Łukasz Kasper, Krzysztof Sładek, Grażyna Bochenek, Mariusz Duplaga, Andrzej Szczeklik

Department of Medicine, Jagiellonian University Medical College, Krakow, Poland
Head of the unit: Prof. J. Musiał

Prevalence of hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) in the population of adult asthmatics in Poland based on an epidemiological questionnaire

Abstract

Introduction: Hypersensitivity reactions to drugs account for 25% of all side effects related to drugs, affecting more than 7% of the population. One in four such reactions is caused by acetylic acid and other non-steroidal anti-inflammatory drugs.
Material and methods: Between 1998 and 2000 epidemiological research was carried out in various centers, with the aim of estimating the frequency of allergy-based diseases in Poland. The objective of the study was to evaluate the frequency of hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs), based on an epidemiological questionnaire, in the Polish adult population.
Results: Bronchial asthma was diagnosed in 582 patients (5.4%). Of that group, 75 patients (12.9%) additionally reported symptoms of hypersensitivity to NSAIDs. Aspirin-induced asthma was diagnosed in 11 patients (14.7%) with clinical manifestations of hypersensitivity responses. Frequency of aspirin-induced asthma with clinical symptoms amounted to 1.9% of asthmatics. In the assessment of severity of the disease, aspirin intolerance was the only statistically significant factor ($p = 0.0003$; odds ratio 28.6 with assumed 95% confidence interval).
Conclusions: In the population of adults in Poland, the frequency of aspirin-induced asthma amounted to 0.1%. Hypersensitivity to NSAIDs was observed in 12.9% of asthmatics. In asthmatics with symptoms of hypersensitivity to non-steroidal anti-inflammatory drugs, which takes the course of clinically demonstrable aspirin-induced asthma, the risk of severe asthma is 30-fold higher.

Key words: asthma, prevalence, aspirin induced asthma, non-steroidal anti-inflammatory drugs, hypersensitivity
Pneumonol. Alergol. Pol. 2009; 77: 431–439

Introduction

Hypersensitivity reactions to drugs account for about 25% of all side effects related to drugs, affecting more than 7% of the population [1]. It has been discovered that one in four of such reactions is caused by acetylic acid and other non-steroidal anti-inflammatory drugs [2].

Like many other drugs, aspirin and non-steroidal anti-inflammatory drugs may lead to hypersensitivity reactions, which can be either related or unrelated to the mechanism of immunological response [3]. In 2001 Stevenson [4] and the European Academy of Allergology and Clinical Immunology published the clinical classification of hypersensitivity reactions to aspirin and NSAIDs. Eight reaction types were distinguished, the first four being related to the suppression of the activity of cyclooxygenase (an important enzyme in the metabolism of arachidonic acid) by aspirin and other non-steroidal anti-inflammatory drugs. The other four reactions are peculiar and characteristic of a given drug substance. They probably occur in the immunological pathway, regardless of cyclooxygenase inhibition. The first two reaction types are most common in clinical practice.

Addres for correspondence: Łukasz Kasper, Department of Medicine, Jagiellonian University Medical College, Skawinska 8, 31–066 Krakow, Poland, tel.: (012) 430 52 66, ext. 277, fax: (012) 430 51 47, mobile: 601 771 511, e-mail: kasper@mp.pl

