Original Article

A Mexican Population-Based Study on Exposure to Paracetamol and the Risk of Wheezing, Rhinitis, and Eczema in Childhood

MM Barragán-Meijueiro,[1] B Morfín-Maciel,[1] AA Nava-Ocampo[2]

[1]Colegio Mexicano de Pediatras con Especialidad en Alergia e Inmunología Clínica, Coyoacan, Mexico
[2]Division of Clinical Pharmacology & Toxicology, The Hospital for Sick Children, Toronto, Ontario, Canada

Abstract. *Background:* There is some evidence suggesting a link between paracetamol exposure and atopy in both adults and children.
Objective: We aimed to investigate whether further epidemiological support for a link between paracetamol intake and allergy could be found in a population of Mexican children.
Methods: In a cross-sectional study design, we applied the ISAAC questionnaire to 3493 children aged 6 to 7 years old. Two analyses were performed: 1) children were classified as cases if they had wheezing, rhinitis, or eczema at any time from their neonatal period up until they reached the age of 6 to 7 years, or as controls if they had never experienced these conditions, and 2) children were classified as cases if they had wheezing, rhinitis, or eczema in the 12 months prior to the study. Paracetamol intake was considered positive if it frequently occurred during the first year of life (first analysis) or in the last 12 months (second analysis).
Results: Paracetamol intake in the first year of life was significantly associated with an increased risk of ever having wheezing (adjusted odds ratio [OR], 1.69; 95% confidence interval [CI], 1.23 to 2.34) and rhinitis (adjusted OR, 1.37; 95% CI, 1.20 to 1.59) but not eczema (adjusted OR, 1.45; 9% CI, 0.91 to 2.32). Frequent paracetamol intake in the last year increased the risk of wheezing (OR, 3.3; 95% CI, 1.54 to 7.18), rhinitis (OR, 1.61; 95% CI, 1.33 to 1.95), or eczema (OR, 1.82; 95% CI, 1.24 to 2.66).
Conclusion: Frequent paracetamol exposure was associated with a significantly increased risk of wheezing and rhinitis and probably eczema in a Mexican population of children.

Key words: Asthma. Eczema. Acetaminophen. Paracetamol.

Resumen. *Antecedentes:* Existe evidencia que asocia el uso de paracetamol y atopia tanto en adultos como en niños.
Objetivo: Investigar la existencia de evidencia epidemiológica que asociara la ingesta de paracetamol y la presencia de alergias en niños Mexicanos.
Métodos: Mediante un estudio de corte transversal, aplicamos el cuestionario ISAAC a 3493 niños de 6-7 años de edad. Se realizaron dos tipos de análisis: 1) los niños se clasificaron como casos si tenían antecedentes de sibilancias, rinitis o eccema en cualquier momento desde su nacimiento hasta la edad de 6-7 años, o como "controles" si nunca presentaron esta sintomatología, 2) los niños se clasificaron como casos si presentaron sibilancias, rinitis o eccema en los 12 meses previos al estudio. El consumo de paracetamol se consideró como positivo si ocurrió en forma frecuente durante el primer año de vida (análisis 1) o en los últimos 12 meses (análisis 2).
Resultados: El uso de paracetamol en el primer año de vida incrementó en forma significativa el riesgo de presentar alguna vez sibilancias (*odds ratio* [OR] ajustado, 1.69:95% límites de confianza [CI], 1.23 a 2.34) y rinitis [OR ajustado, 1.37; 95% CI, 1.20 a 1.59) pero no de eccema (OR ajustado, 1.45; 95% CI, 0.91 a 2.32). El uso frecuente de paracetamol en el ultimo año de vida incrementó el riesgo de sibilancias (OR, 3.3; 95% CI 1.54 a 7.18), rinitis (OR, 1.61; 95% CI, 1.33 a 1.95), o eccema (OR, 1.82; 95% CI, 1.24 a 2.66).
Conclusión: El uso frecuente de paracetamol estuvo asociado a un riesgo significativamente mayor de sibilancias y rinitis, y probablemente de eccema, en una población de niños Mexicanos.

