

## Drug-drug interactions of non-steroidal anti-inflammatory drugs with other drugs in patients with rheumatic diseases

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**Objective:** To determine the prevalence of and identify drug-drug interactions (DDI) between non-steroidal anti-inflammatory drugs (NSAID) and other drugs in a prescription database of patients with rheumatic diseases.

**Material and methods:** This is a cross-sectional study of a drug prescription database saving information on 35,000 individuals who benefited from a pre-paid medical system serving bank employees and their relatives. The analysis included one year period (from January to December 1998). NSAID-DDI were listed and classified into 3 levels (1: minor; 2: moderate, and 3: high health risk or death risk) according to DRUGDEX<sup>®</sup> as well as MEDLINE and EMBASE search.

**Results:** We analyzed 3,207 NSAID prescriptions (1.7 ± 1.6 per patient) to 1,855 rheumatic patients (adults: 76.7%; geriatric: 20.2%, and pediatric: 3.0%; soft tissue rheumatism: 52%; osteoarthritis: 19%, and rheumatoid arthritis: 10%). There were 648 (20.20%) NSAID-DDI prescriptions: 594 (91.66%) corresponded to level 1; 46 (7.09%) to level 2, and 8 (1.23%) to level 3. In addition, 96 (2.99%) prescriptions included NSAID duplications. Interestingly, we found no NSAID-DDI with anticoagulants, anticonvulsants, and oral hypoglycemics were found.

**Conclusions:** The prevalence of NSAID-DDI prescriptions to 1,855 rheumatic patients was 20.20% in one year. NSAID-DDI was mostly (91.66%) level 1, and rarely (1.23%) level 3. NSAID duplications were found in 2.99%. These results provides information on the frequency of prescriptions with DDI, which might potentially produce harmful effects and data, which may help in the development of studies searching for the clinical relevance of NSAID-DDI.

**Key words:** NSAID. Drug-drug interactions. Drug database. Rheumatic diseases. Prescriptions.

### Interacciones entre de antiinflamatorios no esteroideos y otros fármacos en pacientes con enfermedades reumatológicas

**Objetivo:** Determinar la prevalencia e identificar las interacciones (INTMED) entre antiinflamatorios no esteroideos (AINE) y otros fármacos en una base de datos de prescripción a enfermos reumáticos.

**Material y métodos:** Se trata de un estudio transversal de una base de datos de prescripción de 35.000 beneficiarios de un sistema de atención médica de prepago para trabajadores bancarios y sus familiares. El análisis abarca un año (de enero a diciembre de 1998). La lista y la clasificación de las AINE-INTMED en 3 niveles (1: mínimo; 2: moderado, y 3: alto riesgo para la salud/peligro de muerte) se hicieron de acuerdo con DRUGDEX<sup>®</sup> y búsquedas en MEDLINE y EMBASE.

**Resultados:** Se analizaron 3.207 prescripciones de AINE (1,7 ± 1,6 por paciente) a 1.855 pacientes reumáticos (el 76,7% adultos, el 20,2% geriátricos y el 3,0% pediátricos; reumatismo extraarticular: 52%; osteoartrosis: 19%; artritis reumatoide: 10%). Se encontraron 648 (20,20%) AINE-INTMED, de las que 594 (91,66%) correspondieron al nivel 1, 46 (7,09%) al nivel 2 y 8 (1,23%) al nivel 3. Además, encontramos 96 (2,99%) prescripciones con duplicación de AINE. No encontramos AINE-INTMED con anticoagulantes, anticonvulsivos o hipoglucemiantes orales.

**Conclusiones:** La prevalencia de AINE-INTMED en prescripciones a 1.855 pacientes reumáticos en un año fue del 20,20%. La mayoría (91,66%) fue del nivel 1 y raramente del 3 (1,23%). El 2,99% de ellas tuvieron duplicaciones de AINE. Nuestros resultados proporcionan información de la prevalencia de INTMED que potencialmente podrían producir daños al individuo y datos que podrían influir en el desarrollo de estudios de la importancia clínica de las AINE-INMED.

**Palabras clave:** AINE. Interacciones medicamentosas. Bases de datos. Enfermedades reumáticas. Prescripciones.

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## Introduction

Drug-drug interactions (DDI) accounts for a significant proportion of prescriptions in the general population and drug-related problems in certain groups<sup>1,2</sup>. DDI have been specifically implicated in hospital admissions and fatalities associated with drug-adverse events<sup>3-7</sup>. In general, the report of DDI refers to clinical events or pharmacokinetic/pharmacodynamic (PK/PD) assays involving 2 or more drugs, yet they may even be predicted during drug development.