Received: 18.11.2008

ISSN 0867–7077

The first one relates only to asthma patients, who may often be affected by chronic sinusitis and nasal polyps. Following the administration of aspirin and other non-steroidal anti-inflammatory drugs, these patients experience attacks of asthma, chronic inflammation of the nasal mucosa, reddening of the eyes and face, and oedema of soft tissue around the eyes. Some patients may only have symptoms in the lower airways, while in others the symptoms may affect the upper airways, i.e. the nose, sinuses and eyes. Such a clinical form of the condition is referred to as aspirin-induced asthma [5–8]. In some cases patients may also suffer from ailments in the gastrointestinal tract and have skin problems. The reaction of the first type is brought about by aspirin as well as other non-steroidal anti-inflammatory drugs that are capable of inhibiting cyclooxygenase. The reaction of the second type concerns the skin. From 15 minutes to two hours after taking aspirin, and/or other NSAIDs, some patients with chronic idiopathic urticaria develop urticaric wheals on the face, the hairy parts of the head, neck and upper chest. It is often accompanied by angioedema. These reactions depend on the drug dose taken by the patient and also on the intensity of chronic urticaria symptoms. The more aggravated the symptoms, the greater the likelihood that aspirin-induced symptoms will appear and that they will be more bothersome to the patient. This problem affects about 20–40% of patients suffering from idiopathic urticaria. It is often referred to as the urticaria/angioedema-type of aspirin hypersensitivity [9, 10]. The pathomechanism of aspirin hypersensitivity that affects the skin is similar to its bronchial form. It consists in the inhibition of COX by aspirin and an increased synthesis of cysteinyl leukotrienes [11, 12].

Very few reliable studies have been carried out so far with regard to NSAIDs hypersensitivity in patients with bronchial asthma [13, 14]. In the European surveys ECRHS and ISAAC [15–22] the symptoms of drugs hypersensitivity, in particular intolerance to NSAIDs, are not taken into account. Our knowledge about the frequency of aspirin-induced asthma occurrence is based upon studies conducted on select populations, e.g. groups of patients with heavy asthma and disease exacerbation requiring hospital treatment and/or mechanical ventilation [23–25].

Between 1998 and 2000 a multicenter epidemiological survey was carried out which focused on the occurrence of allergic disease in Poland [26, 27]. The survey estimated the occurrence frequency of asthma, seasonal and perennial allergic rhinitis as well as atopic dermatitis. The project also took into consideration the assessment of drug hypersensitivity symptoms, based on a questionnaire prepared by the Department of Medicine, Jagiellonian University Medical College in Krakow.

The study aimed at a retrospective analysis of epidemiological data on the occurrence frequency of non-steroidal anti-inflammatory drugs hypersensitivity in asthma patients. The data was gathered in the period 1998–2000.

Material and methods

The epidemiological study related to the occurrence of asthma, seasonal and perennial rhinitis, as well as atopic and contact dermatitis, was carried out in 11 Polish research centers (in Bialystok, Bydgoszcz, Krakow, Gdansk, Lublin, Lodz, Poznan, Rabka, Warsaw, Wroclaw and Zabrze). It utilised a questionnaire on hypersensitivity to aspirin and other non-steroidal anti-inflammatory drugs. The document was drafted on the initiative of the Department of Medicine, Jagiellonian University Medical College, which also contributed greatly to its development. The detailed questionnaire contained five questions on hypersensitivity to aspirin and other non-steroidal anti-inflammatory drugs. If the respondents confirmed the occurrence of any post-drug symptoms, they were asked to specify the medicine by choosing from the 15 commonest drugs on the market, and to optionally give its name. Further questions detailed the symptoms which followed taking the medication: dyspnea, whizzing, blocked nose with watery nasal secretion, skin symptoms, gastrointestinal tract symptoms and anaphylactic shock symptoms. Then the respondents were asked about the time of the symptoms' occurrence and whether they took the same drug again later on and experienced a similar sequence of symptoms. By collecting data from 16 238 people, including 12 970 adults, the centers reached 98% of the planned number of respondents.

After obtaining consent from the Main Project Coordinator in Wroclaw center, and from all the researchers working in the other ten centers, 104 questionnaires were taken from the database. This data concerned patients whom experts found to be suffering from bronchial asthma and who gave a positive answer to at least one question on hypersensitivity to aspirin and non-steroidal anti-inflammatory drugs.

