

## MONITORING OF NSAIDS ADVERSE EFFECTS BASED ON SPONTANEOUS REPORTS FROM WROCLAW REGIONAL ADVERSE DRUG REACTIONS MONITORING CENTER

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**Abstract:** The mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs) in majority of cases is responsible for adverse reactions of these therapeutic agents. Obtaining post-registration information on adverse drug reactions (ADRs) by means of the Yellow Card System is a significant element in the process of enhancing the safety of pharmacotherapy. The aim of the study was to analyze ADRs of NSAIDs (anti-inflammatory and analgesic drugs) reported to the Regional Centre for the Monitoring of Adverse Drug Reactions (RCMADR) in Wrocław in the years 2007–2009. The study material included 232 spontaneous reports, which were sent by physicians and pharmacists to the RCMADR in Wrocław, out of which 80 concerned mentioned drugs. Analysis of the obtained data revealed a relationship between the incidence and kind of ADRs and the age, gender of the patients, centre from which the data were supplied, geographical region of administered medication. A significant role of post-registration monitoring of adverse drug reactions during therapy with anti-inflammatory and analgesic drugs was confirmed in view of geographically conditioned differences affecting the profile of instituted therapy and the source of information. With an increasing global use of these medications, only thorough monitoring of every adverse reaction, encouraging spontaneous reports, as well as analysis at a global level may increase the knowledge on adverse drug reactions and enable correction of the safety profile of every drug from this group.

**Keywords:** adverse drug reactions, non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) exert their effects through inhibition of cyclooxygenase (COX) enzymes, participating in the synthesis of prostaglandins, what is the underlying mechanism of their analgesic and anti-inflammatory properties. The anti-inflammatory effect of these drugs is associated mainly with the inhibition of COX-2 (inducible form), while their effect on COX-1 (constitutive form) is responsible for the majority of adverse reactions. The classical NSAIDs (e.g., diclofenac, indomethacin, ibuprofen, ketoprofen, naproxen, mefenamic acid, piroxicam, acetylsalicylic acid – ASA) inhibit both isoenzymes. Their use is often accompanied by gastrointestinal intolerance due to decreased production of protective prostaglandin E<sub>2</sub> in the stomach. Preferential (e.g., nimesulide, meloxicam) or selective (e.g., celecoxib) COX-2 inhibitors have better gastric tolerance

profile, but they are characterized by more often occurring cardiovascular and renal adverse events. Hypersensitivity reactions to aspirin and other NSAIDs are also common and could range from hives to exacerbations of asthma or to anaphylaxis and death. These drugs can cause both antibody (IgE) mediated true allergic reactions and non-antibody pseudoallergic reactions (which are more common), with clinical symptoms resembling true allergic reactions (1). NSAIDs belong to drugs most commonly prescribed to patients, moreover, a large number of these drugs are available as non-prescription – OTC (over-the-counter) drugs, and their use increases dramatically from year to year. They are widely applied in all age groups for the treatment of pain, fevers of diverse etiologies and inflammation (2–8). According to some analyses, every day 30 millions of people take anti-inflammatory and anal-

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gesic drugs, 40% of them being over 65 years old (9). NSAIDs account for approximately 41000 hospitalizations and 3300 deaths per annum among the elderly in the United States (10). We can find diclofenac, indometacin, naproxen and piroxicam among the medications that should be prescribed with special attention to elderly patients on the Japanese version of the Beers list and some of them on the French list by Laroche, Beers list and Priscus list in German as well (11–14). Elderly population is particularly vulnerable to inappropriate use of medication. For this reason post-registration monitoring of adverse effects of this drug group by means of The Yellow Card System becomes an important element of enhancing the safety of pharmacotherapy. In Poland physicians, pharmacists and nurses are obligated to report adverse drug reactions (ADRs) to the Pharmacovigilance Center, mostly in The Yellow Cards Scheme. Unfortunately, it doesn't work particularly well due to the psychological barriers existing among medical personnel and lack of active stimulation tools. The ADR reports should be sent to one of Regional Centers for the Monitoring of Adverse Drug Reactions or directly to The Pharmacovigilance Department of The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products.

