ORIGINAL ARTICLE

Study of the Relationship Between Acetaminophen and Asthma in Mexican Children Aged 6 to 7 Years in 3 Mexican Cities Using ISAAC Methodology

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Abstract

Objective: To establish the relationship between the use of acetaminophen and the frequency of asthma in Mexican children in 3 Mexican cities.
Methods: Ours was a multicenter, observational, descriptive, cross-sectional study. Patients from 6 to 7 years of age participating in Phase Three B of the ISAAC (International Study of Asthma and Allergies in Children) living in the north of Mexico City, Victoria City, and Merida were included. After adjusting for confounders, we calculated the odds ratios (OR) for the presence of wheezing ever, wheezing in the last 12 months, asthma ever, and the use of acetaminophen in the first year of life and during the last 12 months.
Results: The ORs for wheezing ever, wheezing in the last year, and asthma ever with respect to use of acetaminophen in the first year of life were not statistically significant (*P*>.05) in Mexico City, but they were significant in Victoria City (*P*<.05) and Merida (*P*<.05). The ORs (95% confidence intervals) for wheezing ever, wheezing in the last year, and asthma ever with respect to use of acetaminophen in the last year were 3.44 (2.96-4.0), 7.97 (5.89-10.78), and 6.10 (3.30-8.81) (*P*<.05) in Mexico City. Values for Victoria City were 1.36 (1.13-1.63), 3.80 (2.88-5.05), and 2.18 (1.57-3.01) (*P*<.05). Those for Merida were 1.61 (1.40-1.85), 2.07 (1.73-2.48), and 1.53 (1.29-1.82) (*P*<.05).
Conclusion: The use of acetaminophen is associated with the presence of wheezing and asthma in 3 different cities in Mexico.

Key words: Asthma. Acetaminophen. ISAAC. Mexico.

Resumen

Objetivo: establecer la relación entre el uso de acetaminofen y la frecuencia de asma en niños mejicanos en tres ciudades mejicanas.
Métodos: Fue un estudio multicéntrico, observacional, descriptivo, en la fase 3b del ISAAC, en niños que vivían en el área norte del Distrito Federal, Ciudad Victoria, Tamaulipas y la ciudad de Mérida, Yucatán. Después de ajustar se calculó la razón de momios (OR) para la presencia de sibilancias alguna vez, sibilancias en los últimos 12 meses y asma alguna vez y el uso de acetaminofen en el primer año de vida y durante los últimos 12 meses.
Resultados: OR para sibilancias alguna vez, sibilancia en el último año y sibilancias alguna vez respecto al uso de acetaminofen en el primer año de vida no fueron estadísticamente significativos (*P*>0,05) en la Ciudad de Méjico, pero significativa en Ciudad Victoria (*P*<0,05) y Mérida (*P*<0.05). OR para sibilancias alguna vez, sibilancia en el último año y sibilancias alguna vez respecto al uso de acetaminofen en el último año fueron 3,44 (2,96; 4,0), 7,97 (5,89; 10,78), y 6,10 (3,30; 8,81) (*P*<0,05) en Ciudad Méjico. Los valores para Ciudad Victoria fueron 1,36 (1,13; 1,63), 3,80 (2,88; 5,05), y 2,18 (1,57; 3,01) (*P*<0,05). Los de Mérida fueron 1,61 (1,40; 1,85), 2,07 (1,73; 2,48), y 1,53 (1,29; 1,82) (*P*<0,05).
Conclusión: el uso de acetaminofen se asocia a la presencia de sibilancias y asma en tres diferentes ciudades de Méjico.

Palabras clave: Asma. Acetaminofen. ISAAC. Méjico.

Introduction

In recent years, the prevalence of asthma in adults has stabilized or decreased, but this phenomenon is not clear in children [1]. The prevalence of asthma in children aged 6 to 7 years ranged from 5.7% to 6.7% in Mexico according to the International Study of Asthma and Allergies in Childhood (ISAAC) [2,3]. Many factors have been related to asthma [4-11], including the consumption of acetaminophen [12-16].

