance with repeated measures was carried out to compare between the 2 groups of children, between solutions and between time points. The interaction terms of

Table 1. Characteristics of Children With Asthma and Healthy Controls

	Healthy Controls (n = 21)	Children With Asthma (n = 42)	P
Age in years; mean $\pm$ SD	11.62 $\pm$ 3.02	12.39 $\pm$ 2.42	.28
Male/female; n	13/8	28/14	.71
Height in cm; mean $\pm$ SD	150 $\pm$ 14.88	149.5 $\pm$ 20.22	.92
Weight in kg; mean $\pm$ SD	45.29 $\pm$ 15	45.58 $\pm$ 14	.94
Smoking parents; n (%)	17 (81)	26 (62)	.13
Smoking during pregnancy; n (%)	3 (14)	2 (5)	.32
Siblings with asthma; n (%)	5 (24)	5 (12)	.22
Parents with asthma; n (%)	5 (24)	24 (57)	.012
Pets at home; n (%)	9 (43)	18 (43)	1.0
Inhaled corticosteroids; n (%)	Not applicable	41 (98)	
Food allergy; n (%)	2 (10)	4 (10)	1.0
Atopic dermatitis; n (%)	2 (9.5)	15 (35.7)	.036
History of viral bronchiolitis; n (%)	1 (5)	14 (33)	.009
Exposure to paracetamol during pregnancy; n (%)	19 (90)	40 (95)	.6

solution by time trend and group by time trend were also included in the models. Linear regression models were applied to each one of studies parameters: FeNO, FEV₁, FEV₁/FVC, and FEF₂₅₋₇₅, to locate possible factors associated with differences between solutions with regard to change over time between baseline and 1-hour results. Explanatory variables that were entered into the models were as follows: age, gender, weight, height, asthma in parents and siblings, exposure to smoking, smoking during pregnancy and pets at home. Three model techniques were used—forced entry, forward selection, and backward elimination. Comparisons between baseline and 1-hour results of lung function indices for each solution and each group were by the paired *t* test. All statistical analyses were performed by a biostatistician using the SAS for Windows, version 9.2.

Results

The participants' characteristics are presented in Table 1. Children with asthma had a higher percentage of atopic dermatitis, of a history of viral bronchiolitis, and of coughing during acute viral upper respiratory disease. There were no other significant differences. Only one of the 42 asthmatic children was not on regular treatment with inhaled corticosteroids.

Although the baseline spirometric values (time 0') for both the asthmatic children and the controls were within normal range, they were significantly lower in the children with asthma compared with the controls: FEV₁% 88 $\pm$ 13 versus 97 $\pm$ 12, *P* = .035; FEV₁/FVC% 96 $\pm$ 10 versus 102 $\pm$ 10, *P* = .002; FEF₂₅₋₇₅% 71 $\pm$ 20 versus 92 $\pm$ 16, *P* = .002 (Table 2). Baseline FeNO levels were significantly higher in children with asthma

compared with controls (39.5 $\pm$ 32.5 ppb vs 11 $\pm$ 3.7 ppb; *P* < .001). There was no significant within-group difference for any of these variables between the 2 baseline measurements (time 0' before acetaminophen and time 0' before placebo). Finally, no significant change was observed for any of the studied variables between time 0' and time 60' before and after ingestion of acetaminophen or placebo for either the study or the control group (Table 2).

Discussion

It had been reported that infection of the respiratory tract by various respiratory viruses evokes airway inflammation and that one consequence may be an acute exacerbation of asthma in susceptible children.¹⁰ The current study was designed to assess the immediate contribution of acetaminophen to such an event during a respiratory illness in these children. Pharmacokinetics and pharmacodynamics analysis of acetaminophen showed maximum serum concentration at 27.0 minutes postconsumption¹⁹ and mean plasma elimination half life of 4 to 16 hours.²⁰ Positive findings would be of major clinical importance if routine use of so much as one dose of acetaminophen indeed has the potential to affect the pathophysiology of airways in asthma. The results of this study demonstrated that a single dose of acetaminophen neither induces an inflammatory reaction nor reduces physiologic properties in the airways of children with asthma. Three children with asthma showed reduction in the percentage predicted value of FEV₁ of 7%, 8%, and 9%, respectively, 1-hour post acetaminophen consumption, but these reductions are not considered to be clinically relevant and were not followed by increased levels of FeNO.