The aim of the study was to analyze adverse effects of non-steroidal anti-inflammatory drugs registered by The Regional Centre for the Monitoring of Adverse Drug Reactions in Wrocław in the years 2007–2009.

## EXPERIMENTAL

The study material included 232 spontaneous reports on adverse drug reactions, which were submitted by physicians and pharmacists to the RCMADR, a branch of the Department of Clinical Pharmacology, Wrocław Medical University. Reported diagnoses were coded using the International Classification of Disease (ICD-10), drugs were coded according to the Anatomical Therapeutic and Chemical codes (ATC) and ADRs were coded according to the Medical Dictionary for Regulatory Activities (MedDra) terminology. The material was stored in a secured database and was analyzed taking into account the age and gender of the patients, the profession of the person reporting (physician-specialty, pharmacist), source of information (hospital ward, outpatient clinic, pharmacy), route of administration (oral, intravenous, intramuscular, external), the kind of reported adverse reactions and administered medication.

## RESULTS

In the analyzed period, 232 reports of adverse drug reactions were sent to the RCMADR, out of which 80 reports (34.5%) concerned anti-inflammatory and analgesic drugs, such as NSAIDs (47 reports, 20.3% of all the reports) and ASA (33 reports, 14.2% of the total number of the reports) applied to patients mostly in anti-inflammatory/analgesic doses with an exception of one case (platelet anti-aggregation dose of ASA). Among 80 reports, 58.7% was related to NSAIDs and 41.2% only to ASA. In some cases one patient developed several adverse reactions.

Out of 80 reports on adverse reactions of anti-inflammatory and analgesic drugs, 53 (66.3%) were observed in women, while 27 (33.8%) in men. The analysis of association between the incidence of ADRs and gender revealed relationship to gender, women developed adverse effects more commonly. All the reports concerned the incidence of adverse reactions in adults. The analyzed population was divided into three age groups: A – aged 18–44 (27 patients), B – aged 45–65 (38 patients), C – aged 66–80 and older (15 patients). The majority of reports concerned the age group 44–65. A relationship was found between the incidence of ADR and the age of group B patients.

The origin of spontaneous reports was also analyzed, taking into account the kind of medical facility (hospital/outpatient clinic) and professional group (physician specialist/pharmacist). The number of ADR reports from outpatient clinics (42 reports – 53.2%) and inpatient health service (36 reports – 46.8%) was comparable.

Among the analyzed reports, none were sent by pharmacists, 75 reports (93.8%) came from physicians – allergologists (AL), 4 (5%) from family doctors (F) and 1 (1.2%) from unknown practitioner (UN).

As far as the route of administration is considered, regardless of the source of the report, the majority of adverse reactions were associated with oral administration – 68 reports (85%). Intramuscular route (IM) was associated with 6 episodes of adverse drug reactions (7.5%), while external and mixed (several drugs administered simultaneously by various routes) routes – with 3 reports each.

The analysis also involved the number of ADRs appearing in patient. A majority of reports included one – 30 reports (37.5%) or two adverse reactions – 31 reports (38.75%). Higher number of events was reported for 19 patients (23.75%).

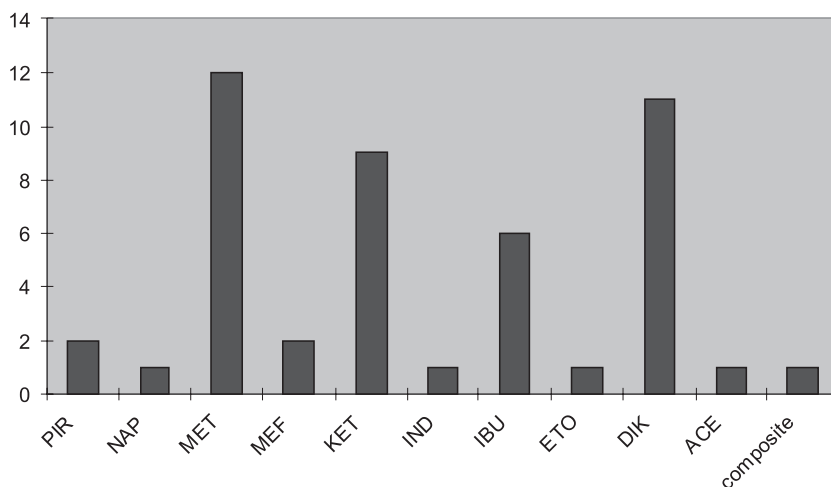


Figure 1. The number of adverse reactions in patients on anti-inflammatory and analgesic drugs therapy in relation to administered pharmacologically active substance