Then a full epidemiological questionnaire study was conducted, focusing on patients suspected of intolerance to anti-inflammatory drugs. The study covered nine of the 11 research centers participating in the project (one center did not obtain

consent for using the survey materials, while in another one the questionnaires were by accident unavailable). Eventually, 75 questionnaires were included in the analysis. Due to the fact that many patients living in distant parts of Poland could not and/or did not want to visit the Department of Medicine in Krakow to perform aspirin challenge tests, the verification of diagnosed aspirin-induced asthma and other types of hypersensitivity reactions was mainly based on detailed history of the patients, the type of drugs taken by them and analysis of patients' medical documentation. In the Krakow center itself, suspected diagnosis of aspirin-induced asthma was mostly confirmed by means of an aspirin challenge test.

To identify the group of patients with NSAID hypersensitivity, and to compare the severity of asthma, the study involved a group of patients showing good tolerance to apirin. This group was selected in the same epidemiological study carried out in the Krakow center. In view of the availability of epidemiological questionnaires in Krakow, patients from this center were qualified for inclusion in the statistical analysis.

The analysis was carried out using Statistica™ PL software. The groups studied were characterized using descriptive statistics. The occurrence frequency of allergic diseases as well as 95% confidence intervals were calculated. Variability within the groups was compared using a t-Student test for independent variables and chi-square test. The multiple factor statistical analysis of bronchial asthma gravity in various subgroups was carried out using the logistic regression method. The significance level assumed for the calculation was $\alpha = 0.05$.

Results

According to the data published by the research team from Wroclaw (37), the frequency of asthma occurrence equals 5.4%. This precisely matches our calculations based on the results from nine centers, which were included in the statistical analyses of hypersensitivity reactions to non-steroidal anti-inflammatory drugs. The representative population from the nine centers amounted to 10 684 adults. The epidemiological history taking allowed for diagnosing bronchial asthma in 582 persons. From this group 75 patients, i.e. 12.9% of the total population studied, additionally reported the symptoms of hypersensitivity to non-steroidal drugs and aspirin.

The distribution analysis of answers to questions on hypersensitivity symptoms showed that most reactions, 60% to be exact, were related to the skin. Skin manifestation of hypersensitivity was the only symptom reported in 25 patients, i.e. 33.3% of the studied group. In the remaining 50 patients, skin manifestations were accompanied by other symptoms such as dyspnea, nasal and abdominal reactions, and general collapse. The second most frequent hypersensitivity reaction was manifestation related to the gastrointestinal tract. Symptoms such as the occurrence of abdominal pain and/or diarrhoea after taking NSAIDs were reported by 28 patients (37.3%). In 12 people (16%) from the group this was the only drug-related reaction. Thirteen asthma patients (17.3%) reported in their medical history that after using non-steroidal anti-inflammatory drugs they experienced a shock, defined as significant asthenia and loss of consciousness.

Following the verification of 18 patients (24%) who reported dyspnea and ten patients with nasal symptoms (13.3%), aspirin-induced asthma was eventually recognised in 11 patients, i.e. 14.7% of the group showing clinical manifestations of hypersensitivity reactions. Figure 1 presents these reactions in a graphic form.

Dyspnea in the remaining patients was associated with other hypersensitivity reactions, especially the ones affecting upper airways. These symptoms took the form of angioedema or, in some patients, a general systemic reaction (shock). A single nasal reaction without dyspnea occurred in two patients (2.7%).

Aspirin-induced asthma is a form of severe, chronic asthma. In our study the occurrence frequency of aspirin-induced asthma with clinical symptoms amounted to 1.9% of the asthma patients. The frequency of aspirin-induced asthma in the whole adult population covered by the Polish study equals 0.1%. Figures 2 and 3 show these results in graphic form.

