

ORIGINAL ARTICLE

Iran J Allergy Asthma Immunol

June 2006; 5(2): 63-67

Acetaminophen Use and the Symptoms of Asthma, Allergic Rhinitis and Eczema in Children

Mehran Karimi¹, Mohsen Mirzaei², and Mohammad Hossein Ahmadi³

¹ Department of Pediatrics, School of Medicine, Shahid Sadoughi University Of Medical Sciences and Health Services, Yazd, Iran

² Health Center of Yazd Province, Shahid Sadoughi University Of Medical Sciences & Health Services, Yazd, Iran

³ Department of Statistic and Epidemiology, School of Public Health, Shahid Sadoughi University Of Medical Sciences & Health Services, Yazd, Iran

Received: 6 December 2005; Received in revised form: 21 February 2006; Accepted: 6 May 2006

ABSTRACT

Allergic diseases are frequent in children and their prevalence and severity differ in the different regions of the world. A number of studies have been performed to determine the factors which are effective in the incidence of these diseases. One of the drugs that might have a role in incidence or intensity of the symptoms of allergic diseases is Acetaminophen.

In our survey conducted with standardized method (International Study of Asthma and Allergies in Childhood), 3000 children 6-7 years old and 3000 teenagers 13-14 years old were questioned regarding asthma, allergic rhinitis and eczema.

The prevalence of ever wheezing in the children of 6-7 years old who took acetaminophen in the first year of their life was 11.3%, which is more than other group (Odds Ratio=1.54, 95% Confidence Interval: 1-2.38, P=0.049) and the prevalence of ever wheezing in older age group who have taken acetaminophen at least once in a month was 25.1% which is more than those taken less acetaminophen (OR=1.7, 95%CI=1.43-2.04, P=0.000). Moreover taking more acetaminophen during past 12 months led to more prevalence of night dry coughs and the symptoms of rhinitis in children 6-7 years old and eczema and rhinitis symptoms in the 13-14 years old.

Our findings suggest that taking more acetaminophen may be associated with increasing allergic symptoms in children.

Key words: Acetaminophen; Allergic Rhinitis; Asthma; Eczema

INTRODUCTION

Atopic diseases are among the prevalent diseases of children. Some factors such as drugs are considered

effective in incidence or intensity of the symptoms of these diseases. Acetaminophen is one of these drugs, that has been reported for 35 years causing bronchospasm in asthmatic patients.^{1,2} The mechanism of this effect maybe due to glutathione decrease, because glutathione is an antioxidant.^{3,4} Acetaminophen decreases the glutathione in liver, kidneys and lungs thus being dose dependent.^{5,6} Overdose levels of

Corresponding Author: Mehran Karimi, MD;
Department of Pediatrics, School of Medicine, Shahid Sadoughi University Of Medical Sciences & Health Services, P.O.Box: 8916657343, Yazd, Iran. Tel: (+98 351) 8246 570, Fax: (+98 351) 724 9898, E-mail: mehrankarimi1@hotmail.com

acetaminophen are cytotoxic to pneumocytes and can cause acute lung damage⁷ whereas the therapeutic doses of acetaminophen cause the glutathione level to decrease in type II pneumocytes and alveolar macrophages.⁸ When glutathione decreases, spasm in the smooth muscles of the airways and release of leukotrienes and other secondary inflammatory mediators occur, leading to bronchial hyper-responsiveness and bronchoconstriction.⁹ The purpose of our survey was to study the prevalence, severity of asthma, allergic rhinitis and eczema symptoms and to determine the variables such as acetaminophen.

PATIENTS AND METHODS

The study has been fulfilled by analytic cross sectional method in two age groups (6-7 and 13-14 years old) of Yazdi students. Cluster sampling was applied and each school was used as a cluster. Sample size was accounted by $P=4\%$ (prevalence of asthma), $\alpha=0.05$ and $d=0.01$ was 1476. Regarding to coefficient clustering and missing data, required sample size was set to 3200 in each group. Our questionnaire was designed on the basis of ISAAC (International Study of Asthma and Allergies in Childhood); then the validity and reliability of the translated questionnaire were tested. The data were first analyzed by Epi6 software

and after being controlled, it was translated into SPSS 11.5 software. The results were then analyzed by using Chi-Square, Fisher-Exact, and Anova tests.