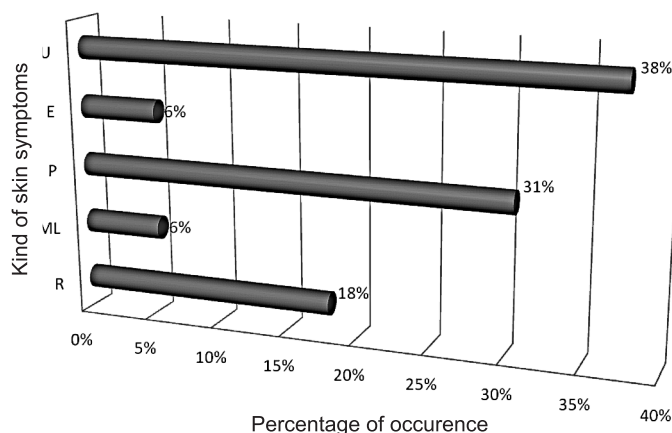


Figure 2. Percentage of skin adverse drug reactions

Among reports monitoring the incidence of adverse reactions to anti-inflammatory and analgesic drugs, 47 (58.75%) reports concerned the whole group of NSAIDs, and 33 (41.25%) to acetylsalicylic acid. Adverse reactions associated with the use of NSAIDs (excluding ASA) were due to: metamizole (MET), diclofenac (DIK), ketoprofen (KET), ibuprofen (IBU), mefenamic acid (MEF), piroxicam (PIR), naproxen (NAP), indometacin (IND), etofenamate (ETO), acemetacin (ACE). Comparison of the incidence of adverse drug reactions in relation to the active substance revealed that the majority of reports concerned metamizole – 12 reports (25.5%) (Fig. 1).

The submitted reports were also used for evaluation of the character of adverse drug reactions. ADRs

were grouped under System Organ Classes (SOC) according to MedDRA code. They included skin symptoms (SOC – skin and subcutaneous tissue disorders), edema (general, localized; SOC – general disorders and administration site condition), impaired respiratory function (SOC – respiratory, thoracic and mediastinal disorders), nervous systems and sense organs symptoms (SOC – nervous system disorders), gastrointestinal tract events (SOC – gastrointestinal disorders), genitourinary system problems (SOC – renal and urinary disorders), cardiovascular system symptoms (hypertension, tachycardia) (SOC – cardiac disorders) and anaphylactic reaction (allergic reactions not otherwise specified (NOS) – which could be related to all SOC terms). Kinds of ADR's related directly to anti-inflammatory and analgesic drugs are presented in Table 1.

Table 1. Description of adverse reactions to anti-inflammatory and analgesic drugs reported to RCMADR in Wrocław (according to the MedDRA PT and SOC classification).

System/organ/symptom	Number of cases	Percentage of all symptoms (%)
Skin lesions/redness, urticaria, pruritus, rash	53	44
Edema	36	30
Respiratory system/cough, spasm, dyspnoea	21	17
Nervous system and sense organs/ headaches, dizziness, blurred vision, tinnitus	5	4
Gastrointestinal tract/pain in the abdomen, constipation, vomiting	3	2
Anaphylactic reaction	1	1
Other	2	2