Acetaminophen decreases levels of glutathione, mainly in the liver, but also in the kidneys and lungs [17]. This decrease is dose-dependent. High doses of acetaminophen are cytotoxic for pneumocytes and may cause acute lung damage [18]. In rats, therapeutic doses of acetaminophen produce decreases in glutathione levels in type II pneumocytes and alveolar macrophages [19].

In the present study, we explore the effect of acetaminophen on the manifestations of asthma in 3 different populations in Mexico after adjusting for associated factors.

Patients and Methods

Ours was a multicenter, observational, descriptive, comparative, and cross-sectional survey that included patients aged 6 to 7 years who participated in Phase Three B of ISAAC in Mexico. We considered 3 areas; North Mexico City (including the city precincts of Azcapotzalco, Gustavo A Madero, Miguel Hidalgo, and Venustiano Carranza); Victoria City, in the state of Tamaulipas; and Merida, in the state of Yucatan.

The list of the elementary schools was obtained from the Public Education Program, as was the number of children registered in each area. The number of children aged 6 to 7 years was obtained from the 2000 national census.

According to the specifications of ISAAC, the sample size for each survey center was 3000 children aged 6 to 7 years. The number of schools was determined based on the school population and a nonresponse rate of 20%. The sampling unit was the school, and primary schools were randomly selected in each area. Children in first and second grade (6-7 years) in the selected schools and their parents were invited to participate. Parents gave written informed consent and children gave oral consent for their participation.

The study was approved by the Clinical Investigation Ethics Committee of the Hospital Infantil de México Federico Gómez. The ISAAC questionnaire used corresponds to Phase One and covers the prevalence of symptoms of asthma, rhinitis, atopic dermatitis, participant environment, diet, and background. The Spanish-language version of the questionnaire was validated by the coordinator for Latin America and has been used in other studies [20,21]. The questions on acetaminophen use are shown in the Appendix in English and Spanish.

The centers were analyzed individually to look for differences between the cities, as preliminary reports showed differences in asthma prevalence between the cities. The odds ratios (ORs) for wheezing ever, wheezing in the last year, asthma ever, use of acetaminophen during the first year of life, and use of acetaminophen during the last year were calculated before and after adjustment for confounders such as gender, antibiotic use during the first year of life, contact with farm animals during pregnancy, current maternal smoking, and use of acetaminophen during the first year of life or in the last year. Covariates were selected based on previous analyses of the survey databases as the possible factors involved in the prevalence of asthma [22-28]. Additionally, logistic regression was used to calculate the ORs for wheezing in the last year, asthma ever, use of acetaminophen during the first year of life, and use of acetaminophen in the context of other confounders such as use of antibiotics in the first year of life, contact with farm animals during the first year of life, contact with farm animals during pregnancy, current maternal smoking, older siblings, younger siblings, breast feeding, smokers at home, cat in the first year of life, cat in the last year, dog in the first year of life, and dog during the last year.

Results

In the 4 northern precincts of Mexico City, there were 2098 boys and 2008 girls, corresponding to 3.4% of the total population of 6- to 7-year-olds in the area. Forty-seven schools out of 50 agreed to participate and the rate of response to the survey was 97.1%.

In Victoria City, 1261 boys and 1341 girls corresponding to 4.4% of the total population of this age in the area were included. All 47 invited schools agreed to participate with a survey response rate of 91%.

In Merida, 1483 boys and 1413 girls corresponding to 4.0% of the total population of that age in the area were included. All 24 invited schools agreed to participate and the rate of response to the survey was 98%.

The prevalence of wheezing ever, wheezing in the last 12 months, and asthma ever were, respectively, as follows: 19.4%, 7.3%, and 4.7% in Mexico City (n=4106); 17.7%, 8.6%, and 4.8% in Victoria City (n=2602); and 26.6%, 12.7, and 12.5% in Merida (n=2896).

The ORs for wheezing ever, wheezing in the last year, and asthma ever caused by acetaminophen during the first year of life or during the last year using unadjusted and adjusted databases are shown in Figures 1 and 2. When the ORs were adjusted for acetaminophen use in the first year of life, the range of the confidence intervals also decreased; the values for Mexico City were not statistically significant after adjustment. As for the ORs with acetaminophen during the last year, the range of the confidence intervals decreased after adjustment in all 4 precincts. However, these values decreased for Victoria City and Merida.