RESULTS

From October 1, 2003, through May 10, 2004, 2768 children in the age group of 6-7 years old and 3201 children in age group of 13-14 years old were enrolled in the study.

Age Group of 6-7 Years (Table 1)

The prevalence of ever wheezing (means wheezing from birth until the time of study) in the children who took acetaminophen in the first year of life was 11.3%, which was more than others who did not use acetaminophen (OR=1.54, 95%confidence interval [CI] 1-2.38, $P=0.049$). Also the prevalence of past 12 months night dry coughs was 18.6% being more than the children not taking acetaminophen in the first year of life (OR=1.86, 95%CI=1.28-2.69, $P=0.001$). The prevalence of allergic rhinitis symptoms in those who took acetaminophen in the first year of their life was 16.2% being higher than the children not taking it ($P=0.02$, 95%CI=1.07-2.23, OR=1.55). However, regarding eczema, there was no meaningful difference between the two groups.

Table 1. Acetaminophen usage in the first year of life and during the last year of acetaminophen usage and the record of asthma and rhinitis symptoms in the children age 6-7 year olds.

Acetaminophen usage	In the first year of life				In the past 12 months			
	Yes		No		Less than once a month		At least once a month	
The record of :	No.	%	No.	%	No.	%	No.	%
Ever wheezing	270	11.3	24	7.6	87	9.3	57	10
	P value= 0.049 95% CI: 1 –2.38 OR = 1.54				P value= 0.687 95% CI: 0.76 –1.53 OR = 1.08			
Dry night coughs in the last 12 months	439	18.6	34	11	130	14.1	110	19.5
	P value = 0.001 95% CI: 1.28-2.69 OR = 1.86				P value= 0.006 95% CI: 1.12 –1.95 OR = 1.48			
Ever sneezing, runny, or blocked nose	387	16.2	35	11.1	104	11.2	94	16.3
	P value= 0.02 95% CI: 1.07 – 2.23 OR = 1.55				P value= 0.004 95% CI: 1.14-2.09 OR = 1.54			

Acetaminophen and Allergy in Children

The allergic rhinitis symptoms showed a meaningful relation with the amount of acetaminophen taken in the past 12 months so that the prevalence of these symptoms in those who had taken acetaminophen at least once in a month was 16.3% and in those who had taken this drug with longer intervals the prevalence was 11.2% (OR=1.54, 95%CI=1.14 –2.09, P=0.004).

Age Group of 13-14 Years (Table 2)

The prevalence of ever wheezing in those who had taken acetaminophen at least once in a month was 25.1% which was more than the prevalence of those taken acetaminophen with longer intervals (OR=1.7, 95%CI=1.43-2.04, P=0.000).

Positive history of asthma and allergic rhinitis symptoms from birth until the time of our study and wheezing, dry night coughs, wheezing during or after exercise and rhinoconjunctivitis during the past 12 months in the group taking more acetaminophen were more than others with a meaningful difference.

Daily activity disturbance due to rhinitis symptoms in the past 12 months was 28.3% in those consumed acetaminophen at least once in a month, which was significantly more than other group (p= 0.044). Eighteen percent of the persons taking more

acetaminophen had eczema symptoms which 67.5% of them showed these symptoms during the last year and 19.1% experienced severe sleep disturbances because of itchy rash which the differences were meaningful in all cases.

DISCUSSION

In our study, wheezing in children of 6-7 years old who had taken acetaminophen in the first year of life was more frequent. Also the prevalence of the dry coughs in the last year was more in the children taking acetaminophen in the first year of their life. Cohet and his colleagues studied 1584 children at the age of 6-7 year old and compared them with 2539 children from the society to assess the relation between infant infections, taking antibiotic and acetaminophen with increasing risk of asthma. They found that there was a relation between recently taking acetaminophen and taking this drug in the first year of life and the present of wheezing.¹²

Since paracetamol (Acetaminophen) decrease the glutathione of the lungs in the experimental animals, a lot of studies have been conducted to inspect these effects in human and its relation with asthma.

