Impact of antipyretics on acute asthma exacerbation during respiratory infection—A nationwide population-based study

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Received Jun 20, 2018; accepted Mar 31, 2020
Available online 4 April 2020

Key Words
asthma exacerbation (AE);
acetaminophen;
NSAID COX-1

Background: Antipyretics are frequently used in pediatric practice. Both acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to increase the risk of asthma exacerbation. The study investigated antipyretic use during respiratory infection in children and analyzed the risk of acetaminophen and NSAID for severe asthma exacerbation (AE) in asthmatic children in Taiwan.

Methods: We used the data from the National Health Insurance Research Database in 2005. There were 27,095 pediatric asthmatic patients having at least one respiratory infection episode, and 27,095 age- and sex-matched non-asthmatic children with respiratory infection served as controls. These patients were divided into groups with acetaminophen use, NSAID cyclooxygenase-1 (COX-1) use, and no antipyretic use. The rate of AE occurrence within the first 7 days after respiratory infection diagnosis was compared among the groups.

Results: During a single episode of respiratory infection, asthmatic patients used fewer antipyretics than controls (48.51% vs. 55.50%,  p < 0.001). No difference was observed in the risk of AE occurrence within 7 days after respiratory infection between antipyretic users and antipyretic nonusers (22/13,144 [0.167%] vs. 12/13,951 [0.086%],  p = 0.058). Compared with asthmatic children using acetaminophen, those using no antipyretic and COX-1 have lower risks for AE
1. Introduction

Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) COX-1 are the most widely used antipyretics in children. NSAIDs are frequently used for their analgesic, antipyretic, and anti-inflammatory properties. Although widely used, NSAIDs exert adverse effects on the gastrointestinal tract and kidneys.\(^1\) NSAIDs can cause acute deterioration of respiratory function or bronchospasm in a specific group of people with asthma and chronic sinusitis, which is known as NSAID–exacerbated respiratory disease (NERD).\(^3\)–\(^5\) Though NERD is considered an adult disease, the prevalence of NERD in children was 5% determined by oral provocation test in one available study.\(^6\) The 2017 guidelines of the Global Initiative for Asthma (GINA) recommended that clinicians must “always ask about asthma before prescribing NSAIDs, and advise patients to stop using them if asthma worsens”.\(^7\) Therefore, evaluating the risk of NSAID-induced severe asthma exacerbation in our pediatric population with unknown NERD prevalence is essential.

In addition to NSAIDs, acetaminophen is frequently prescribed for febrile conditions in pediatric patients, including patients with asthma. Studies have indicated that acetaminophen use is associated with increased rate of childhood asthma and asthma exacerbation (AE). The 2017 GINA recommended to avoiding use of acetaminophen “when possible” “during the first year of life” as the primary prevention strategy of asthma.\(^7\)

Respiratory tract infection (RTI) is a major trigger of AE, but it was frequently overlooked as a confounding factor in the study involving antipyretics on pediatric asthma.\(^8\)–\(^13\) Limited reports took RTI into consideration.\(^9\)–\(^11\) In this study, we used a nationwide health insurance research database (NHIRD) to compare the risk of NSAID and acetaminophen for severe asthma exacerbation in a single episode of respiratory tract infection.

2. Materials and methods

2.1. Data source

Taiwan implemented the National Health Insurance program in 1995, and more than 98% of Taiwan’s residents are insured under this program. The medical records of all insurers are collected and stored in the NHIRD, which is maintained by the National Health Research Institutes of Taiwan. The diagnostic codes in the database are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study used data from the 2005 Longitudinal Health Insurance Database (LHID), which contains the original claims data of 1,000,000 beneficiaries randomly sampled from the whole population in 2005.