Neither group of asthma patients: the study group (75 people) and controls without any hypersensitivity reactions (72 people), differed statistically with regard to number or age. The average age in the group of patients with NSAID hypersensitivity was 44.7 ± 14.9 years, whereas in the control group it was 44.3 ± 16.5. In both populations studied there were significantly more women, who prevailed particularly in the hypersensitivity group (73.3% and 61.1%, respectively). In the chi-square test no statistically significant differences were found in the age structure of both groups. These groups were also similar with regard to the duration of the disease (11.7 ± 9.6 years in the hypersensitivity patients vs. 14.0 ± 14.4 years in the control group), and the percentage of cigarette

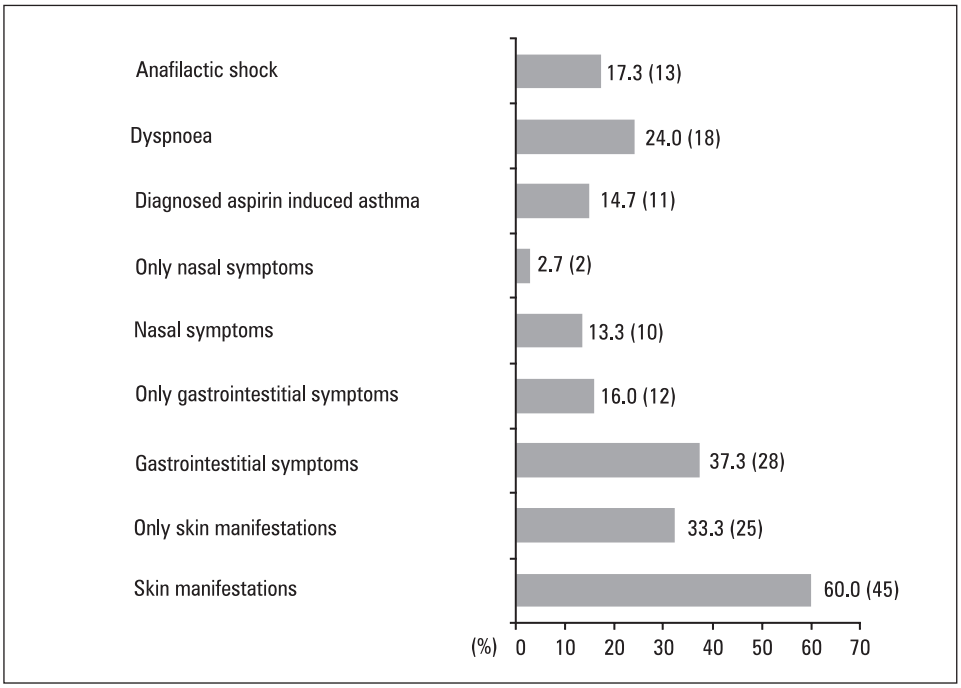

Figure 1. The prevalence of reactions after NSAIDs among asthmatics (n = 75)

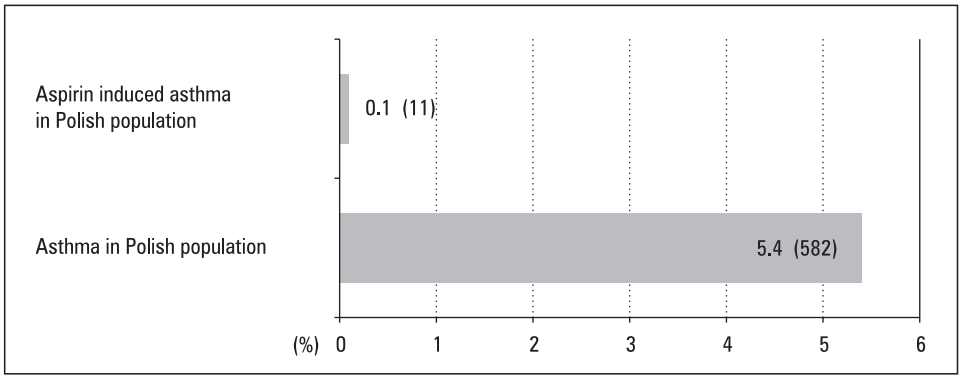

Figure 2. The frequency of asthma and aspirin induced asthma in the population of adults in Poland