Table 2. The Results of All the Assessed Parameters at 0, 30, and 60 Minutes After Consuming Acetaminophen or Placebo in Both Groups

Group/Solution	Time (Minutes)	FeNO ppb	FEV ₁ % predicted	FEV ₁ /FVC % predicted	FEF ₂₅₋₇₅ % predicted
Asthma/A	0	39 ± 32	88 ± 12	95 ± 9	70 ± 21
Asthma/A	30		89 ± 14	96 ± 11	73 ± 22
Asthma/A	60		88 ± 17	93 ± 18	73 ± 25
P (60 vs 0 min)		NS (.14)	NS (.87)	NS (.53)	NS (.48)
Asthma/B	0	40 ± 32	88 ± 12	95 ± 10	72 ± 21
Asthma/B	30		89 ± 12	97 ± 10	74 ± 23
Asthma/B	60	40 ± 36	89 ± 17	96 ± 10	74 ± 23
Asthma mean baseline (0 min)	0	39.5 ± 32.5 ^a	88 ± 13 ^b	96 ± 10 ^c	71 ± 20 ^d
P (60 vs 0 min)		NS (.86)	NS (.33)	NS (.18)	NS (.16)
Control/A	0	11 ± 2	98 ± 13	102 ± 12	95 ± 18
Control/A	30		97 ± 11	104 ± 5	91 ± 15
Control/A	60	11 ± 3	96 ± 12	103 ± 6	90 ± 18
P (60 vs 0 min)		NS (.79)	NS (.29)	NS (.50)	NS (.20)
Control/B	0	11 ± 5	96 ± 10	104 ± 6	92 ± 16
Control/B	30		94 ± 11	101 ± 6	85 ± 16
Control/B	60	15 ± 5	95 ± 12	101 ± 6	87 ± 18
Control mean baseline (0 min)	0	11 ± 3.7 ^a	97 ± 12 ^b	102 ± 10 ^c	92 ± 16 ^d
P (60 vs 0 min)		NS (.64)	NS (.42)	NS (.60)	NS (0.14)

Abbreviations: A, acetaminophen; B, placebo; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF₂₅₋₇₅, forced expiratory flow between 25% and 75% of expiration; NS, nonsignificant.

^aP = .001 for baseline FeNO difference between children with asthma and controls.

^bP = .035 for baseline FEV₁ difference between children with asthma and controls.

^cP = .002 for baseline FEV₁/FVC difference between children with asthma and controls.

^dP = .002 for baseline FEF₂₅₋₇₅ difference between children with asthma and controls.

The rationale for the likelihood of a deleterious effect of acetaminophen on the airways in asthmatic patients involves its effect on the glutathione system.¹¹ Increased production of reactive oxygen species occurs in the airways of asthmatics during exacerbation, leading to airway inflammation with oxidation of cellular constituents,²¹ and this correlates with the degree of airway hyperresponsiveness as quantified by methacholine challenge.²² The excessive production of reactive oxygen species causes depletion of glutathione,²³ which is a major nonenzymatic antioxidant of the lungs found in the respiratory tract lining fluid.¹² Glutathione depletion can lead to increased severity of the asthmatic inflammation.²⁴ Its levels in the exhaled breath condensate of asthmatics during acute exacerbations were found to be significantly lower compared with control population,²⁵ suggesting impairment of the glutathione redox system in handling reactive oxygen species. Acetaminophen decreases glutathione levels, principally in the liver and kidneys, but also in the lungs,¹¹ thereby augmenting oxidative damage and airways inflammatory response.²⁶ Although almost all our patients were on inhaled corticosteroids, this treatment does not affect glutathione airway levels. No

differences had been observed by others in total and oxidized glutathione levels between steroid-naïve and steroid-treated asthmatic patients.²⁷