2.2. Study design

Fig. 1 summarizes the flowchart of group division in this study. Among 28,475 pediatric asthmatic patients in 2004, 27,095 had at least one respiratory infection episode in 2005. In total, 27,095 sex- and age-matched non-asthmatic patients with respiratory infection from LHID2005 were used as controls. The diagnosis of asthma was based on the ICD-9-CM code 493.X in at least three outpatient visits or one emergency department (ED) visit or hospitalization. The diagnosis of RTI was based on ICD-9-CM codes 460.X—466.X, 480—488.X, and 490.X. We analyzed antipyretic use during the first RTI episode in 2005. Patients using antipyretics were divided into five groups according to their drug use: acetaminophen only, NSAID COX-1 inhibitor only, acetaminophen + COX-1, antipyretics not categorized into the aforementioned groups, and no antipyretic use. Subsequently, we determined the rate of AE occurrence in these five groups.

AE was defined as an ED visit or hospitalization with the ICD-9-CM code 493.X, 1–7 days after RTI diagnosis through the ICD-9-CM codes; there also had to be β-2 agonist inhalation therapy during the ED visit/hospitalization. We analyzed the risk of AE by adjusting age, gender and urbanization level. The urbanization level was divided into four categories, with level 1 representing the most urbanized area and level 4 representing a rural area. Taiwan includes 359 areas; their urbanization levels had been described previously.\(^14\) We assigned patients’ level of urbanization from the area in which they lived.

This study was approved by the Institutional Review Board of Taichung Veterans General Hospital (No. CE16220B). To ensure privacy, the identities of the patients, physicians, and institutions were scrambled in accordance with the Personal Electronic Data Protection Law.

2.3. Statistical analyses

Data retrieval and analysis were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Chi-square and T tests were used to compare the age and sex distributions among the groups. The odds ratio (OR) of drug use for AE was analyzed. Logistic regression was adjusted for age, sex, and urbanization level to determine the odds ratio (OR) and 95% confidence interval (95% CI) for identifying the possible risk factors for severe asthma exacerbation. All statistical
tests were two-sided, conducted at a significant level of 0.05 and were reported with the p value and/or 95% CIs.

3. Results

In total, 28,475 pediatric asthmatic patients were identified from LHID2004 according to the study inclusion criteria. Among these patients, 27,095 had at least one RTI episode in 2005. The comparison of drug use during the first RTI episode between asthmatic patients and their age- and sex-matched controls is presented in Table 1. The average age was 8.6 ± 3.9 years; and the male to female ratio was 1.48:1. The overall antipyretic use was lower in asthmatic patients (48.51% vs. 55.50%, p < 0.001). In addition, the distribution of antipyretic use was different in asthmatic patients and controls (p < 0.001). On average, the percentages of acetaminophen, COX-1, acetaminophen + COX-1, and other drug use as antipyretics were approximately 46.55%, 36.07%, 15.99%, and 1.38%, respectively.

In the asthmatic group, the number of antipyretic users and nonusers were 13,144 (48.51%) and 13,951 (51.48%), respectively. The distributions of age, sex, urbanization level, and asthma exacerbation are presented in Table 2. In the asthmatic group, antipyretic users were older than antipyretic nonusers (9.3 ± 3.8 vs. 7.8 ± 3.5 years, p < 0.001). The distributions of sexes and urbanization levels were slightly different (p = 0.029 and 0.015, respectively). Nevertheless, no difference was observed in the rate of AE occurrence between these two subgroups (p = 0.058). The rate of severe AE occurrence after a single RTI episode in children with asthma was 0.14% (0.09%–0.17%). During the first 7 days after respiratory infection diagnosis, 22 antipyretic users (0.17%) and 12 antipyretic nonusers (0.09%) developed AE. Compared with antipyretic nonusers, the ORs of antipyretic users were 2.48 (95% CI: 0.94–6.51, p = 0.066) in those under 6 years old and 2.12 (95% CI: 0.75–6.03, p = 0.158) in those above 6 years old, after adjusting for age, sex, and urbanization level, as shown in Table 3.

