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Accidental ingestion of aspirin and non-steroidal anti-inflammatory drugs is common in patients with aspirin-exacerbated respiratory disease

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TO THE EDITOR:

Aspirin-exacerbated respiratory disease (AERD) is characterized by asthma, nasal polyposis, and reactions to nonsteroidal anti-inflammatory drugs (NSAIDs).(1) Acute reactions to NSAIDs classically involve respiratory symptoms (2) and some patients also develop skin and gastrointestinal symptoms.(3) Reactions are dose-dependent; smaller doses may elicit nasal congestion that resolves without medical treatment while larger doses may induce severe bronchospasm that requires intubation.

NSAIDs are among the most commonly used medications, as more than one in four Americans take them frequently.(4) Physicians write over 100 million NSAID prescriptions per year(5) and there are more than 20 commercially-available NSAIDs. Patients with AERD who have not been desensitized to aspirin should avoid all cyclooxygenase-1-inhibiting NSAIDs. Outside of the specialties of allergy and otolaryngology, physician knowledge about AERD is limited. One survey study sent to faculty and residents at a university medical center found that only 15.6% of physicians were aware that aspirin desensitization, the gold standard of care for AERD, could be performed to treat these patients.(6) Given the ubiquity of NSAIDs and lack of widespread awareness about AERD among physicians, we hypothesized that unintentional ingestion of NSAID medications occurs commonly even after patients are aware they have AERD. The purpose of this study

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was to determine the incidence of accidental NSAID ingestion in this patient population and to identify causes and outcomes of these medication errors.

Subjects were adults with physician-diagnosed AERD who were part of our AERD registry between September 2013 and January 2018. Partners IRB approved the study (2013-P-001659). At registry enrollment, demographic information and AERD-related medical history were collected. Researchers input these data from the electronic medical records of subjects seen at the allergy/asthma clinics at Brigham and Women's Hospital or Massachusetts General Hospital. Subjects who did not receive care within the Partners Health Care network completed the enrollment online themselves. Data were stored in Research Electronic Data Capture (REDCap; Vanderbilt University, Nashville, Tenn).

Subjects in the registry were offered an online questionnaire which collected their history of accidental NSAID ingestion (eFigure 1), either as an emailed online survey or as part of their online registry enrollment. Respondents who indicated "yes, after I knew I had AERD, I have unintentionally taken or been given an NSAID" were further questioned and asked to complete a follow-up survey. This survey asked subjects to indicate the number of separate occasions since being diagnosed with AERD that they had accidentally ingested an NSAID. The questionnaire collected the following information for up to three incidents of accidental NSAID ingestion: whether the ingested medication was prescribed or self-administered, the diagnosis or condition that warranted ingestion of the medication, the identity of the NSAID, and the treatment(s) used for any reactions. Subjects who indicated that the medication had been prescribed were asked to indicate the specialty of the prescribing provider. Subjects were assigned an asthma severity score as described.(7)

Asthma severity was modeled as a binary variable with categories 1,2 and 3 as mild/moderate asthma and categories 4 and 5 as severe asthma. Because of the sparsity of data in some race categories, race was classified as white vs non-white. Descriptive statistics, including mean $\pm$ SD and frequencies for continuous and categorical data, were represented for all patients. Two-sample t-test and chi-squared test were used to compare AERD patients who had accidentally ingested an NSAID and those who had not. Risk factors such as age, sex, race, age at asthma or nasal polyp diagnosis, age at first reaction to an NSAID and asthma severity were examined using Poisson regression. The risk factors are reported as Rate Ratios. 95% intervals are represented and an $\alpha = 0.05$ was used to assess significance. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Four hundred fifty-five of 715 registry patients chose to complete the accidental ingestion questionnaire. Seventy-one percent (322) of respondents were female, and the average age was 48.2 years $\pm$ 12.8 (Table I). The demographic distribution of respondents was similar to that of the full cohort of AERD patients in the REDCap AERD registry (65% female, age 49.2 years $\pm$ 12.8, with similar racial distribution). There were proportionally more males than females who did not complete the questionnaire, though this is consistent with the gender distribution of our other survey response rates. Twenty-four percent (111) of respondents indicated that they had accidentally ingested an NSAID after they were diagnosed with AERD and knew to avoid them. Of the 97 patients who had been evaluated by a specialist in the Partners Health Care system, 18.6% (18) reported having accidentally

ingested an NSAID as compared to 26.0% (93) of the 358 external patients, a non-significant difference ($p=0.13$). Fifty-four percent of accidental ingestions occurred at home with 43% occurring in an emergency department, clinic, or hospital. About half (54%) of respondents indicated that they had taken the medication because they were not aware it was an NSAID, and 25% indicated that they had chosen the wrong bottle (e.g. they intended to take acetaminophen and mistakenly took ibuprofen).