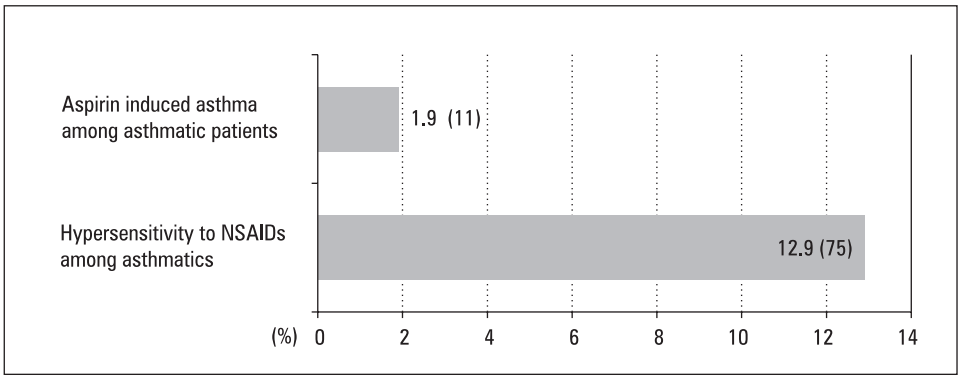

Figure 3. The frequency of any kind of hypersensitivity to nonsteroid anti-inflammatory drugs (NSAIDs) (with aspirin induced asthma) and aspirin induced asthma among asthmatics

Table 1. Characteristic of study subgroups

	Patients with symptoms of hypersensitivity to NSAIDs (n = 75) $\overline{\chi}$ ± SD (min, max)	Patients without symptoms of hypersensitivity to NSAIDs (control group; n =72) $\overline{\chi}$ ± SD (min, max)	Statistic significance p
Age (years)	44.7 ± 14.9 (18, 79)	44.3 ± 16.5 (17, 79)	0.9
Duration of disease (years)	n = 65* 11.7 ± 9.6 (0. 45)	n = 62* 14.0 ± 14.4 (0. 52)	0.29
Gender (female/male)	55/20 73.3%/26.7%	44/28 61.1%/38.9%	0.11
Smoking status	44 (58.7%)	34 (47.2%)	0.16

*Diagnosed patients

Table 2. Clinical characteristics of asthmatics in study subgroups

	Patients with symptoms of hypersensitivity to NSAIDs (n = 75) $\overline{\chi}$ ± SD (min, max)	Patients without symptoms of hypersensitivity to NSAIDs (control group; n =72) $\overline{\chi}$ ± SD (min, max)	Statistic significance p
Duration of disease (years)	n = 65* 11.7 ± 9.6 (0, 45)	n = 62* 14.0 ± 14.4 (0, 52)	0.29
Severity of disease episodic + mild moderate + severe	 59 (78.7%) 16 (21.3%)	 65 (90.3%) 7 (9.7%)	 0.052 (chi^2)
Antiasthmatic treatment	41 (54.7%)	20 (27.8%)	0.0009
Beta-mimetics	32 (42.7%)	16 (22.2%)	0.86
Anticholinergic drugs	9 (12.0%)	6 (8.3%)	0.49
Inhaled steroids	15 (20.0%)	10 (13.9%)	0.32
Systemic steroids	12 (16.0%)	6 (8.3%)	0.95
Intravenous steroids	14 (18.7%)	3 (4.2%)	0.12
Theophylline	26 (34.7%)	11 (15.3%)	0.53
Cromons	15 (20.0%)	10 (13.9%)	0.32
Asthma attack during last year	27 (36%)	18 (25%)	0.92

*Diagnosed patients

smokers (58.7% vs. 47.2%). The demographic data are presented in Table 1.

Although the control group was not representative nationwide, both populations (the study group and controls from Krakow) have been selected correctly with regard to their size (75 and 72 people, respectively), sex structure, cigarette smoking and duration of the disease.

Table 2 contains clinical characteristics of bronchial asthma in both groups.