Aspirin-induced asthma is a clinical syndrome characterized by chronic rhinosinusitis, nasal polyps and asthma. It has been shown that adult asthmatics with aspirin-induced asthma may experience severe bronchospasm following ingestion of a single dose of aspirin and other nonsteroidal anti-inflammatory drugs.²⁸ Notwithstanding evidence on the effects of repeated exposure to acetaminophen on the risk to have asthma,²⁻⁸ there are no data whether a single dose of acetaminophen can also be deleterious, as had been found with aspirin in patients with aspirin-induced asthma. It may be argued that a single dose is not capable of depleting the glutathione content, and therefore neither significant inflammation nor bronchoconstriction should be expected. Nonetheless, Nuttall et al²⁹ showed a significantly lower serum antioxidant capacity in healthy young volunteers following 2 weeks of daily ingestion of 1 g of acetaminophen.

There is a direct dose-response relationship between acetaminophen and asthma. The increase in the severity of asthma with higher cumulative doses and with increasing

daily or monthly acetaminophen use had been documented in retrospective studies.³⁰ An opposing conclusion was raised by Schnabel et al³¹ according to the results of the LISA (Lifestyle-related Factors on the Immune System and the Development of Allergies in Childhood) study. Their analysis results provided evidence that the increased number of respiratory tract infections in children vulnerable to asthma and not the paracetamol medication per se is associated with the development of asthma. In the current study, we evaluated the response to acetaminophen using both physiologic variables and a marker of airway inflammation. Our results did not show any significant reduction in FEV₁, FEV₁/FVC, and FEF₂₅₋₇₅ percentage predicted values at 60 minutes postconsumption of a single dose of acetaminophen, suggesting that no bronchoconstriction had occurred. Given that dysfunction of small conducting airway is associated with airway inflammation in pediatric asthma,³² we chose to also evaluate FeNO in relation to acetaminophen administration. FeNO has been shown to be much more sensitive and specific than spirometry in the diagnosis of pediatric asthma.³³ Importantly, FeNO is a well-established marker of active airway inflammation in asthmatic children,^{34,35} and it correlates with airways eosinophilic inflammation and airways hyperresponsiveness.³⁶ FeNO levels increase after exposure to environmental triggers even before symptoms and spirometry indices change.³⁷ In accordance with there not having been changes in spirometry variables, the present study results did not find a significant increase in FeNO levels after the consumption of a single dose of acetaminophen in both studied groups. Since it had been shown that there is no effect of inhaled corticosteroids on airways glutathione levels,²⁷ the fact that almost all the studied children with asthma received regular treatment with inhaled corticosteroids would not be expected to affect the results. Since the study results did not indicate a significant bronchoconstriction or elevated FeNO levels, we did not measure the glutathione levels or genetic polymorphism.

There are several limitations in this study. First, the number of participating children was relatively small. Second, the children with asthma were studied for their response to a single dose during a stable phase when they were free of a viral illness. Theoretically, an acute exacerbation of asthma following one dose of acetaminophen consumption can be evoked if there is an underlying uncontrolled asthma with an already ongoing oxidative stress, and further reduction of glutathione can cause deterioration due to an ongoing respiratory infection. Hence, there is the possibility that a single dose of acetaminophen can induce asthma deterioration when another significant trigger, that is, a viral respiratory infection, is present. These limitations position this investigation as a pilot study. Nevertheless, no other controlled data exist

for the possible effects of a single dose of acetaminophen on asthma state. These unresolved issues may be answered by a similar study designed to evaluate the response to acetaminophen in asthmatic children who have a viral respiratory illness but who had not already experienced an exacerbation.

It should be noted that the recent review by McBride³⁸ concluded that acetaminophen is detrimental to children with asthma. He suggested that children diagnosed as having asthma or even at risk for asthma should avoid the use of acetaminophen altogether. The results of our study do not support this conclusion, at least for a single dose. Moreover, since acetaminophen is an inexpensive medication that is used worldwide, we do not suggest withholding a single acetaminophen administration in asthmatic children who need antipyretic or analgetic treatment. To provide more solid recommendations, especially for repeated administration of acetaminophen, and since there are major public and health implications for such recommendations, further prospective, randomized double-controlled studies are warranted.

In conclusion, one single dose of acetaminophen does not evoke bronchoconstriction or increased airway inflammation in children with asthma.

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Declaration of Conflicting Interests

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