Among the 22 patients with AE, 17, 2, 2, and 1 used acetaminophen, COX-1, acetaminophen + COX-1, and other drugs, respectively. The rate of AE occurrence in each drug use group was as follows: acetaminophen only: 0.27%; COX-1 only: 0.04%; acetaminophen + COX-1: 0.1%; and other drugs: 0.62%. After adjusting sex, age, and urbanization, the analysis of risk factors for AE are presented in Table 4. Compared with acetaminophen users, the ORs of COX-1 only, and non-antipyretic users were 0.14 (95% CI: 0.03–0.61, p = 0.009), 0.26 (95% CI: 0.12–0.54, p < 0.001). The acetaminophen + COX-1 group showed no difference in the OR (OR = 0.38, 95% CI: 0.09–1.64, p = 0.194).

4. Discussion

In this study, we found higher risk of AE in asthmatic children using acetaminophen in a single episode of RTI. The risk was higher than those not using antipyretic or using

![Flow chart of group division in this study.](image)
COX-1 under similar conditions. Compared with age- and sex-matched controls, the patients with asthma used fewer antipyretics during their first RTI episode in 2005 (48.51% vs. 55.50%, \( p < 0.0001 \)). In this study, a potential reason for low antipyretic use in children with asthma was the co-morbid respiratory disorders of asthma, such as chronic bronchitis, chronic rhinitis, pneumonia, and vasomotor or allergic rhinitis, which worsened respiratory infection symptoms and caused patients to seek medical help even when they had no fever. This result corresponds to studies from Germany and Korea.\(^{15,16}\)

Respiratory infection has been documented to be the major trigger of AE; as high as 80% of pediatric AE episodes are caused by viral respiratory infections.\(^{13}\) Thus, respiratory infection must be considered when analyzing the adequacy of acetaminophen/NSAID COX-1 use in pediatric asthmatic patients.

In patients with NERD, NSAIDs/COX inhibitors block PGE\(_2\) production, which leads to the overproduction of cysteinyl leukotrienes and induces a severe asthma attack.\(^{17}\) NSAID-intolerant asthmatic patients have been reported to tolerate selective COX-2 inhibitory NSAIDs.\(^{18}\) In the current study, we categorized aspirin and COX-2 as other drugs because aspirin and COX-2 inhibitors are seldom prescribed in pediatric practice.

Acetaminophen use during pregnancy or childhood has been considered to be associated with an increased risk of asthma; however, it may be confounded with respiratory

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 54,190)</th>
<th>Asthma children (n = 27,095)</th>
<th>Matched controls (n = 27,095)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>8.6 ± 3.9</td>
<td>8.5 ± 3.7</td>
<td>8.6 ± 4.1</td>
<td>0.482</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>1.000</td>
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<tr>
<td>Female</td>
<td>21880 (40.37)</td>
<td>10,940 (40.37)</td>
<td>10,940 (40.37)</td>
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<tr>
<td>Male</td>
<td>32310 (59.62)</td>
<td>16,155 (59.62)</td>
<td>16,155 (59.62)</td>
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</tr>
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<td>Antipyretic use</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>26006 (47.99)</td>
<td>13,951 (51.48)</td>
<td>12,055 (44.49)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28184 (52.00)</td>
<td>13,144 (48.51)</td>
<td>15,040 (55.50)</td>
<td></td>
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<tr>
<td>Antipyretics</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Acetaminophen only</td>
<td>13122 (46.55)</td>
<td>6145 (46.75)</td>
<td>6977 (46.38)</td>
<td></td>
</tr>
<tr>
<td>Cox-1 only</td>
<td>10166 (36.07)</td>
<td>4851 (36.90)</td>
<td>5315 (35.33)</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen + Cox-1</td>
<td>4507 (15.99)</td>
<td>1987 (15.11)</td>
<td>2520 (16.75)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>389 (1.38)</td>
<td>161 (1.22)</td>
<td>228 (1.51)</td>
<td></td>
</tr>
</tbody>
</table>

