RESEARCH PAPER

Short-term Ibuprofen Treatment and Pulmonary Function in Children with Asthma

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Objective*:* To investigate the association between ibuprofen use and pulmonary function in children with Asthma.

Methods*:* Ninety 9- to 10-year-old children were classified into 3 groups: *Study group,* mild to moderate stable asthmatic children with self-reported aspirin allergy and no history of anaphylaxis; *Allergy control group:* atopic children (allergic rhinitis/atopic dermatitis); *Healthy control group:* non-atopic healthy children. None of the participants in the atopic and healthy control groups had a history of aspirin allergy. All received ibuprofen 4 times a day for 3 consecutive days. Forced expiratory volume in the first second (FeV_1) and fractional exhaled nitric oxide (FeNO) measurements were performed before and after ingestion of ibuprofen daily for 3 days.

Results*:* In the study group, a decrease in FeV_1 and increase in FeNO levels were observed after taking ibuprofen for 2 days. The atopic control group showed only an increase in FeNO but not FEV_1. In the healthy control group, both FeV_1 and FeNO were unchanged from baseline.

Conclusions*:* The results showed that cross-reactive non-steroidal anti-inflammatory drug hypersensitivity may exist between ibuprofen and aspirin. This raises the possibility that asthma exacerbation could be mediated by ibuprofen ingestion.

Keywords: *Asthma, Exhaled nitric oxide, FeV_1, Ibuprofen, NSAID.*

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly involved groups of medicines in hypersensitivity drug reactions. About 76% of patients who are hypersensitive to NSAIDs have cross-intolerance, and atopy can be a predisposing factor in patients with cross-intolerance [1,2]. Aspirin intolerance in asthmatic patients has been reported to be underdiagnosed [3]. In those who are allergic to NSAIDs, acetylsalicylic acid (18.2%) and ibuprofen (18.2%) are the most frequently identified drugs [4]. In patients with hypersensitivity reactions to NSAIDs, 76% have cross-intolerance and 24% are selective responders. The most important drugs involved in cross-intolerance are propionic acid derivatives, in most cases ibuprofen, and in sustained-release pyrazolones. In cross-intolerance, the most frequently reported clinical entities are urticaria and angioedema; however, the airway can also be involved [1]. It has been suggested that the possibility of ibuprofen-induced bronchospasms should be considered before administering ibuprofen to children with asthma [5]. Moreover, this asthmatic reaction is dose-dependent and can occur with sub-therapeutic doses [6]. We, therefore, investigated the effect of short-term ibuprofen treatment on pulmonary function in asthmatic children.

METHODS

Ninety 9- to 10-year-old children (49 males) were enrolled and divided into three groups of 30 children each. The Study group comprised of children with mild to moderate asthma as classified by the GINA guidelines and a self-reported history of aspirin-allergy. The Allergic control group had children with allergic rhinitis or atopic dermatitis, and the Healthy control group included healthy children attending our hospital for vaccination. The children in the allergy and healthy control groups had no history of aspirin-allergy. Forced expiratory volume in the first second (FeV_1) and Fractional exhaled nitric oxide (FeNO) measurements (NIOX MINO system, Phadia) were performed for each participant every morning before breakfast for 3 consecutive days. The participants took ibuprofen 2.5 mg/kg 4 times a day. We defined bronchospasm as a ≥20% decrease from baseline in FeV_1, and ibuprofen-sensitivity as bronchospasm following administration of ibuprofen. Asthma exacerbation was defined as an increase in FeNO level

from baseline (20 ppb) with increased coughing frequency and chest tightness clinically, increased use of inhaled corticosteroids (ICS) or short-acting beta-agonists, and a decrease in PaO_2 of less than 90%. Children taking systemic steroids within one week of the initiation of the study were excluded. This study was approved by the Institutional Review Board of our hospital, and all of the participants' parents or guardians provided written informed consent.

The Statistical Package for Social Sciences software version 12 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Statistical significance was set at $P<0.05$.

RESULTS

After the children had received the intervention for two days, a worsening of pulmonary function and asthma exacerbation was seen in a significant number of children in the study group (***Table* I**). The allergy control group only showed an increased FeNO level but no change in FeV_1. In the healthy control group, both PFT and FeNO were maintained at the baseline level (***Fig.* 1**).