PK/PD DDI involving anti-rheumatic drugs, particularly non-steroidal anti-inflammatory drugs (NSAID) have been described as well<sup>8</sup>. Although NSAID-DDI involve few specific agents, it is rarely stated as such and people assume that all NSAID interact with all anticonvulsants, oral hypoglycemics, diuretics, and antihypertensives. Until now, however, the prevalence and clinical relevance of such interactions in the population are unknown.

The purpose of this cross-sectional study was to identify the prevalence and characteristics of NSAID-DDI in a drug-prescription database of patients with rheumatic disease.

## Material and methods

The drug prescription database analysed in this study saved information on 35,000 individuals in Mexico City who benefited from a pre-paid medical system serving private bank employees and their relatives. Such medical system included 1,688 general physicians and 1,518 specialists. NSAID prescription had no restrictions at all; physicians have access to all NSAID available in the market. The period of analysis was of one year, from January to December 1998. The information was retrieved from an Oracle 7.3.4 database, which saved the information generated at the pharmacy through an on-line claim processing system in a UNIX environment. This software was designed with the aforementioned purposes. The customers of this system (2 private banks) gave consent MEDCO for the analyses performed in this study.

NSAID-DDI were listed and classified by a group of clinicians and pharmacologists according to 2 major modules of DRUGDEX<sup>®</sup>, which is a database of drugs already approved or in phase III studies recognized by the Food and Drug Administration and the medications most frequently used in the world. One of the modules—the drug evaluation monographs—contains 170,000 registries with monographs on 1,700 medications, and the other—the adverse drug reactions index—refers to drug interactions reported all over the world. NSAID-DDI information was complemented by MEDLINE and EMBASE databases search. Accord-

**TABLE 1. General characteristics of the population included in the study**

	Patient data (n = 1,855)		Prescription data (n = 3,207)	
	N	%	N	%
Males	698	37.6	1,196	37.3
Females	1,157	62.4	2,011	62.7
Mean age (± SD), years	46.67 ± 18.30		51.38 ± 18.49	
<i>Age groups (years)</i>				
< 16	56	3.0	66	2.0
17-64	1,424	76.7	2,235	69.7
> 65	375	20.2	906	28.2
<i>Diagnoses</i>				
Soft tissue rheumatism	1,090	51.9	1,502	46.9
Osteoarthritis	390	18.6	744	23.2
Rheumatoid arthritis	204	9.7	439	13.7
No specific diagnosis	117	5.6	136	4.2
Gout	68	3.2	100	3.1
Myopathies	41	1.9	51	1.6
Spondyloarthropathies	36	1.7	72	2.2
Other diagnosis	154	7.4	163	5.1

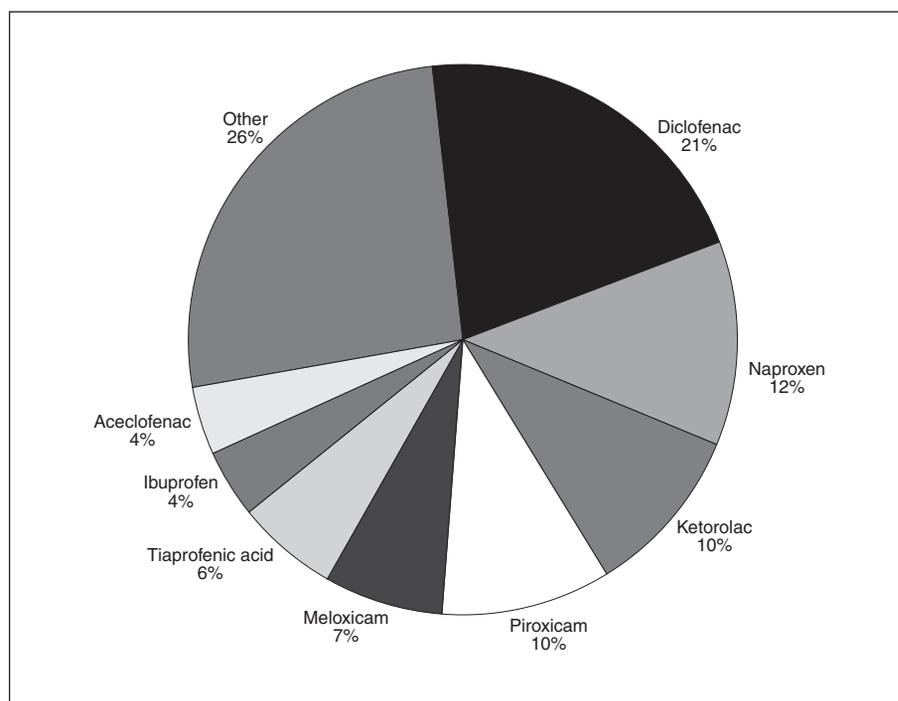
SD: standard deviation.