Using logistic regression, diverse confounders were taken into account to obtain ORs for wheezing ever, wheezing in the last year, and asthma ever with the use of acetaminophen (see Table 1 for Mexico City, Table 2 for Victoria City, and Table 3 for Merida). In all 3 cities, wheezing ever was related to the use of acetaminophen during the first year of life and last year, whereas wheezing in the last year and asthma ever were related only to the use of acetaminophen in the last year.

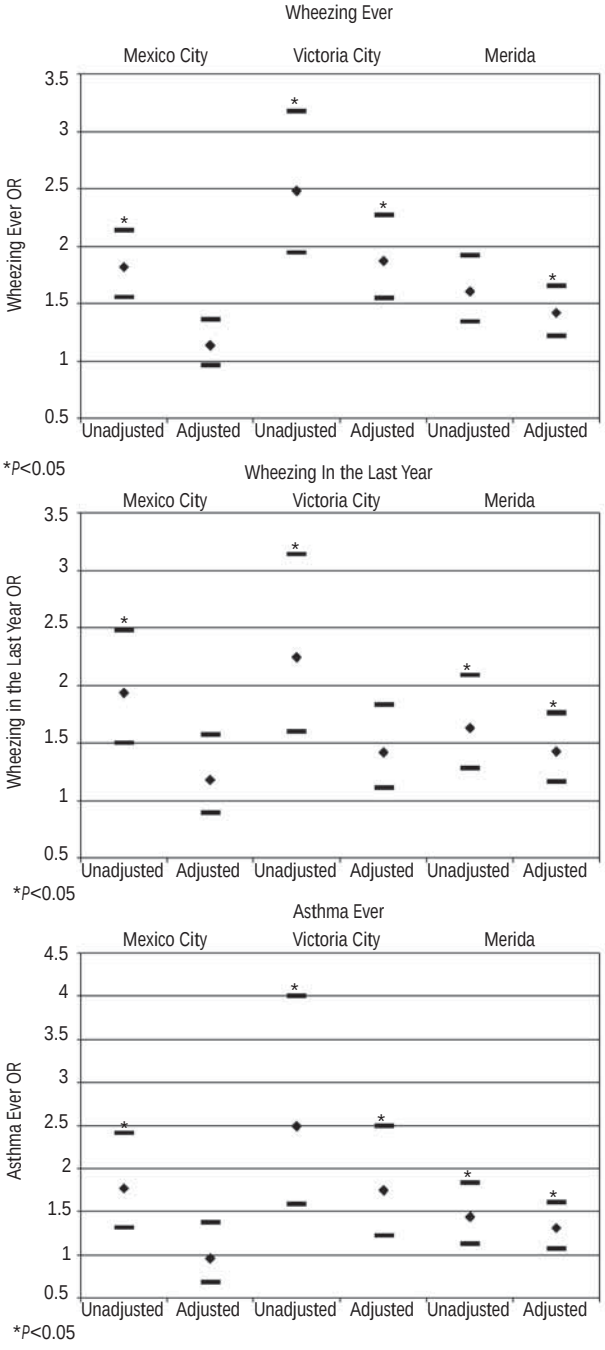

Figure 1. Odd ratios and 95% confidence interval for wheezing ever, wheezing in the last year, and asthma ever and use of acetaminophen during the first year of life using unadjusted and adjusted data in Mexico City, Victoria City, and Merida.