Palabras claves: Asma bronquial. Dermatitis eccematosa. Acetaminofén. Paracetamol.

Introduction

There is extensive evidence of the relationship between allergic disorders such as asthma, rhinitis, and eczema and oxidative stress. Inflammatory cells such as eosinophils, neutrophils, and macrophages produce reactive oxygen species that can cause epithelial damage and increase inflammation by reducing natural antioxidant defenses, and this may contribute to the pathogenesis of allergic diseases [1-3]. Additionally, a number of drugs and toxins produce free radicals during their metabolism, and these may also deplete physiological antioxidant defenses [4]. Paracetamol is an analgesic and antipyretic drug that inhibits the activity of cyclooxygenases 1 and 2. A large fraction (60 %) of this drug is bound to glucuronic acid, whereas a small fraction undergoes an N-hydroxylation mediated by cytochrome P450 to form N-acetyl-benzoquinone-imine, which can react with glutathione (GSH), a tripeptide that regulates intracellular redox and other aspects of cell physiology [4, 5]. The paracetamol–dose-dependent depletion of GSH occurs not only in the liver but also in the lung [6].

In a case–control study of dietary antioxidants and asthma in adulthood, the use of paracetamol was positively associated with asthma and rhinitis [7]. This association was stronger in cases with more severe asthma. In addition, an ecological analysis showed a positive association between paracetamol sales and prevalence of atopic diseases in children across centers in European countries participating in the International Study of Asthma and Allergy in Children (ISAAC) [8]. In order to provide more epidemiological support for the link between paracetamol intake and allergy, we have studied the association between wheezing, rhinitis, or eczema and a history of frequent exposure to paracetamol in a group of Mexican children.

Material and Methods

Study Design

The study was approved by the Institutional Review Board of the Secretaría de Educación Pública in Mexico, and parental informed consent to participate in the study was obtained for eligible children. The study was performed by applying the standardized ISAAC questionnaire in its Spanish version, to a sample of public elementary schools located in the southern part of Mexico City. The sample size of at least 3000 children was stipulated by ISAAC in Auckland, New Zealand. This sample gave the study a 99% power to detect differences between centers in prevalence of wheezing of 30% versus 25% at a 1% level of significance (ISAAC Manual, methods: http://isaac.auckland.ac.nz). Based on the number of students and the total population in the counties of Tlalpan, Milpa Alta and Xochimilco, 41 schools were selected by means of a computer-generated list of random numbers. From every school, 90 to 100 children aged 6 to 7 years old were randomly selected by a similar computerized procedure. During a 2-month period, the questionnaires were provided to parents to be answered at home over a period no longer than 2 weeks. During this period parents were reminded to return the questionnaires every other day. The classification of whether or not children were frequently exposed to paracetamol was based on questions asking about that point; the drug's name was followed by several of its popular brand names by way of example. Any questions about the terms used in the questionnaires were referred to 2 of the investigators (MMB-M and BM-M). However, according to the ISAAC survey procedure, whether children had wheezing, rhinitis, or eczema was decided by the parents, who did not receive information on the definitions of these terms.

Relationship Between Exposure to Paracetamol and Wheezing, Rhinitis, or Eczema

The relationship between exposure to paracetamol and risk of wheezing, rhinitis, or eczema was analyzed in 2 different ways. First, children were grouped as cases if they ever had wheezing, rhinitis, or eczema at any time from their neonatal period through the age of 6 to 7 years, or as controls if they did not have symptoms during this period of life. Frequent intake of paracetamol was considered as positive if the parents recalled that their child frequently received this drug during his/her first year of life. The frequent use of antibiotics by children during the same period of time was included in the analysis as a potential major confounder. For the second analysis, children were grouped as cases if they had wheezing, rhinitis, or eczema in the 12 months prior to the study. Frequent exposure to paracetamol was considered as positive if the children had frequently received this drug during that time period. Thus, there was a group of children who had never had symptoms and another group of children who did not have symptoms in the last 12 months.