ding to DRUGDEX<sup>®</sup>, the severity of NSAID-DDI was classified into 3 categories: 1, minor health risk; 2, moderate health risk; and 3, high health risk or death risk.

The analysis performed in this study concerned with information on NSAID prescriptions saved throughout one year in the drug database. In consequence, we did not aim to investigate whether NSAID-DDI found in the database could ever lead to any clinical event or not. The analysis included patient's demographics; diagnoses (10<sup>th</sup> World Health Organization International Classification of Diseases, ICD-10); drug prescription (ingredient, therapeutic class, dose, duration, and date supplied); and physician specialty. The unit of this analysis was the data on the prescription file.

## Statistical analysis

Descriptive statistics were calculated for demographic variables and ICD-10 diagnoses. Drug prescription analysis by age group, specialty, and diagnosis was carried out by  $\chi^2$  and one way analysis of variance (ANOVA). All data were analyzed using the STATVIEW 5



**Figure 1.** Percentage of non-steroidal anti-inflammatory drugs in 3,207 prescriptions.

(SAS Institute Inc., Cary, NC, USA), and STATA 6.0 for Windows.

## Results

### General characteristics

There were 3,207 NSAID prescriptions to 1,855 rheumatic patients or  $1.72 \pm 1.60$  prescriptions per patient (table 1). Most prescriptions were given to adult patients with soft tissue rheumatism. Nearly one half (52.4%) of all NSAID prescriptions came from general physicians, 24.2% from orthopedic surgeons, and 11.5% from rheumatologists; less frequently, from internists (5.5%), geriatricians (3.6%), pediatricians (0.5%), and other specialists (2.6%). The NSAID most frequently prescribed was diclofenac (fig. 1).

### NSAID-DDI

Six-hundred and forty-eight (20.20%) prescriptions fulfilled the NSAID-DI pre-specified criteria. Most of NSADI-DDI ( $n = 594$ ; 91.66%) corresponded to level 1; 46 (7.09%) corresponded to level 2, and only 8 (1.23%) to level 3 (table 2). Level 1 interactions varied widely, but the 2 most frequently found included ketorolac ( $n = 87$ ) and metoprolol ( $n = 32$ ). Level 2 interactions involved NSAID and loop-diuretics in most cases

( $n = 10$ ); 21 prescriptions involved NSAID and methotrexate. There were only 8 prescriptions with level 3 NSAID-DDI, which consisted of NSAID and thiazides or antihypertensives. There were no significant tendencies regarding patient's age or medical specialty in NSAID-DDI generation.

In addition to NSAID-DDI, we identified 96 (2.99%) prescriptions involving the simultaneous use of 2 or more NSAID (table 2).

## Discussion

In this study, the prevalence of NSAID-DDI interactions in 3,207 prescriptions to 1,855 patients was 20.20%. As reference, the prevalence of DDI –including NSAID– in Swedish pharmacies was 13.65%<sup>2</sup> and around one-third in nursing homes<sup>9</sup>. Most of such NSAID-DDI pose mild (91.66%) or moderate (7.09%) health risk. The low prevalence of level 3 NSAID-DDI (1.23%) found in the study may be comparable to those reported in studies considering all types of drugs: 1.4% of 962,013 prescriptions in Sweden<sup>2</sup>, 5.0% of 464 in Canada<sup>10</sup>, and 4.4% of 26,337 to elderly patients in Denmark<sup>11</sup>.