Table 2. Acetaminophen usage during the past 12 months and the symptoms of asthma, rhinitis and eczema symptoms in the children age 13-14 year olds

Acetaminophen usage in the last year	Less than once a month		At least once a month		P-value	95% CI	OR
	No.	%	No.	%			
The record of:							
Ever wheezing	274	16.4	347	25.1	0.000	1.43-2.04	1.7
wheezing in the past 12 months	128	46	195	56.2	0.012	1.1-2.07	1.5
Positive history of asthma	54	3.2	64	4.7	0.044	1.01-2.11	1.46
wheezing during or after exercise in the past 12 months	310	18.9	357	26	0.000	1.27-1.8	1.51
Dry night coughs in the past 12 months	323	19.5	398	28.9	0.000	1.42-1.99	1.68
Ever Sneezing, runny, or blocked nose	638	38	680	48.5	0.000	1.33-1.77	1.54
Sneezing, runny, or blocked nose in the past 12 months	449	70.4	500	73.4	0.219	0.91-1.48	1.16
Sneezing, runny, or blocked nose and itchy-watery eyes during the past 12 months	156	36	221	46.1	0.002	1.17– 1.99	1.52
Daily activity disturbance because of Sneezing, runny, or blocked nose in the past 12 months	93	22.4	135	28.3	0.044	1 –1.86	1.37
Ever itchy rash	203	12.2	248	18	0.000	1.3-1.94	1.59
itchy rash during the past 12 months	118	58.4	168	67.5	0.047	1- 2.17	1.47
Severe sleep disturbance because of itchy rash during the past 12 months	9	7.9	29	19.1	0.01	1.25-6.07	2.75

Since glutathione is an antioxidant in lungs which decrease the inflammation of airways, acetaminophen - related bronchospasm maybe due to the effects of this drug on glutathione.^{3,4}

Recently, a research has shown that acetaminophen used in late pregnancy (20–32 weeks), associated with an increased risk of wheezing in the offspring being at their 30–42 months of gestation but did not increase the prevalence of eczema.¹⁰

Lesko and his colleagues studied 1879 patients at the 6-12 years old suffering from asthma; they found that the risk of an outpatient visit for asthma was significantly lower in the ibuprofen group, compared with children who were randomized to acetaminophen; however, the rates of hospitalization for asthma did not vary significantly.¹¹

It seems that high acetaminophen intake in infancy especially in those who have family history of asthma or other atopic diseases increases the risk of wheezing in the childhood but this view requires more studies.

Shaheen and his colleagues studied 664 adults (16-49 years old) having asthma and determine them with 910 persons without asthma in the south of London, to compare the effect of acetaminophen and aspirin. They found that there was a direct relation between taking acetaminophen and asthma but it was not so about aspirin.¹⁰ Graham found that the risk of asthma in women with a positive history of taking acetaminophen was more than other group.⁹

In our study in the older age group who took acetaminophen at least once in a month, the symptoms of ever rhinitis, ever eczema, recent rinoconjunctivitis (during the last year) and recent eczema were more than other group and the differences was meaningful (Table 2).

Settipane and his colleagues studied 50 patients who suffered from bronchospasm or rhinosinusitis after taking aspirin and found out that the symptoms following acetaminophen use were less severe than the cases taking aspirin. Because acetaminophen is a replacement therapy in aspirin sensitive patients, it should be advised for these patients not to take acetaminophen more than 650 mg daily.¹³

Shaheen and his colleagues studied the effects of paracetamol and aspirin use in pregnancy and the risk of wheezing in their offsprings at the age of 30– 42 months (n= 9400) and eczema at 18–30 months (n=10 216). They found that frequent paracetamol use in pregnancy was not associated with an increased risk of eczema.¹⁴

McKeever and his colleagues investigated the associations between use of pain medication, particularly acetaminophen, and asthma, COPD, and FEV₁ in adults. Increased use of acetaminophen had a positive, dose-dependent association with COPD (adjusted odds ratio for increasing category of intake, 1.16; 95% confidence interval [CI], 1.09–1.24; p value for trend < 0.001) and an inverse association with lung function (daily user compared with never users, –54.0 ml; 95% CI, –90.3 to –17.7, adjusted). They confirmed a dose response association of acetaminophen use and asthma (adjusted odds ratio, 1.20; 95% CI, 1.12–1.28; p value for trend < 0.001).¹⁵