Data Analysis

As mentioned above, 2 groups were analyzed: children who ever had wheezing, rhinitis, or eczema and those who had these symptoms in the 12 months prior to the study. Each group had its corresponding controls. The children's age (years), weight (kg) and height (cm) were summarized as mean ± SD and were compared between cases and controls with a Student *t* test. The numbers of male and female children were summarized as percentages and were compared between groups with a χ^2 test. The number of children who ever had wheezing, rhinitis, or eczema and were exposed to paracetamol in their first year of life was compared to the number of controls exposed to paracetamol in the same period of life with a

χ^2 test and the odds ratio (OR) and 95 % confidence interval (CI) were estimated. Similar procedures were performed with children who had wheezing, rhinitis, or eczema and were exposed to antibiotics in the same period of time. When differences in the number of children exposed to paracetamol were observed between cases and controls, a logistic regression analysis including exposure to both paracetamol and antibiotics (predictor variables) was performed.

For the second analysis, the number of children who had wheezing, rhinitis, or eczema in the last 12 months and were frequently exposed to paracetamol was compared to the number of controls exposed to this drug with a χ^2 test and the OR and 95% CI were estimated.

Descriptive statistics were obtained with Epi Info v 3.3.2 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA). The statistical analyses were performed with StatsDirect v 2.4.1 (StatsDirect Ltd., Cheshire, United Kingdom). A 2-sided test was used and $P < .05$ was considered as the limit of statistical significance.

Results

Of 3600 questionnaires, 97% (n = 3493) were returned and analyzed. The age, weight, and height of children included in either of the 2 analyses averaged approximately 6.5 years, 23 kg, and 120 cm, respectively. In the group of children who ever had wheezing, rhinitis, or eczema (Table 1), the percentage of male children was approximately 10% higher in the group of cases who never had wheezing, a differences that was significant ($P < .01$). However, we observed no significant differences between these cases and controls in relation to children's age, weight, or height. Similarly, there were no significant differences in the number of male children or in the children's age, height, and weight between cases who ever had rhinitis or eczema and their corresponding controls. In the analysis of children who had wheezing, rhinitis, or eczema in the last year, we observed no significant difference in any of the demographic variables between cases and controls (Table 2).

Paracetamol intake during the first year of life was approximately 20% more frequent in children who ever had wheezing, 10 % more in children who ever had rhinitis, and 13 % more in those who ever had eczema (Table 3). The ORs were 2.09, 1.54, and 1.68, respectively ($P < .001$). In addition, antibiotic intake within the first year of life was approximately 18 % more frequent in children who ever had wheezing, 10 % more in children who ever had rhinitis ($P < .0001$, both factors), and 5 % more in those who ever had eczema ($P > .05$) (Table 3). The OR was respectively 2.47, 1.60, and 1.25. According to the logistic regression analysis, frequent paracetamol and antibiotic intake in the first year of life were risk factors for ever having wheezing and rhinitis even when the analysis for ever wheezing was adjusted for sex (Table 4). In contrast, frequent paracetamol and antibiotic intake in the first year of life was ruled out as risk factors for eczema.

Finally, exposure to paracetamol in the last year was

Table 1. Demographic Data of Children Included in the Analysis of Children Ever Having Wheezing, Rhinitis, or Eczema*