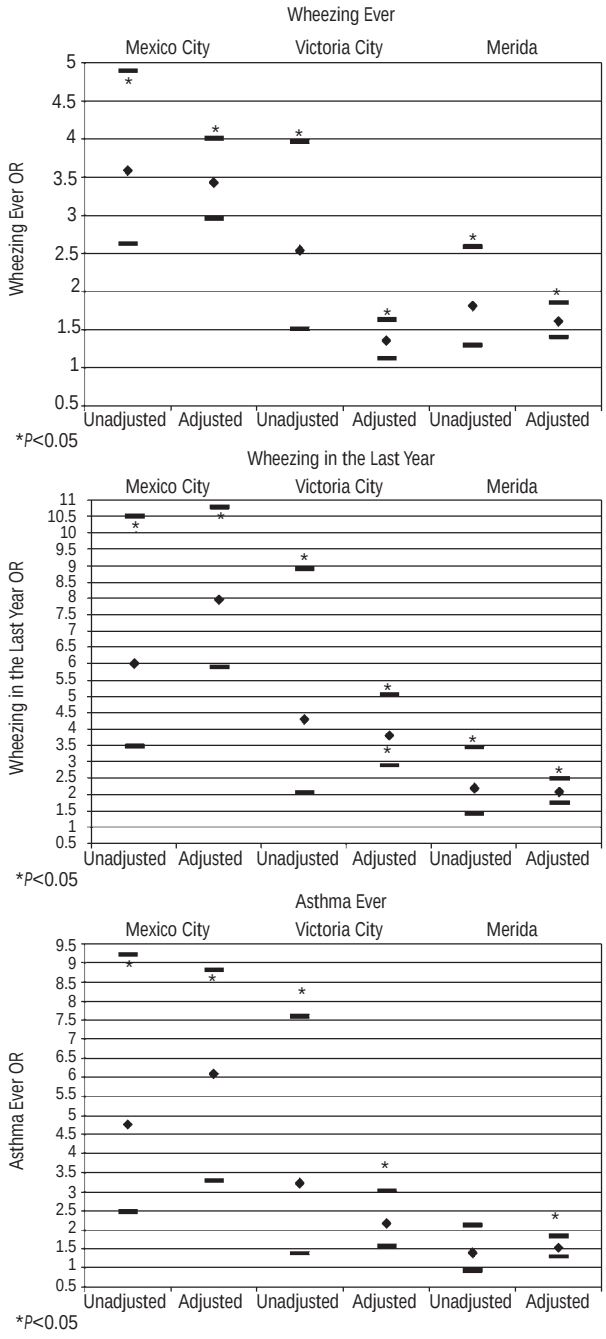

Figure 2. Odd ratios and 95% confidence interval for wheezing ever, wheezing in the last year, and asthma ever and use of acetaminophen during the last year using unadjusted and adjusted data in Mexico City, Victoria City, and Merida.

Table 1. Logistic Regression for Wheezing Ever, Wheezing In the Last Year, and Asthma Ever With Use of Acetaminophen in the First Year of Life and the Last Year in Mexico City

Wheezing Ever

Variable	*P*	R	OR	95% CI Lower Limit	95% CI Upper Limit
Acetaminophen in the first year of life	.030	0.028	1.230	1.118	1.354
Antibiotic in the first year of life	.000	0.126	2.265	2.033	2.524
Acetaminophen in the last year	.000	0.088	1.579	1.451	1.719
Farm animals in first year of life	.700	0.000	1.077	0.883	1.314
Farm animals during pregnancy	.001	0.048	1.845	1.520	2.238
Current maternal smoking	.950	0.000	0.992	0.884	1.114
Older siblings	.357	0.000	1.011	0.999	1.023
Younger siblings	.050	0.023	1.022	1.010	1.034
Smokers at home	.571	0.000	0.992	0.980	1.005
Breast feeding	.876	0.000	1.018	0.904	1.147
Cat in the first year of life	.360	0.000	1.154	0.986	1.350
Cat in the last year	.803	0.000	0.967	0.845	1.106
Dog in the first year of life	.721	0.000	1.036	0.936	1.147
Dog in the last year	.399	0.000	1.081	0.985	1.187

Wheezing in the Last Year

Variable	*P*	R	OR	95% CI Lower Limit	95% CI Upper Limit
Acetaminophen in the first year of life	.417	0.000	1.136	0.972	1.305
Antibiotic in the first year of life	.000	0.102	2.233	1.874	2.662
Acetaminophen in the last year	.000	0.123	1.997	1.758	2.268
Farm animals in the first year of life	.168	0.000	1.445	1.105	1.888
Farm animals during pregnancy	.060	0.029	1.652	1.265	2.159
Current maternal smoking	.102	-0.019	0.733	0.600	0.886
Older siblings	.806	0.000	1.004	0.986	1.023
Younger siblings	.326	0.000	0.98	0.965	1.000
Smokers at home	.989	0.000	1.000	0.981	1.019
Breast feeding	.485	0.000	0.885	0.742	1.054
Cat in the first year of life	.002	0.064	1.914	1.551	2.362
Cat in the last year	.395	0.000	0.840	0.684	1.031
Dog in the first year of life	.720	0.000	1.056	0.906	1.230
Dog in the last year	.742	0.000	0.954	0.827	1.100