Interestingly, we found no instance of NSAID-DDI with anticoagulants, anticonvulsants, and oral hypoglycemics despite the fact that most prescriptions were given to adult and elderly patients (approximately 70% and 28%, respectively). The prevalence of this type of

**TABLE 2. Non-steroidal anti-inflammatory drugs-drug interactions (total = 744) classified according to risk level**

Risk level	N	%
Level 3, high health risk or death risk (n = 8; 1.54%)*		
Acemetacin/triamterene-hydrochlorothiazide	2	1.9
Diclofenac/triamterene-hydrochlorothiazide	2	1.9
Ketorolac/triamterene-hydrochlorothiazide	1	9.6
Piroxicam/triamterene-hydrochlorothiazide	1	9.6
Diclofenac/hydrochlorothiazide	1	9.6
Meloxicam/hydrochlorothiazide	1	9.6
Level 2, moderate health risk (n = 46; 7.09%)*		
Indomethacin/torasemide	7	0.9
Diclofenac/methotrexate	3	0.4
Ketoprofen/furosemide	3	0.4
Ketorolac/methotrexate	3	0.4
Naproxen/methotrexate	2	0.3
Piroxicam/methotrexate	2	0.3
Diclofenac/digoxin	2	0.3
Piroxicam/digoxin	2	0.3
Ibuprofen/methotrexate	2	0.3
Level 1, minor health risk (n = 594; 91.66%)*		
Diclofenac/metoprolol	11	1.8
Naproxen/metoprolol	11	1.8
Ketorolac/metoprolol	10	1.7
Diclofenac/methotrexate	9	1.5
Meloxicam/metoprolol	9	1.5
Piroxicam/metoprolol	8	1.3
Ibuprofen/metoprolol	7	1.2
Piroxicam/atenolol	5	0.8
Aceclofenac/metoprolol	5	0.8
Ketorolac/methotrexate	5	0.8

\*Level 3 section lists all observed interactions. Level 1 and 2 sections list the most frequent interactions.

NSAID interactions in general prescription databases is low, but its risk for health high.

In contrast, we found NSAID duplication, consisting in the simultaneous prescription of 2 or more NSAID in 96 (2.99%) prescriptions, which is slightly lower than the 4.3% figure reported in 2,631 elderly patients in Canada<sup>12</sup>. Ketorolac, which in this study appears in 90% of NSAID duplication, is posed in our country as an analgesic and antipyretic drug when it is actually a NSAID.

**TABLE 3. Non-steroidal anti-inflammatory drugs duplications (n = 96)**

Generic name	N	%
Diclofenac/ketorolac	36	37.5
Meloxicam/ketorolac	15	15.6
Tenoxicam/ketorolac	14	14.6
Naproxen/ketorolac	13	13.5
Piroxicam/ketorolac	9	9.4
Diclofenac/nabumetone	9	9.4

Although the list and classification of NSAID-DDI was based on DRUGDEX<sup>®</sup> as well as PK/PD and clinical reports, it is questionable that PK/PD may be of clinical relevance, particularly in regards to producing harm. While PK DDI refers to drug concentration increase or reduction at the sites where it exerts its action, PD DDI does it to the additive or inhibitory effects of various drugs at their receptors<sup>13</sup>. Such are the cases of NSAID-methotrexate PK DDI, which in clinical practice seems irrelevant<sup>14</sup>, and NSAID-triamterene and hydrochlorothiazide, which may rarely induce water and sodium retention as well as refractory hypertension<sup>15-17</sup>. In the literature, most NSAID-DDI refer to drug-class interactions (i.e., NSAID and anticoagulants) and not to specific interactions (i.e., phenylbutazone, ibuprofen, or acetylsalicylic acid specific interactions with warfarin); and most lack details on the dose, length-use, and dose-intervals that may harm. Clinical reports mostly consist, on the other hand, of cases with complicated clinical conditions presenting specific drug interactions. Overall, this confusing situation, which attains not only NSAID, but most drugs, prevents proper definitions and DDI classifications<sup>18</sup>.

Our study lacks of information on the consequences of NSAID-DDI at the patient level. Nor, it provides information on the ciclooxigenase-2 inhibitors, a drug class with anti-inflammatory properties widely used today because they were still not available at the time when our database was implemented. PK/PD and clinical properties of ciclooxigenase-2 inhibitors are now subjected to numerous studies.

Interestingly, the role of databases in the recognition of DDI may reduce the risk of DDI of clinical significance. Specifically, in one previous study, the proportion of prescriptions posing severe drug-drug interactions and patient's exposure to them was reduced by 62% and 20%<sup>19</sup>.

Although the relevance of the information provided by this database is unknown, it could orientate medical care providers on the frequency of prescriptions with DDI which may potentially produce harmful effects. It

may also help in the developing of studies assessing the clinical significance of NSAID-DDI prescriptions.

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