	Cases	Controls	95% CI for the Difference†
Ever had wheezing, n	192	3290	
Sex, M;F	59.4 %;40.6 %	48.7 %;51.3 %	3.5% to 17.9 %
Age, y	6.4 ± 0.5	6.4 ± 0.5	– 0.07 to 0.07
Weight, kg	23.5 ± 5.0	23.6 ± 4.6	– 0.8 to 0.6
Height, cm	120.3 ± 80.7	119.6 ± 71.0	– 9.71 to 11.1
Ever had rhinitis, n	1724	1762	
Sex, M;F	49.9 %;50.1 %	48.8 %;51.2 %	– 2.2% to 4.4 %
Age, y	6.5 ± 0.5	6.5 ± 0.5	– 0.03 to 0.03
Weight, kg	23.5 ± 4.7	23.7 ± 4.6	– 0.5 to 0.1
Height, cm	119.5 ± 73.8	119.7 ± 69.2	– 5.0 to 4.6
Ever had eczema, n	342	3150	
Sex, M;F	48.0 %;52.0 %	49.5 %;50.5 %	– 7.1% to 4.1 %
Age, y	6.5 ± 0.5	6.5 ± 0.5	– 0.06 to 0.06
Weight, kg	23.8 ± 4.8	23.6 ± 4.6	– 0.3 to 0.7
Height, cm	119.7 ± 81.1	119.6 ±– 70.4	– 7.9 to 8.1

* Controls were children who had never had wheezing, rhinitis, or eczema, and cases were children who had had those conditions. CI indicates confidence interval. Values are mean ± SD, or percentages.
† The percentage of male children was approximately 10% higher in the group of cases who had ever had wheezing ($P < .01$; χ^2).The other differences were not significant (comparisons: Student *t* test for means, χ^2 for percentages).

Table 2. Demographic Data of Children Included in the Analysis of Having Wheezing, Rhinitis, or Eczema in the Last 12 Months*

	Cases	Controls	95% CI for the Difference†
Wheezing in the last year, n	126	3047	
Sex, M:F	54.0%:46.0%	49.6%:50.4%	−4.5% to 13.3%
Age, y	6.5 ± 0.5	6.5 ± 0.5	−0.09 to 0.09
Weight, kg	23.7 ± 4.8	23.5 ± 4.6	−0.6 to 1.0
Height, cm	120.8 ± 62.6	119.6 ± 71.2	−11.4 to 13.8
Rhinitis in the last year, n	1729	1548	
Sex, M:F	49.9%:50.1%	49.1%:50.9%	−2.6% to 4.2%
Age, y	6.4 ± 0.5	6.4 ± 0.5	−0.03 to 0.03
Weight, kg	23.5 ± 4.7	23.6 ± 4.6	−0.42 to 0.22
Height, cm	119.6 ± 73.1	119.6 ± 70.2	−4.9 to 4.9
Eczema in the last year, n	313	2786	
Sex, M:F	48.6%:51.4%	49.0%:51.0%	−6.2% to 5.4%
Age, y	6.5 ± 0.5	6.5 ± 0.5	−0.06 to 0.06
Weight, kg	23.8 ± 5.0	23.5 ± 4.6	−0.24 to 0.84
Height, cm	119.8 ± 78.0	119.6 ± 70.4	−8.1 to 8.5

* Controls were children who did not have wheezing, rhinitis, or eczema in the year previous to the study, and cases were children who had had those conditions in that period. CI indicates confidence interval. Values are mean ± SD, or percentages.
† Differences in comparisons were not significant (Student *t* test for means, χ^2 for percentages).

Table 3. Frequent Paracetamol and Antibiotics Intake in the First Year of Life as Risk Factors for Ever Having Wheezing, Rhinitis, or Eczema in Childhood*

	Cases	Controls	OR (95% CI)
Wheezing, n	192	3290	
Exposed to paracetamol	64.6%	46.6%	2.09 (1.54 to 2.83)
Exposed to antibiotics	79.5%	61.1%	2.47 (1.72 to 3.53)
Rhinitis, n	1724	1762	
Exposed to paracetamol	53.1%	42.2%	1.54 (1.35 to 1.77)
Exposed to antibiotics	67.7%	56.6%	1.60 (1.39 to 1.84)
Eczema, n	342	3150	
Exposed to paracetamol	59.1%	46.3%	1.68 (1.33 to 2.10)
Exposed to antibiotics	66.6%	61.6%	1.24 (0.98 to 1.57)

*All comparisons between controls and cases were significant at $P < .0001$ (χ^2 test), except for exposure to antibiotics and risk of eczema. Controls were children 6-7 years old who had never had wheezing, rhinitis, or eczema and cases were children 6-7 years old who had had those conditions. OR indicates odds ratio; CI, confidence interval.