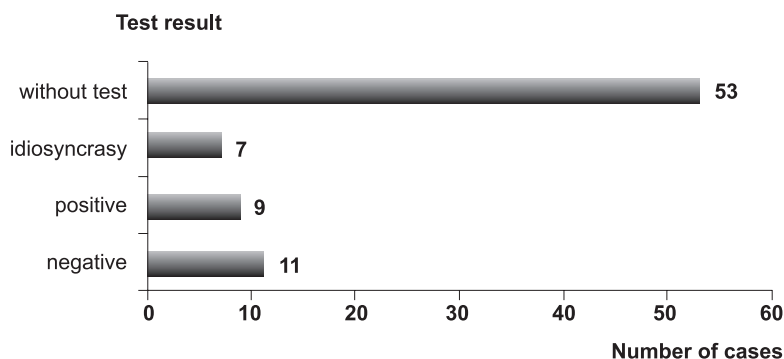


Figure 3. The number of diagnostic tests in patients treated with anti-inflammatory and analgesic drugs

ADR's involving skin and mucous membranes predominated among the adverse reactions. They occurred in 70 patients either as the only symptom or in coexistence with other symptoms. This group included such symptoms as: pruritus (P) observed in 22 patients (31%), urticaria (U) – 27 patients (38%), rash (R) – 13 (18%), mucous membranes lesions (ML) – 4 (6%), and erythema (E) in 4 (6%) cases (Fig. 2). All mentioned terms used here correspond to MedDRA Preferred Terms (PT). The incidence of reported symptoms from this group was 44% (53 reports). The second most common group of ADR's included swelling (edema) of a generalized or localized character, including angioedema, 30% (36 cases) (Table 1).

Suspecting that the above reactions were caused by drugs hypersensitivity, 27 patients (33.7%) out of 80 reports were submitted to diagnostic tests. They confirmed allergy to drugs in 9 patients (metamizole, ASA, ibuprofen, mefenamic acid, ketonal), idiosyncrasy in 7 patients (ASA, piroxicam), while 11 patients were found to have no

allergic background to the reported ADRs. However, a majority of patients did not undergo any examinations in order to confirm/exclude hypersensitivity mechanisms as the underlying cause of observed adverse reactions (53 subjects) (Fig. 3).

## DISCUSSION AND CONCLUSIONS

In the material collected by RCMADR in Wrocław, 34.5% of all submitted reports concerned the adverse reactions to anti-inflammatory and analgesic drugs, were predominant are caused by ASA. In comparison, in the analysis of the American Association of Poison Control Centers National Poison Data System (AAPCC NPDS) drugs from this group were responsible for almost 25% of all reported adverse reactions (8). Sanchez-Borges et al. (7) noted that NSAIDs are responsible for 21 to 25% of all adverse reactions to drugs. Aspirin intolerance occurs in 4.3 to 11% of adult asthmatics and in 25.6% of patients with asthma and polyposis. Moreover, the risk factors for NSAIDs hypersensi-

tivity, which is observed in 0.5–1.9% of the general population, are female gender, atopy, their intermittent use for the relief of acute pain (7). Aspirin was identified as a causal medication in 18% of cases of all admissions to hospital for ADRs, and other NSAIDs were implicated in 12% (15). The difference with our observations may probably be attributed to different specialties of the reporting physicians, since as many as 76 reports (95%) were submitted by allergologists, and only 4 (5%) by family doctors, what affected significantly the obtained results. ADRs were most commonly observed in women (66.3%) than in men (33.8%). The relationship between the incidence of ADRs and gender was also confirmed by Balińska-Miśkiewicz et al. in the analysis of epidemiological evaluation of the incidence of risk factors for drugs hypersensitivity in selected Lower Silesia towns (16). However, the findings presented in AAPCC NPDS report were different and did not provide any evidence for the association between the incidence of adverse reactions to anti-inflammatory and analgesic drugs and gender. Such discrepancy in obtained data results most probably from qualitative difference in the number of submitted reports (8, 16). It is worth noting that all ADR reports submitted to The Regional Centre for the Monitoring of Adverse Drug Reactions in Wrocław were originated by physicians, while pharmacists submitted none.

It should be stressed that as many as 33 out of 80 reports pointed to the reactions to ASA applied to patients mostly in anti-inflammatory/analgesic doses. Among other anti-inflammatory and analgesic drugs, most ADR's reports concerned metamizole, diclofenac and ketoprofen. According to statistics, the three types of NSAIDs most commonly used to treat many types of back pain and neck pain include: ibuprofen, naproxen, celecoxib and ketoprofen or diclofenac (depended on geographical region). It is worthy to point that metamizole isn't the most often used among the NSAID group but in our analysis has the first position (17).