Fifty-nine participants (53.2%) also completed our follow-up survey. Two subjects were removed from analysis because one subject reported ingestion of a non-NSAID medication and the second subject reported ingestion of an NSAID as part of an aspirin challenge. Results showed that in 26.3% of cases, the NSAID was prescribed by a medical provider. Respondents had most often ingested the medication for headaches (36.6%), and the most common NSAID medications mistakenly ingested were ibuprofen (39.5%) and aspirin (26.3%). Respondents treated the greatest proportion of reactions with antihistamines (27.4%) and albuterol (24.4%). Eleven (8.4%) of the reactions were severe enough to require epinephrine treatment, with two patients reporting that they required treatment with epinephrine for two separate accidental NSAID-induced reactions. No treatment was used for 12.2% of accidental ingestions, and one ingestion (0.8%) was reported to have elicited no reaction at all. Nearly a third (31.6%) of patients required an emergency visit or hospitalization for one or more of their reactions (Supplemental Table E1).

Table II shows the rate of accidental ingestion of NSAIDs using a Poisson regression to account for time since AERD diagnosis. Under-dispersion was corrected by dscaling the variance using the quasi-likelihood method. Current age and race were not significantly associated with the rate of accidental NSAID ingestion. However, sex and age of patient at the time of their first NSAID-induced reaction were significant. After adjusting for all other variables, the rate of accidental ingestion of aspirin or NSAIDs was 1.89 times higher in women than men. In the fully-adjusted model, for each year older in age at the time of first NSAID-induced reaction, the rate of accidental ingestion of an NSAID increased by a factor of 1.04.

This study demonstrates that after being diagnosed with AERD, some patients do not achieve complete avoidance of NSAIDs. One in four respondents reported having unintentionally ingested an NSAID even though they knew to avoid them. While a small subset of ingestions elicited no reaction or resolved without treatment, in nearly a fourth of the cases of accidental ingestion, the patients were treated with a short-acting beta agonist indicating that the reaction had induced bronchoconstriction. In almost 15% of cases, patients visited the emergency department or were hospitalized for their reactions, and more than eight percent of these reactions were treated with epinephrine. These findings show that failure to avoid NSAIDs in AERD can have severe and even life-threatening outcomes.

The majority of patients took the NSAID medication themselves, indicating a greater need for patient education about NSAID avoidance. Women were more likely than men to have accidentally ingested an NSAID, which likely reflects the greater use of NSAIDs by in women than men, as has been previously reported.(8)

In over a quarter of cases, the accidentally ingested medication was a prescribed drug. These results highlight the need for physician education about AERD and NSAID avoidance. Incidences of NSAID prescription for patients with AERD were highest among ER doctors and non-ENT surgeons/anesthesiologists, suggesting that these were most likely intended for pain management. Finally, there is a trend suggesting that patient and referring physician education in a health care system with a large AERD center may improve patient safety. Participants who were seen within our network showed a trend toward being less likely to have unintentionally ingested an NSAID.

One strength of our AERD registry is that it contains information about patients from all over the country and not just patients seen at the Brigham and Women's Hospital. The questionnaire respondents for this study have a distribution similar to that of the full cohort of AERD patients in our registry, suggesting the lack of selection bias. However, participation in the registry itself may be a potential bias, as most participants have been seen at a center that specializes in AERD treatment, suggesting a patient population that may have more medical access or be more healthcare savvy than the general population.