Asthma Ever

Variable	*P*	R	OR	95% CI Lower Limit	95% CI Upper Limit
Acetaminophen in the first year of life	.361	0.000	1.173	0.984	1.399
Antibiotic in the first year of life	.001	0.083	1.994	1.626	2.446
Acetaminophen in the last year	.000	0.109	1.908	1.639	2.220
Farm animals in first year of life	.997	0.000	1.001	0.699	1.430
Farm animals during pregnancy	.319	0.000	1.412	0.998	1.997
Current maternal smoking	.824	0.000	0.953	0.770	1.180
Older siblings	.570	0.000	1.012	0.990	1.034
Younger siblings	.420	0.000	1.016	0.995	1.030
Smokers at home	.984	0.000	1.000	0.977	1.023
Breast feeding	.397	0.000	1.210	0.966	1.516
Cat in the first year of life	.085	0.026	1.578	1.211	2.057
Cat in the last year	.180	0.000	0.706	0.544	0.915
Dog in the first year of life	.754	0.000	0.943	0.783	1.135
Dog in the last year	.825	0.000	1.037	0.876	1.228

Table 2. Logistic Regression for Wheezing Ever, Wheezing in the Last Year, and Asthma Ever With Use of Acetaminophen in the First Year of Life and the Last Year in Victoria City

Wheezing Ever

Variable	*P*	R	OR	95% CI Lower Limit	95% CI Upper Limit
Acetaminophen in the first year of life	.000	0.087	1.82	1.584	2.095
Antibiotic in the first year of life	.000	0.153	2.695	2.351	3.090
Acetaminophen in the last year	.001	0.063	1.419	1.275	1.579
Farm animals in first year of life	.343	0.000	1.230	0.988	1.531
Farm animals during pregnancy	.934	0.000	0.9	0.767	1.251
Current maternal smoking	.012	0.044	1.697	1.372	2.099
Older siblings	.787	0.000	0.995	0.97	1.011
Younger siblings	.674	0.000	1.006	0.991	1.021
Smokers at home	.217	0.000	1.021	1.004	1.039
Breast feeding	.53	0.000	0.903	0.767	1.063
Cat in the first year of life	.326	0.000	1.212	0.996	1.475
Cat in the last year	.906	0.000	1.019	0.865	1.201
Dog in the first year of life	.245	0.000	1.164	1.02	1.327
Dog in the last year	.964	0.000	0.994	0.882	1.121

Wheezing in the Last Year

Variable	*P*	R	OR Limit	95% CI Lower Limit	95% CI Upper
Acetaminophen in the first year of life	.058	0.034	1.448	1.191	1.760
Antibiotic in the first year of life	.000	0.125	2.530	2.086	3.067
Acetaminophen in the last year	.000	0.154	2.355	2.03	2.726
Farm animals in the first year of life	.625	0.000	0.862	0.636	1.168
Farm animals during pregnancy	.290	0.000	1.401	1.018	1.93
Current maternal smoking	.601	0.000	1.16	0.867	1.576
Older siblings	.126	-0.015	0.966	0.945	0.988
Younger siblings	.726	0.000	1.007	0.986	1.028
Smokers at home	.294	0.000	1.025	1.001	1.049
Breast feeding	.013	-0.055	0.610	0.500	0.745
Cat in the first year of life	.039	0.040	1.671	1.302	2.144
Cat in the last year	.302	0.000	0.789	0.628	0.992
Dog in the first year of life	.161	0.000	1.279	1.072	1.525
Dog in the last year	.852	0.000	1.031	0.873	1.216