Table 4. Logistic Regression Analysis of Frequent Paracetamol and Antibiotics Exposure in the First Year of Life as Risk Factors for Ever Suffering From Wheeze, Rhinitis, or Eczema*

	OR (95% CI)		
	Paracetamol, X_1	Antibiotics X_2	Logit Y
Ever had wheezing	1.68 (1.22 to 2.32)	2.03 (1.39 to 2.96)	$-3.6 + 0.5\ X_1 + 0.7\ X_2$
Ever had wheezing (sex-adjusted)	1.69 (1.23 to 2.34)	2.02 (1.38 to 2.95)	$-3.9 + 0.4$ Sex $+ 0.5\ X_1 + 0.7\ X_2$
Ever had rhinitis	1.37 (1.20 to 1.59)	1.41 (1.21 to 1.63)	$-0.4 + 0.3\ X_1 + 0.34\ X_2$
Ever had eczema	1.45 (0.91 to 2.32)	1.53 (0.91 to 2.59)	NA

* OR indicates odds ratio; CI, confidence interval; NA, not applicable due to the lack of statistical significance in the ORs of paracetamol and antibiotics. The ORs for wheezing and rhinitis were significant at a level of $P < .0025$ (χ^2 test). In the logistic regression analysis (Logit Y), X_1 indicates the exposure to paracetamol; X_2, the exposure to antibiotics.

Table 5. Recent Intake of Paracetamol as a Risk Factor for Having Wheezing, Rhinitis, or Eczema in the Last Year*

	Cases	Controls	OR (95% CI)
Wheezing, n	125	3009	
Exposed to paracetamol	94.6%	83.5%†	3.33 (1.54 to 7.18)
Rhinitis, n	1614	1527	
Exposed to paracetamol	87.3%	80.9‡	1.61 (1.33 to 1.95)
Eczema, n	312	2752	
Exposed to paracetamol	90.1%	83.3%†	1.81 (1.24 to 2.66)

* OR indicates odds ratio; CI, confidence interval. Controls were children aged 6-7 years who did not have wheezing, rhinitis, or eczema in the year prior to the study, and cases were children aged 6-7 years who had had those conditions and were exposed to paracetamol in the same period of time.
†$P < .05$ (χ^2 test); ‡$P < .001$. (χ^2 test)

approximately 10% more frequent among cases of children who had wheezing in the same period of time and 7% more in children who had rhinitis or eczema.

Discussion

In this study, frequent paracetamol intake in the first year of life was associated with an increased risk for ever having wheezing or rhinitis in children aged 6 to 7 years old. Similar results were observed for frequent paracetamol use in the year prior to the study and risk of wheezing, rhinitis, or eczema in the same period of time. The airways contain antioxidants which may protect epithelial lining against oxidative stress, limiting the degree of airway inflammation [1]. Some pro-inflammatory cytokines (interleukin 1ß and tumor necrosis factor α) which are elevated in asthma can enhance the transvascular passage of paracetamol across endothelial cells at sites of tissue inflammation [9]. Furthermore, paracetamol can deplete GSH content in alveolar macrophages and type 2 pneumocytes in both rodents and humans [10, 11]. However, it is unknown whether paracetamol alters clinical course for patients with allergic diseases through GSH depletion.