T test, chi-square test for all p values. Cox-1, cyclooxygenase-1 inhibitor; n, number; SD, standard deviation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 27,095)</th>
<th>With antipyretics use (n = 13,144)</th>
<th>Without antipyretics use (n = 13,951)</th>
<th>p value^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>8.5 ± 3.7</td>
<td>9.3 ± 3.8</td>
<td>7.8 ± 3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;6</td>
<td>7600 (28.04)</td>
<td>2796 (21.27)</td>
<td>4804 (34.43)</td>
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<td>6-11</td>
<td>14,451 (53.33)</td>
<td>7098 (54.00)</td>
<td>7353 (52.70)</td>
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<tr>
<td>12-17</td>
<td>5044 (18.61)</td>
<td>3250 (24.72)</td>
<td>1794 (12.85)</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.029</td>
</tr>
<tr>
<td>Female</td>
<td>10,940 (40.37)</td>
<td>5395 (41.04)</td>
<td>5545 (39.74)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16,155 (59.62)</td>
<td>7749 (58.95)</td>
<td>8406 (60.25)</td>
<td></td>
</tr>
<tr>
<td>Urbanization^b</td>
<td></td>
<td></td>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>1</td>
<td>7836 (29.4)</td>
<td>3909 (30.2)</td>
<td>3927 (28.7)</td>
<td></td>
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<tr>
<td>2</td>
<td>8402 (31.5)</td>
<td>4064 (31.4)</td>
<td>4338 (31.7)</td>
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<tr>
<td>3</td>
<td>4452 (16.7)</td>
<td>2160 (16.7)</td>
<td>2292 (16.7)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5950 (22.3)</td>
<td>2804 (21.7)</td>
<td>3146 (23.0)</td>
<td></td>
</tr>
<tr>
<td>Asthma recurrence (≤7 days after respiratory infection)</td>
<td></td>
<td></td>
<td></td>
<td>0.058</td>
</tr>
<tr>
<td>No</td>
<td>27,061 (99.9)</td>
<td>13,122 (99.9)</td>
<td>13,939 (99.8)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34 (0.13)</td>
<td>22 (0.17)</td>
<td>12 (0.09)</td>
<td></td>
</tr>
</tbody>
</table>

^a P-value
^b Urbanization: 1 is the most urbanized, followed by 2, 3; 4 is rural.
including level of asthma control, rhinosinusitis, obesity and confirmed food allergy. Second, we did not know the doses of antipyretics our patients used. However, a 2016 double-blind study reported no relationship between the rate of asthma exacerbation and the accumulated dose of acetaminophen or ibuprofen. Another limitation was that the severity of asthma and controlled level could not be assessed. Poor asthma control increases the risk of severe AE exacerbation. To the best of our knowledge, antipyretic prescription was not specially considered in pediatric asthma studies other than antipyretic itself. We did a small scale survey in our out-patient department (OPD). We compared the level of asthma control and the recent antipyretic prescriptions in consecutive 60 children. The results shown in Supplementary information revealed no difference in asthma control between the acetaminophen and the NSAID groups. Our result revealed that acetaminophen or NSAID COX-1 use during respiratory infection did not confer a higher risk of severe asthma exacerbation in children with asthma. Although not a well-controlled study, the present study does provide real-world data.

5. Conclusion

In asthmatic children, the risk of severe AE following respiratory infection is higher in those taking acetaminophen. To reduce the risk of severe AE, avoidance of acetaminophen prescription can be considered.

Declaration of Competing Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.
Acknowledgements

This study is based in part on data from the National Health Insurance Research Database provided by the National Health Insurance Administration, Ministry of Health and Welfare and managed by National Health Research Institutes (Registered number 101095, 102148). The interpretation and conclusions contained herein do not represent those of National Health Insurance Administration, Ministry of Health and Welfare or National Health Research Institutes. The authors would like to thank the Healthcare Service Research Center of Taichung Veterans General Hospital for statistical support. This study was supported by grants from Taichung Veterans General Hospital, Taiwan (TCVGH-NHR10901, TCVGH-1097306C, TCVGH-1097328D, TCVGH-1086502B).

References


Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpeds.2020.03.018.