In Conclusion the result of our research showed that in children aged 6-7 years taking acetaminophen in the first year of the life follows an increase in the prevalence of asthma and allergic rhinitis symptoms. Also asthma, rhinitis and eczema symptoms in the children aged 13-14 years who took more acetaminophen during the last year were more than other group. Since acetaminophen is one of the highly used drugs in the childhood, we can not easily advise the patients not to use it and this needs more studies in this field. However in the children who have allergic diseases, they should be advised to use low dose of acetaminophen if necessary, and not to use it without physicians prescription.

ACKNOWLEDGEMENTS

We are grateful to deputy for research of Yazd Medical Science University and Health Services due to financial supporting and all the mothers and children who took part in this study. Also, thanks to Mr. Rokoe, Mrs Mobin, Mrs Rahim and the whole ISAAC study team for their cooperation and help in data collection. Also thanks goes to M.R. Mozayan for cooperation in editing the paper.

REFERENCES

1. Chafee FH, Settipane GA. Asthma caused by FD and C approved dyes. *J Allergy* 1967; 40(2):65-72.
2. Smith AP. Response of aspirin-allergic patients to challenge by some analgesics in common use. *BMJ* 1971; 2(760):494-6.
3. Jenkinson SG, Black RD, Lawrence RA. Glutathione concentrations in rat lung bronchoalveolar lavage fluid: effects of hyperoxia. *J Lab Clin Med* 1988; 112(3):345-51.

Acetaminophen and Allergy in Children

4. Smith LJ, Anderson J, Shansuddin M, Hsueh W. Effect of fasting on hyperoxic lung injury in mice: the role of glutathione. *Am Rev Respir Dis* 1990; 141(1):141-9.
5. Chen TS, Richie JPJ, Lang CA. Life span profiles of glutathione and paracetamol detoxification. *Drug Metab Dispos* 1990; 18(6):882-7.
6. Micheli L, Cerretani D, Fiaschi AI, Giorgi G, Romeo MR, Runci FM. Effect of paracetamol on glutathione levels in rat testis and lung. *Environ Health Perspect* 1994; 102(Suppl 9):63-4.
7. Baudouin SV, Howdle P, O'Grady JG, Webster NR. Acute lung injury in fulminant hepatic failure following paracetamol poisoning. *Thorax* 1995; 50(4):399-402.
8. Dimova S, Hoet PH, Nemery B. Paracetamol (acetaminophen) cytotoxicity in rat type II pneumocytes and alveolar macrophages in vitro. *Biochem Pharmacol* 2000; 59(11):1467-75.
9. Barr RG, Wentowski CC, Curhan GC, Somers SC, Stampfer MJ, Schwartz J, et al. Prospective study of acetaminophen use and newly diagnosed asthma among women. *Am J Res Crit Care Med* 2004; 169(7):836-41.
10. Shaheen SO, Sterne JAC, Songhurst CE, Burney PGJ. Frequent paracetamol use and asthma in adults. *Thorax* 2000; 55(4):266-70.
11. Lesko SM, Louik C, Vezina RM, Mitchell AA. Asthma morbidity after the short-term use of ibuprofen in children. *Pediatrics* 2002; 109(2):E20.
12. Cohet C, Cheng S, MacDonald C, Baker M, Foliaki S, Huntington N, et al. Infections, medication use, and the prevalence of symptoms of asthma, rhinitis, and eczema in childhood. *J Epidemiol Commun Health* 2004; 58(10):852-7.
13. Settupane RA, Schrank PJ, Simon RA, Mathison DA, Christiansen SC, Stevenson DD. Prevalence of cross sensitivity with acetaminophen in aspirin-sensitive asthmatic subjects. *J Allergy Clin Immunol* 1995; 96(4):480-5.
14. Shaheen SO, Newson RB, Sherriff A, Henderson AJ, Heron JE, Burney PGJ, et al. Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002; 57(11):958-63.
15. McKeever TM, Lewis SA, Smit HA, Burney P, Britton JR, Cassano PA. The association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function. *Am J Res Crit Care Med* 2005; 171(9):966-71.