Asthma Ever

Variable	*P*	R	OR Limit	95% CI Lower Limit	95% CI Upper
Acetaminophen in the first year of life	.302	0.000	1.309	1.008	1.699
Antibiotic in the first year of life	.000	0.136	3.3062	2.505	4.363
Acetaminophen in the last year	.000	0.148	2.434	2.010	2.948
Farm animals in first year of life	.124	0.020	1.699	1.20	2.398
Farm animals during pregnancy	.366	0.000	1.405	0.963	2.050
Current maternal smoking	.664	0.000	1.182	0.803	1.741
Older siblings	.26	0.000	0.967	0.93	0.996
Younger siblings	.306	0.000	1.028	1.0006	1.056
Smokers at home	.664	0.000	1.013	0.982	1.044
Breast feeding	.086	-0.032	0.64	0.494	0.830
Cat in the first year of life	.072	0.037	1.750	1.281	2.391
Cat in the last year	.960	0.000	0.986	0.742	1.308
Dog in the first year of life	.368	0.000	0.805	0.632	1.024
Dog in the last year	.941	0.000	0.984	0.794	1.220

Table 3. Logistic Regression for Wheezing Ever, Wheezing in the Last Year, and Asthma Ever With Use of Acetaminophen in the First Year of Life and the Last Year in Merida

Wheezing Ever

Variable	*P*	R	OR	95% CI Lower Limit	95% CI Upper Limit
Acetaminophen in the first year of life	.046	0.024	1.221	1.104	1.350
Antibiotic in the first year of life	.000	0.091	1.789	1.607	1.992
Acetaminophen in the last year	.001	0.052	1.351	1.233	1.48
Farm animals in first year of life	.205	0.000	1.257	1.049	1.506
Farm animals during pregnancy	.627	0.000	1.095	0.907	1.321
Current maternal smoking	.057	0.022	1.315	1.139	1.51
Older siblings	.085	0.017	1.021	1.009	1.034
Younger siblings	.199	0.000	1.015	1.003	1.027
Smokers at home	.950	0.000	1.000	0.987	1.014
Breast feeding	.821	0.000	0.969	0.846	1.111
Cat in the first year of life	.498	0.000	0.902	0.776	1.050
Cat in the last year	.607	0.000	1.065	0.940	1.206
Dog in the first year of life	.727	0.000	1.036	0.936	1.146
Dog in the last year	.682	0.000	1.03	0.946	1.140

Wheezing in the Last Year

Variable	*P*	R	OR	95% CI Lower Limit	95% CI Upper Limit
Acetaminophen in the first year of life	.126	0.012	1.232	1.075	1.413
Antibiotic in the first year of life	.013	0.043	1,427	1.235	1.649
Acetaminophen in the last year	.000	0.087	1.663	1.476	1.873
Farm animals in the first year of life	.928	0.000	1.020	0.810	1.285
Farm animals during pregnancy	.150	0.005	1.396	1.107	1.762
Current maternal smoking	.632	0.000	1.091	0.908	1.311
Older siblings	.282	0.000	1.018	1.001	1.035
Younger siblings	.468	0.000	1.011	0.995	1.027
Smokers at home	.630	-0.026	0.968	0.951	0.985
Breast feeding	.563	0.000	0.902	0.754	1.078
Cat in the first year of life	.489	0.000	1.135	0.944	1.365
Cat in the last year	.071	0.024	1.321	1.13	1.543
Dog in the first year of life	.088	0.020	1.254	1.09	1.432
Dog in the last year	.171	0.000	0.843	0.745	0.955

Asthma Ever

Variable	*P*	R	OR	95% CI Lower Limit	95% CI Upper Limit
Acetaminophen in the first year of life	.432	0.000	1.111	0.971	1.271
Antibiotic in the first year of life	.000	0.070	1.686	1.455	1.954
Acetaminophen in the last year	.009	0.047	1.364	1.211	1.538
Farm animals in the first year of life	.539	0.000	1.154	0.913	1.457
Farm animals during pregnancy	.901	0.000	1.030	0.807	1.31
Current maternal smoking	.878	0.000	1.030	0.848	1.250
Older siblings	.416	0.000	1.013	0.99	1.030
Younger siblings	.920	0.000	1.001	0.985	1.017
Smokers at home	.807	0.000	0.995	0.977	1.01
Breast feeding	.790	0.000	1.050	0.872	1.264
Cat in the first year of life	.252	0.000	1.237	1.027	1.491
Cat in the last year	.302	0.000	1.177	1.005	1.379
Dog in the first year of life	.570	0.000	0.926	0.809	1.060
Dog in the last year	.260	0.000	1.148	1.014	1.300

