Original Article

Adverse and Hypersensitivity Reactions to Prescription Nonsteroidal Anti-Inflammatory Agents in a Large Health Care System

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What is already known about this topic? Nonsteroidal anti-inflammatory drugs (NSAIDs) can cause a variety of adverse drug reactions (ADRs), including side effects as well as allergic or pseudoallergic reactions (hypersensitivity reactions [HSRs]).

What does this article add to our knowledge? A total of 1.7% of patients prescribed diclofenac, indomethacin, nabumetone, or piroxicam have ADRs, of which 18.3% are HSRs. Patients with prior HSRs, female sex, autoimmune diseases, and those prescribed a high NSAID dose have an increased risk of an NSAID HSR.

How does this study impact current management guidelines? Clinician awareness of NSAID hypersensitivity in patients with risk factors can guide patient counseling and safe prescribing practices.

BACKGROUND: Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medications in the United States. NSAID use can be limited by adverse drug reactions (ADRs), including hypersensitivity reactions (HSRs).
OBJECTIVE: We aimed to use electronic health record data to determine the incidence and predictors of HSRs to prescription NSAIDs.
METHODS: We performed a retrospective cohort study of all adult outpatients in a large health care system prescribed diclofenac, indomethacin, nabumetone, or piroxicam between January 1, 2004, and September 30, 2012. The primary outcome was an ADR or HSR attributed to the prescribed NSAID within 1 year of prescription, determined from a longitudinal allergy database. We used natural language processing to classify known ADRs as either HSRs or side effects. Multivariable logistic regression models were used to identify independent risk factors for NSAID HSRs.
RESULTS: Of 62,719 patients prescribed NSAIDs, 1,035 (1.7%) had an ADR, of which 189 (18.3%) were HSRs. Multivariable regression analysis identified that patients with prior drug HSR history (odds ratio [OR] 1.8 [95% CI 1.3, 2.5]), female sex (OR 1.8 [95% CI 1.3, 2.4]), autoimmune disease (OR 1.7 [95% CI 1.1, 2.7]), and those prescribed the maximum standing NSAID dose (OR 1.5 [95% CI 1.1, 2.0]) had increased odds of NSAID HSR.
CONCLUSIONS: NSAID therapeutic use can be limited by ADRs; about 1 in 5 NSAID ADRs is an HSR. Both patient and drug factors contribute to HSR risk and are important to guide patient counseling. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

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Abbreviations used
ADR- Adverse drug reaction
AERD- Aspirin-exacerbated respiratory disease
COX-2- Cyclooxygenase 2
EHR- Electronic health record
HSR- Hypersensitivity reaction
ICD-9- International Classification of Diseases, ninth edition
NSAID- Nonsteroidal anti-inflammatory drug
OR- Odds ratio
PEAR- Partners Enterprise Allergy Repository
PHS- Partners HealthCare System
PO- Oral route

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications.[1] NSAIDs can cause a variety of adverse drug reactions (ADRs) that range from minor to severe.[2-4] Reactions to NSAIDs include side effects (eg, gastrointestinal upset, bleeding, nephrotoxicity)[1,5] as well as allergic or pseudoallergic reactions (ie, hypersensitivity reactions [HSRs]).[5] Although some side effect reactions do not preclude future use of NSAIDs, HSRs warrant particular caution, as allergic (ie, IgE-mediated) reactions predictably worsen with re-exposure and pseudoallergic reactions often exhibit dose-dependent recurrence.[6] NSAIDs have been identified as one of the most common causes of drug-induced anaphylactic reactions.[7,8]

Prior studies suggest a 1.9% to 3.5% prevalence of self-reported allergy to NSAIDs,[9-11] with 2 studies finding self-reported incidence ranging from 0.2% to 6.0%.[10,12] However, these studies have included all "allergies"—inclusive of both HSRs and side effects—in their frequency estimates. In addition, although electronic health records (EHRs) contain both coded and noncoded (ie, free text) data, prior incidence estimates of NSAID allergy from EHR data used only coded elements, which may have underestimated HSR burden.