Recall bias by parents participating in the study about whether their children were frequently exposed to paracetamol and antibiotics in their first year of life was probably the major limitation of the study. However, the association between frequent use of paracetamol and wheezing and rhinitis was confirmed when exposure to this drug frequently occurred in the last year. Other possible sources of bias also need to be considered. Over the past 2 decades, the prescriptions for acetylsalicylic acid in children were redirected to paracetamol due to the association between exposure to the former and Reye's syndrome in this population. Therefore, paracetamol is now being widely prescribed to pediatric patients [12, 13]. Allergic patients often have associated upper airway infections (eg, sinusitis, otitis, etc) [14, 15] that may increase paracetamol and antibiotic use, overestimating the association between these drugs and allergic symptoms. In fact, a retrospective study in adults receiving antibiotics within the first 5 years of life found that the relationship between antibiotic intake and asthma could be explained by a "reverse causation," the tendency for prescriptions to be written for early manifestations of pre-existing asthma [16].

In relation to the link between frequent antibiotic intake in the first year of life and risk of allergic symptoms, according to the "hygiene hypothesis," exposure to microbes or their products (eg, endotoxin) in early life may decrease the subsequent risk of asthma and other allergic diseases [17]. Then, frequent exposure to antibiotics may limit the benefits of exposure to microbes. Two recent studies also found that administration of antibiotics or paracetamol in the first year of life is associated with an increased risk of atopy in children [18, 19]. In contrast, a study in children with parental history of atopy who were monitored from birth to the age of 5 years did not find this association [20]. Furthermore, the pooled results of the ISAAC Phase I Study Group were not consistent with the hypothesis that antibiotic use may increase the risk of asthma, rhinitis, or eczema; nor did those results explain the differences in the prevalence of asthma across different populations of children [21]. Unfortunately, the ISAAC questionnaire was designed to obtain information about exposure to antibiotics in the first year of life only. Therefore, we were not able to verify whether recent exposure to antibiotics was also linked to a risk for having wheezing or rhinitis in the last year.

The ISAAC questionnaire assumes that if the children had wheezing, rhinitis, or eczema, their parents should know the terms and should be able to answer the questions related to those symptoms. If parents are not sure about whether their child had experienced any of these diseases or exposures, then the questions were to be left unanswered. Although this may be correct for those children who already had the diagnosis, it would be difficult to identify those children in whom the diagnosis was not yet established at the time of the study. However, this would more likely alter the analysis by decreasing the estimated OR rather than by increasing it. In addition, the questionnaire provided no information that could allow us to discern a dose-response relationship or to know how often the children were exposed to paracetamol or to antibiotics.

In conclusion, despite the limitations of the study design, we found that a history of paracetamol and antibiotics intake in the first year of life was associated

with a significant risk of ever having wheezing and rhinitis in childhood. Recent intake of paracetamol was also linked to a risk of recent wheezing, rhinitis, and eczema. These results in a Mexican population of children support previous evidence on these associations in other populations and therefore the potential risks when prescribing paracetamol to children who are at risk or already have allergic diseases should be considered.

Acknowledgments

This study was partially supported by Astra-Zeneca, Mexico. Part of the study was presented, and published as an abstract, at the American Academy of Allergy, Asthma and Immunology Annual Meeting 2004, San Francisco, California, USA.

Alejandro A Nava-Ocampo is a member of the Sistema Nacional de Investigadores and was recipient of the award "Dr Rafael Ramos Galván" from the Sociedad Mexicana de Pediatría, AC, (April 29, 2006, Mexico DF) in Mexico. The opinion expressed by the authors in the manuscript cannot be ascribed to the Colegio Mexicano de Pediatras con Especialidad en Alergia e Inmunología Clínica or to the Secretaría de Educación Pública in Mexico.