DISCUSSION

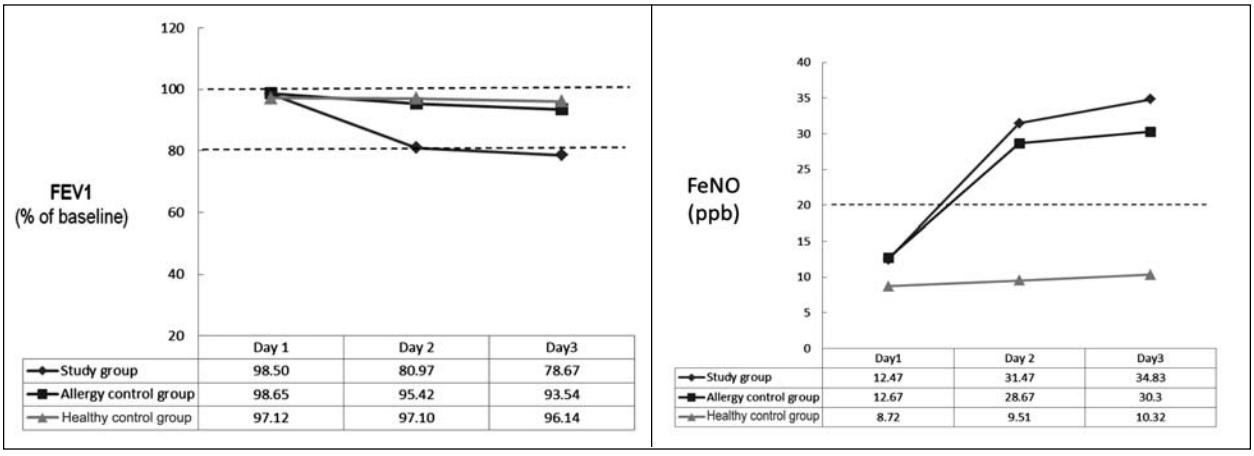
As ibuprofen has cross-intolerance with aspirin, the children with mild to moderate asthma in this study had an increased frequency of coughing with or without short of breath, and required double the dose of ICS or the use of short acting beta-agonists to ease the exacerbation of asthma symptoms. Patients with aspirin-exacerbated respiratory diseases typically experience severe bronchoconstriction and/or rhinoconjunctival reactions to aspirin and other NSAIDs, even those which they have not encountered previously [7]. Aspirin-intolerance, as determined in broncho-provocation studies, may be apparent in 5% of asthmatic children [8]. Palmer reported that NSAID-exacerbated asthma may occur in up to 2% of asthmatic children [6].

Kanabar, *et al*. [9] reported that ibuprofen use was associated with a low relative risk for hospitalization (0.63) and outpatient visits (0.56) for asthma compared with acetaminophen. In addition, Kidon, *et al*. [10] also

TABLE I CLINICAL AND LABORATORY PARAMETERS IN THE STUDY POPULATION AFTER TAKING IBUPROFEN FOR TWO DAYS

	Study group (n=30)	*Allergic control group (n=30)*	*Healthy control group (n=30)*	*P value*
FEV_1 (% of prediction)	80.97 ± 5.35	95.42 ± 4.79	97.10 ± 1.12	<0.001
FeNO (ppb)	31.47 ± 4.78	28.67 ± 3.85	9.50 ± 1.57	<0.001
PaO_2 (mm Hg)	85.23 ± 2.40	92.60 ± 3.45	97.17 ± 2.09	<0.001
*Increased cough and/or chest tightness	30 (100)	6 (20.0)	0	<0.001
*Increased ICS dose and/or SABA use	30 (100)	5 (16.7)	0	<0.001

*FEV_1: Forced expiratory volume in the first second; FeNO: Fractional exhaled Nitric Oxide; PaO_2: Partial pressure of Oxygen in arterial blood; ICS: Inhaled corticosteroid; SABA: short acting beta-agonist. Values in mean ± SD or * No. (%).*



(*a*) (*b*)

FIG. 1 *(a) The FEV1 changes in the study group after treatment of ibuprofen for 3 consecutive days; (b) The FeNO changes in the study group after treatment with ibuprofen for 3 consecutive days.*

WHAT THIS STUDY ADDS?

- Exposure to ibuprofen worsens the pulmonary functions and exacerbates asthmatic symptoms in children with asthma having aspirin-allergy.

reported that ibuprofen at antipyretic doses may cause acute respiratory problems in only a very small number of mild to moderate asthmatic children. Furthermore, a cross-reactive hypersensitivity response to NSAIDs was reported in 45% of young Asian atopic children through their history, and in 25% through diagnostic challenge [11]. Of the patients with hypersensitivity reactions to NSAIDs, 76% had cross-intolerance and 24% were selective responders. The most important drugs involved in cross-intolerance are propionic acid derivatives, in most cases ibuprofen, and in selective responders, pyrazolones. In cross-intolerance, the most frequent clinical entities are urticaria and angioedema, and to a lesser extent airway involvement [1]. Jenkins, *et al*. [12] reported that cross-intolerance to doses of NSAIDs was present in most patients with aspirin-induced asthma (ibuprofen, 98%; naproxen, 100%; and diclofenac, 93%). On the other hand, beneficial effects of ibuprofen have been reported in cystic fibrosis [13]. In addition, due to the inflammatory pathogenesis of asthma, the anti-inflammatory effect of ibuprofen may possibly reduce morbidity in children with asthma.

There are several limitations to this study. First, the number of enrolled subjects was limited. Second, other NSAIDs such as diclofenac sodium and naproxen were not evaluated for cross-intolerance comparative studies. Third, both sub-clinical and high doses of ibuprofen were not included.

Ibuprofen is used extensively among children as an analgesic and antipyretic agent. However, whether children with asthma or are at risk of developing asthma should avoid the use of ibuprofen still remains to be elucidated [15]. In Taiwan, ibuprofen is commonly used over-the counter and in hospitals due to the advantage of a less frequent dose and a longer duration of action. In clinical practice, the possibility of ibuprofen-induced bronchospasm should be considered before administering ibuprofen to children with asthma.

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