This is the first study to examine the incidence and nature of accidental NSAID ingestion in patients with AERD. We have found that nearly a quarter of all patients with AERD have accidentally ingested an NSAID, and that the resulting reactions can be very severe. Our data strongly suggest that increased awareness and education, both for the patients and for their prescribing physicians, is needed to improve patient safety.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: A meta-analysis of the literature. *The Journal of allergy and clinical immunology*. 2015;135(3):676–81 e1. [PubMed: 25282015]
2. Hope AP, Woessner KA, Simon RA, Stevenson DD. Rational approach to aspirin dosing during oral challenges and desensitization of patients with aspirin-exacerbated respiratory disease. *The Journal of allergy and clinical immunology*. 2009;123(2):406–10. [PubMed: 19056109]
3. Cahill KN, Bensko JC, Boyce JA, Laidlaw TM. Prostaglandin D(2): a dominant mediator of aspirin-exacerbated respiratory disease. *The Journal of allergy and clinical immunology*. 2015;135(1):245–52. [PubMed: 25218285]
4. Davis JS, Lee HY, Kim J, Advani SM, Peng HL, Banfield E, et al. Use of non-steroidal anti-inflammatory drugs in US adults: changes over time and by demographic. *Open Heart*. 2017;4(1):e000550. [PubMed: 28674622]
5. Laine L Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology*. 2001;120(3):594–606. [PubMed: 11179238]
6. Sturm JM, Temprano J. A survey of physician practice and knowledge of drug allergy at a university medical center. *J Allergy Clin Immunol Pract*. 2014;2(4):461–4. [PubMed: 25017537]

7. National Asthma E, Prevention P. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *The Journal of allergy and clinical immunology*. 2007;120(5 Suppl):S94–138. [PubMed: 17983880]
8. Kingsbury SR, Hensor EM, Walsh CA, Hochberg MC, Conaghan PG. How do people with knee osteoarthritis use osteoarthritis pain medications and does this change over time? Data from the Osteoarthritis Initiative. *Arthritis Res Ther*. 2013;15(5):R106. [PubMed: 24008023]

Clinical Implications: This study demonstrates that nearly one in four patients with AERD have accidentally ingested an NSAID and that the subsequent NSAID-induced reactions can be life-threatening. In many cases, the NSAID was mistakenly prescribed by a physician, and our findings indicate a need for improved patient and physician education about NSAID avoidance in AERD.

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TABLE I.

Demographic characteristics of study population

Characteristic	Accidental NSAID ingestion?	
	Yes	No
Sample size, n (%)	111 (24.4)	344 (75.6)
Age (y), mean (range)	48.7 (20-79)	46.9 (19-77)
Sex, n (%)		
Male	27 (24.3)	106 (30.8)
Female	84 (75.7)	238 (69.2)
Race, n (%)	108 *	344 *
White	101 (93.5)	320 (93.0)
Black or African-American	—	10 (2.9)
Asian	—	6 (1.7)
American Indian/Alaska Native	2 (1.9)	—
More than 1 race	4 (3.8)	6 (1.7)
Other	1 (0.9)	2 (0.6)
Age at asthma diagnosis (y), mean $\pm$ SD	28.7 $\pm$ 14.1	30.7 $\pm$ 14.0
Age at nasal polyps diagnosis (y), mean $\pm$ SD	32.4 $\pm$ 12.5	35.4 $\pm$ 12.8
Age at first reaction to NSAIDs (y), mean $\pm$ SD	32.1 $\pm$ 13.0	35.4 $\pm$ 12.6
Asthma step, n (%)	95 *	313 *
1	3 (3.2)	22 (7.0)
2	23 (24.2)	75 (24.0)
3	18 (18.9)	65 (20.8)
4	21 (22.1)	76 (24.3)
5	30 (31.6)	75 (24.0)

* Sample size excludes missing data.

TABLE II.

Poisson regression model to estimate the rate of accidental ingestion of NSAIDs in patients with AERD

Covariate	Rate ratio (95% CI)	P value
Age of patient	0.99 (0.97-1.01)	.39
Sex (male vs female)	0.53 (0.29-0.98)	.04
Race (white vs nonwhite)	1.02 (0.37-2.81)	.96
Age of patient at asthma diagnosis	0.99 (0.96-1.01)	.29
Age of patient at nasal polyp diagnosis	0.99 (0.96-1.02)	.49
Age of patient at first NSAID reaction	1.04 (1.00-1.07)	.04
Asthma severity (severe vs moderate/mild)	1.43 (0.90-2.26)	.13

Bold indicates statistical significance ($P < .05$).