References

1. Kanazawa H, Kurihara N, Hirata K, Takeda T. The role of free radicals in airway obstruction in asthmatic patients. Chest. 1991;100:1319-22.
2. Bowler RP, Crapo JD. Oxidative stress in allergic respiratory diseases. J Allergy Clin Immunol. 2002;110:349-56.
3. Polla BS, Ezekowitz RA, Leung DY. Monocytes from patients with atopic dermatitis are primed for superoxide production. J Allergy Clin Immunol. 1992;89:545-51.
4. Maddrey WC. Drug-induced hepatotoxicity: 2005. J Clin Gastroenterol. 2005;39(Suppl 2):s83-9.
5. Villa-Caballero L, Nava-Ocampo AA, Frati-Munari AC, Ponce-Monter H. Oxidative stress. Should it be measured in the diabetic patient? Gac Med Mex. 2000;136:249-56.
6. Chen TS, Richie JP, Lang CA. Life span profiles of glutathione and acetaminophen detoxification. Drug Metab Dispos. 1990;18:882-7.
7. Shaheen SO, Sterne JA, Songhurst CE, Burney PG. Frequent paracetamol use and asthma in adults. Thorax. 2000;55:266-70.
8. Newson RB, Shaheen SO, Chinn S, Burney PG. Paracetamol sales and atopic disease in children and adults: an ecological analysis. Eur Respir J. 2000;16:817-23.
9. Bohlin K, Cotgreave IA. Pro-inflammatory cytokines increase the permeability of paracetamol across a human endothelial-smooth muscle cell bilayer model. Scand J Clin Lab Invest. 1999;59:259-66.
10. Dimova S, Hoet PH, Nemery B. Paracetamol (acetaminophen) cytotoxicity in rat type II pneumocytes and alveolar macrophages in vitro. Biochem Pharmacol. 2000;59:1467-75.
11. Smith LJ, Houston M Anderson J. Increased levels of glutathione in bronchoalveolar lavage fluid from patients with asthma. Am Rev Respir Dis. 1993;147:1461-4.
12. Rahwan GL, Rahwan RG. Aspirin and Reye's syndrome: the change in prescribing habits of health professionals. Drug Intell Clin Pharm. 1986;20:143-5.
13. Velazquez-Armenta Y, Nava-Ocampo AA. Is pharmacy dispensing information useful to identify problems with analgesic prescribing in children? Paed Perinatal Drug Ther. 2003;5:135-8.
14. Lemanske RF Jr. Is asthma an infectious disease? Thomas A. Neff lecture. Chest. 2003;123(Suppl):385s-90s.
15. Steele RW. Chronic sinusitis in children. Clin Pediatr (Phila). 2005;44:465-71.
16. Cullinan P, Harris J, Mills P, Moffat S, White C, Figg J, Moon A, Newman Taylor AJ. Early prescriptions of antibiotics and the risk of allergic disease in adults: a cohort study. Thorax. 2004;59:11-5.
17. Douwes J, Le Gros G, Gibson P, Pearce N. Can bacterial endotoxin exposure reverse atopy and atopic disease? J Allergy Clin Immunol. 2004;114:1051-4.
18. Cohet C, Cheng S, MacDonald C, Baker M, Foliaki S, Huntington N, Douwes J, Pearce N. Infections, medication use, and the prevalence of symptoms of asthma, rhinitis, and eczema in childhood. J Epidemiol Community Health. 2004;58:852-7.
19. Johnson CC, Ownby DR, Alford SH, Havstad SL, Williams LK, Zoratti EM, Peterson EL, Joseph CL. Antibiotic exposure in early infancy and risk for childhood atopy. J Allergy Clin Immunol. 2005;115:1218-24.
20. Celedon JC, Litonjua AA, Ryan L, Weiss ST, Gold DR. Lack of association between antibiotic use in the first year of life and asthma, allergic rhinitis, or eczema at age 5 years. Am J Respir Crit Care Med. 2002;166:72-5.
21. Foliaki S, Nielsen SK, Bjorksten B, Von Mutius E, Cheng S, Pearce N, ISAAC Phase I Study Group. Antibiotic sales and the prevalence of symptoms of asthma, rhinitis, and eczema: the International Study of Asthma and Allergies in Childhood (ISAAC). Int J Epidemiol. 2004;33:558-63.

Dr María de las Mercedes Barragán-Meijueiro

Colegio Mexicano de Pediatras con
Especialidad en Alergia e Inmunología Clínica
Paris Nº 227, Colonia Del Carmen
Coyoacán, México DF 04100, México
E-mail: mercedes_barragan@yahoo.com.mx