In the NSAID hypersensitivity group, according to the GINA guidelines, moderate-persistent asthma and severe-persistent asthma could be recognised in 21.3% of patients. In the control group without hypersensitivity, this percentage amounted to 9.7%. The difference observed verges upon statistical significance ($p = 0.052$). Figure 4 shows the percentage of severe asthma in every subgroup of the populations covered by the study.

The assessment of disease severity must also take into account anti-asthmatic treatment. Table 2 compares drugs used by the patients in both groups. The group of patients with hypersensitivity to non-steroidal anti-inflammatory drugs, including

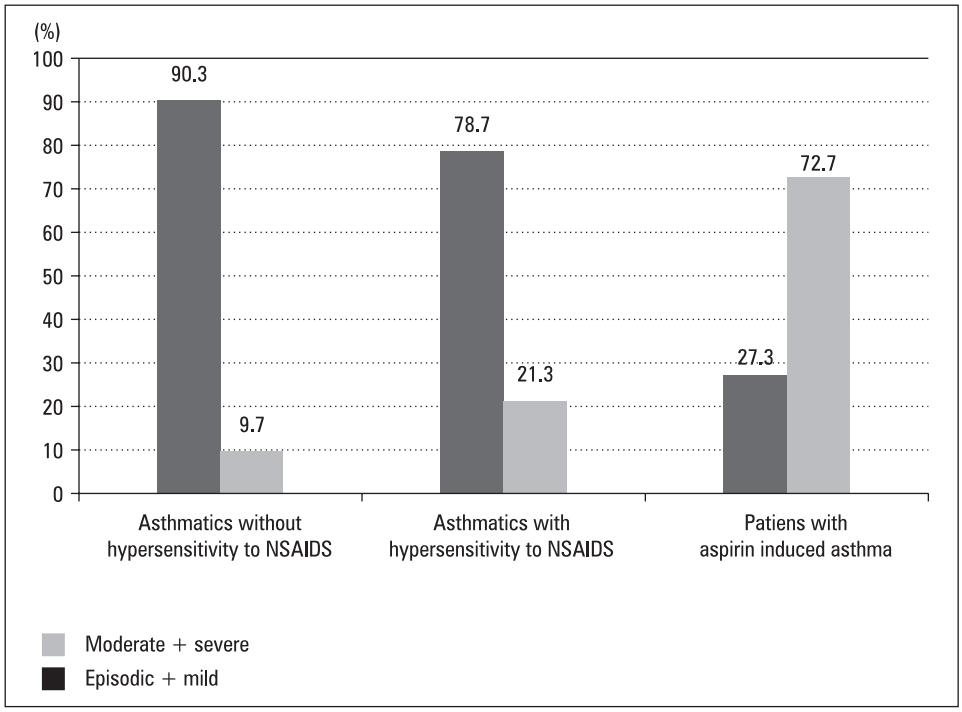

Figure 4. Severity of persistent asthma in subgroups of patients

the people with aspirin-induced asthma, used anti-asthmatic treatment statistically much more frequently ($p = 0.0009$; assuming 95% confidence interval the odds ratio is 3.14) for better control of the symptoms. The analysis of anti-asthmatic drug groups revealed no statistical significance. It should be stressed, however, that in the group of patients with aspirin-induced asthma, 45.5% (five out of 11 people) required the intravenous administration of glycocorticosteroids during disease exacerbation, which in a way shows the severity of dyspnea attacks they experienced.