Previously reported risk factors for NSAID HSRs include chronic urticaria/angioedema, prior HSRs, aspirin-exacerbated respiratory disease (AERD), and atopy.[6,13-18] One study using US insurance claims data identified that the NSAID indications of acute pain and inflammatory arthritis increased the risk of NSAID HSRs.[19] In the present study, we applied novel informatics methods using EHR data to estimate the incidence of ADRs and HSRs to prescription NSAIDs, and defined risk factors for developing these HSRs.

METHODS

Study design, population

We performed a retrospective cohort study using the EHR data available within Partners HealthCare System (PHS), an integrated health care delivery network in the Boston area of the United States. To identify which NSAIDs to use for this study, we first identified the most common NSAIDs in a cross-sectional analysis of the Partners Enterprise Allergy Repository (PEAR), a database of allergy and adverse effect information that contains more than 4 million active allergy records for more than 2 million PHS patients (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).[11,20] Our analysis focused on NSAIDs that were: (1) prescription-only in the United States, (2) inhibitors of both of the cyclooxygenase 1 and cyclooxygenase 2 (COX-2) enzymes, and (3) used predominantly by the oral route (ie, PO). Diclofenac, indomethacin, nabumetone, and piroxicam met these criteria and were included in this study.

The study population included all adult outpatients (age $\geq$ 18 years) prescribed any of the 4 oral NSAIDs from January 1, 2004, through September 30, 2012, and who had at least 1 visit within 1 year at any PHS outpatient clinic after the NSAID prescription.

We subsequently ran a separate analysis of patients prescribed only celecoxib or meloxicam, 2 selective COX-2 inhibitors.

Primary outcome

The primary outcome was an ADR or HSR to the prescribed NSAID within 1 year. We chose to evaluate the fixed time frame of 1 year to allow sufficient time for patients to have a repeat visit and report an ADR/HSR. We identified ADRs and HSRs from PEAR, which contained detailed symptoms reported by patients and/or observations made by health care providers. PEAR reactions could be entered in a coded format that used a predefined list of reactions selected by providers for each drug, or a free-text format, which comprised approximately 6% of entries. For free-text reaction entries, informatician investigators (KHL, LZ) used natural language processing algorithms to automatically map reactions to a standardized form.[11,21] For example, the free-text reaction "full body hives" was mapped to the coded reaction "hives." All mapped free-text reactions were manually verified by another investigator (KGB).

We considered all PEAR reaction entries an ADR. We defined HSRs as the subset of ADRs that included reactions mapped to anaphylaxis, hypotension, angioedema, swelling, rhinitis, bronchospasm, asthma, wheezing, shortness of breath, hives, urticaria, itching, or rash.[22] We additionally considered nonimmediate HSRs previously attributed to NSAIDs by performing key word searches of the PEAR reaction field for serum sickness, drug rash eosinophilia and systemic symptoms syndrome, erythema multiforme, acute interstitial nephritis, fixed drug eruption, erythema nodosum, Stevens-Johnson syndrome, toxic epidermal necrolysis, pneumonitis, meningitis, lichenoid drug eruptions, and leukocytoclastic vasculitis.[6,23] Remaining known reactions were considered side effect reactions, which we grouped and sorted by frequency. "Unknown" reactions were considered separately, and could reflect that the patient and/or the provider did not know the reaction details.

Because PEAR allows for drug class entries (eg, NSAIDs) as well as specific drug entries (eg, diclofenac), we conducted a sensitivity analysis of ADR and HSR incidence by assuming that all PEAR allergy entries of "NSAID" were related to the NSAID that was prescribed. For this expanded definition, we similarly distinguished HSRs, side effects, and unknown reactions.

We used identical methods to identify the incidence of ADRs and HSRs among adult outpatients prescribed only celecoxib or meloxicam from January 1, 2004, through September 30, 2012, and who had at least 1 visit within 1 year at any PHS outpatient clinic after the prescription.

Predictor variables

Age (at the time of first NSAID prescription), gender, and race/ethnicity were identified from EHR demographic tables. We defined ADR and HSR histories using the PEAR database. We identified NSAID treatment indications (eg, rheumatoid arthritis, joint pain, chronic pain) as a coded or free-text entry into the EHR "Problem List" or presence of the relevant code(s) from the International Classification of Diseases, ninth edition (ICD-9) entered within 30 days of the NSAID prescription. All ICD-9 codes were informed by prior studies, when available (Table E2, available in this article's