The AAPCC NPDS report claimed that the drugs with the highest potential for evoking adverse drug reactions are phenylbutazone, mefenamic acid and sodium meclofenamate. However, it did not involve ASA in the analysis. The evaluation of ADR's reports on NSAIDs performed in Spain demonstrated the highest association between the incidence of adverse reactions and the use of diclofenac, naproxen, ketoprofen, indometacin, flurbiprofen and piroxicam (8, 9). Thus, it may be stated that the reported ADRs profile is specific for a given geographic region and at least partly results from a

tendency to use country specific medications from the group of anti-inflammatory and analgesic drugs.

Skin changes, swellings (generalized and localized) as well as respiratory distress predominated among adverse reactions to anti-inflammatory and analgesic drugs reported in Lower Silesia. Such a distribution of adverse effects is different from generally acknowledged specificity of these medications safety profile, which lists among the most common adverse reactions effects gastrointestinal complications such as abdominal pain, dyspepsia, peptic ulceration, bleeding and enteropathy. It is estimated that up to 15–30% of patients taking NSAIDs develop gastrointestinal adverse reactions. High dosage of indomethacin, meclofenamate and piroxicam were associated with an increased risk of dyspepsia. It is a strong risk factor for an NSAIDs related ulcer complication. Dyspepsia, nausea and vomiting occur in 2–6% of patients after aspirin administration. The mentioned signs are a significant cause of treatment discontinuation and limit patient compliance (6, 18–20). Non-steroidal anti-inflammatory drugs, especially ketoprofen and metamizole, are a frequent cause of acute tubulointerstitial nephritis (21). Moreover, during NSAIDs administration, the following problems can be observed: hepatic (hepatotoxicity), cardiovascular (changes in blood pressure), bone marrow (agranulocytosis, aplastic anemia, coagulation problems, platelet aggregation inhibition) and ototoxicity (transient deterioration of hearing, tinnitus) (3, 7–9, 16). However, it is characteristic that among the notifications submitted at the RCMADR in Wrocław there were no reports of severe gastrointestinal disturbances, and obtained data point to hypersensitivity to drugs (intolerance, idiosyncrasy, allergy) as the reason for observed ADRs. This is an obvious consequence of the sources of origin of the Yellow Cards (physicians-allergologists). Diagnostic procedures performed in 27 patients for drug hypersensitivity as the cause of adverse reactions identified allergy in 9 patients and idiosyncrasy in further seven cases as the underlying mechanisms of observed adverse drug reactions. According to Sanchez-Berges et al. the prevalence of hypersensitivity to NSAIDs has been estimated between 0.5 to 1.9% of the general population (20).

Analysis of obtained data confirmed a significant role of strategies to minimize anti-inflammatory and analgesic drugs adverse effects including avoidance of inappropriate drug prescription trends, using the smallest effective doses during effective number of days, avoiding co-administration of other agents with the same toxicity, and post-registration

monitoring of adverse drug reactions occurring in the therapy due to geographical variability affecting the profile of instituted therapy and the source of information. With an increasing world tendency to use anti-inflammatory and analgesic drugs, only scrupulous monitoring of every adverse reaction, encouraging spontaneous reports, as well as their analysis at a global level may increase the knowledge on adverse drug reactions and enable correction of the safety profile of every drug from this group. It should be changed the role of pharmacists, community and hospital, in the pharmacovigilance. They can have important position in the all activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem.

#### Conflict of interest

All authors confirmed that they don't have any conflict of interest.

#### Acknowledgments

We would like to acknowledge the contributions of the following individuals to the development of this paper: Elżbieta Pelc, Regional Medical Centre, Wrocław-Śródmieście No. 1, Magdalena Hurkacz and Piotr Milejski, Department of Clinical Pharmacology, Wrocław Medical University who in years 2007–2009 regularly sent reports on adverse drug reactions to The Regional Centre for the Monitoring of Adverse Drug Reactions (RCMADR) in Wrocław.

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*Received: 3. 06. 2011*