Discussion

On the basis of the results obtained in our study, we found that the consumption of acetaminophen was associated with higher frequencies of wheezing and asthma. Several studies have shown a relationship between acetaminophen consumption and presence of asthma. Newson et al [12] found that acetaminophen sales correlated positively with the prevalence of asthma, rhinitis, atopic eczema, and wheezing in children who participated in ISAAC. Cohet et al [22] studied the association between infections in children aged 0 to 4 years and medications used (antibiotics and acetaminophen) and the subsequent presentation of asthma at age 6 to 7; the authors observed that the use of acetaminophen in the first year of life was weakly associated with wheezing, asthma, rhinitis, and eczema. Shaheen et al [23] conducted a study showing that the increasing use of acetaminophen was strongly associated with presence of asthma and its severity-, before and after adjusting for confounders. In their prospective study, Barr et al [24] found that acetaminophen use was associated with the presence of newly diagnosed asthma among women.

In a cohort study of pregnant women, Shaheen et al [25] observed an association between daily or almost-daily use of acetaminophen during late pregnancy (20-32 weeks) and presence of wheezing in their children at age 3. Later, following the same cohort, Shaheen et al [26] reported that the use of acetaminophen during pregnancy was associated with a higher frequency of asthma and wheezing when the children reached 6 to 7 years.

This effect of acetaminophen can arise because this drug decreases the glutathione deposits that are necessary to counteract the effects of reactive oxygen species. Nuttal et al [27] observed that a regular intake of maximal therapeutic doses of acetaminophen reduced antioxidant capacity in healthy volunteers.

In a previous study based on an ISAAC survey in North Mexico City [28], we looked for the factors associated with asthma symptoms using forward logistic regression. We found that use of acetaminophen was one of the main factors associated with asthma symptoms: in boys aged 6 to 7 years, wheezing ever was associated with the use of acetaminophen in the last year, while in girls it was associated with use of acetaminophen both during the first year of life and during the last year; wheezing in the last year was related to acetaminophen during the last year in these children. We could speculate that acetaminophen depletes glutathione levels when consumed in the last year, whereas it modifies the airway response when taken in the first year.

Barragan-Meijuero et al [29] conducted a cross-sectional survey using the ISAAC questionnaire applied to 3493 children aged 6 to 7 years in the south of Mexico City. These authors found that the use of acetaminophen in the first year of life was significantly associated with wheezing (OR 1.69, 95% CI 1.23-2.34) and the use of acetaminophen in the last year of life with wheezing (OR 3.3, 95% CI 1.54-7.18). However, they did not take into account the possible influence of confounders.

Variations in glutathione levels due to genetic polymorphism, environmental stimulus, diet, and flora could determine individual susceptibility to developing asthma manifestations after exposure to acetaminophen. Nevertheless, other factors—concomitant viral infection, and the use of antibiotics or other medications to treat infection—cannot be ruled out.

Acetaminophen is commonly used alone or in combination both as a prescription drug and an over-the-counter product. It is regarded as safe and indicated for children, with the result that patients are frequently exposed to acetaminophen without there being a general awareness of the fact.

Exposure to acetaminophen must be avoided by patients with asthma or respiratory symptoms, and a family history of asthma.

Asthma is influenced by both genetic and environmental factors; therefore, it is difficult to study the effect of a single factor. As the present study is a cross-sectional survey, we may only postulate the relationship between acetaminophen and asthma symptoms. Further studies to prove the relationship between acetaminophen and asthma must be longitudinal and prospective with strict definitions of asthma, incidence of asthma, and accurate recording of acetaminophen and other medications. They must also control for known confounders related to asthma and allergy.

Conclusion

We showed that use of acetaminophen was related as a risk factor to the presence of wheezing and asthma. This relationship was similar in 3 metropolitan areas in Mexico. It is necessary to conduct prospective studies to establish the relationship between the use of acetaminophen and asthma in pediatric populations.

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