For statistical analyses we used the logistic regression model, where severity of asthma (both moderate-persistent and severe-persistent) was a dependent variable, whereas age, gender, disease duration, tobacco smoking and drug hypersensitivity were independent variables. Statistically significant results were obtained only with relation to the patients' age and drug hypersensitivity. Following the elimination of cigarette smoking, statistically significant results were obtained only with relation to the patients' age ($p = 0.03$; assuming 95% confidence interval the odds ratio was 1.04) and hypersensitivity to cyclooxygenase inhibitors ($p = 0.04$; assuming 95% confidence interval the odds ratio was 2.9). These conclusions were confirmed by further statistical analyses. In the logistic regression model used to assess the disease severity in the study group ($n = 75$), the diagnosis of aspirin-induced asthma was included as a dependent variable, together with age, gender, disease duration and tobacco smoking. No statistically significant results were obtained in this case with regard to gender, disease duration, cigarette smoking or patients' age. Only aspirin intolerance has a significant bearing upon asthma severity ($p = 0.0003$; assuming 95% confidence interval the odds ratio was 28.6).

Discussion

This epidemiological study on the frequency of allergy disease occurrence in Poland was conducted in 1998–2000. It was the first large-scale epidemiological study of the Polish population to be carried out using correct and accurate scientific methods. The study encompassed 10 000 adults and children, and covered the whole of Poland. In order to achieve the most precise assessment of the frequency of allergic disease occurrence, the project required immense workload related to the execution of the study protocol.

No studies on hypersensitivity reactions to non-steroidal anti-inflammatory drugs have been conducted so far in Poland. Neither has this problem been studied in asthma patients. It should be noted that asthma patients are particularly vul-

nerable due to the possibility of disease exacerbation, or even death, caused by the use of aspirin and NSAIDs [24, 25].

In our study, hypersensitivity reactions to NSAIDs appeared in 12.9% of bronchial asthma patients. The most frequent symptom of NSAID hypersensitivity was the skin manifestation. Such a single hypersensitivity reaction was reported as the only symptom by 33% of patients. In 60% of patients it was accompanied by other symptoms. In our study the skin changes were analysed jointly, without distinction into oedema and urticaria. Similar results were obtained by Schubert et al. [28]. Their study was based on a preliminary anamnesis of 260 people who underwent a challenge test to check the diagnosis of hypersensitivity to non-steroid drugs. It was discovered that hypersensitivity was not confirmed in almost half the population participating in the German study.

Our data also corresponds with a Turkish study. Kalyoncu et al. [29] found that in a group of 132 patients with drug hypersensitivity diagnosed in their medical history, 28% had skin manifestations in the form of persistent urticaria, whereas 24.2% of bronchial asthma patients suffered from oedemic skin changes. A similar percentage of people (2.4% in the Turkish study vs. 2.7% in the Polish study) experienced a single reaction affecting the nasal mucosa. When compared to the Turkish study, which reported anaphylactic shock reactions in 6.8% of bronchial asthma patients, we have noted twice as many similar reactions: 17.3%. In the German study Schubert [28] reported only 3.5% systemic reactions.

In our opinion, the relatively high percentage of gastrointestinal tract reactions (37.3%, and 16% of cases as a single reaction) contradicts the findings of the Turkish study, which reported an abdominal manifestation in just one patient (0.8%). This disparity might result from misunderstanding of the question by some respondents. In the questionnaire we asked about reactions related to the gastrointestinal tract („*stomach ache and diarrhoea*"). There is some likelihood that while answering this question, the respondents took into account only its first part, i.e. abdominal pain. We know, however, that dyspeptic symptoms or even ulcerous disease are quite frequent and sometimes life-threatening side-effects of persistent use of non-steroidal anti-inflammatory drugs. Ulceration of gastrointestinal tract mucosa and all the related complications occur in ca. 25% of patients taking NSAIDs [30–32]. Peura [33] reports that the frequency of dyspeptic symptoms occurrence in people using these kinds of drugs amounts to as much as 50%. Given this, we cannot rule out that reactions reported by the patients in our study could be linked to such symptoms, thus leading to slightly higher results.

In the paper we presented the frequency of aspirin-induced asthma occurrence in Poland. It equals 1.9% of bronchial asthma patients, or 0.1% of the adult population. Study results published in 2003 [34] indicated a higher aspirin-induced asthma frequency, which amounted to 4.3%. This significant (almost 50%) difference in the frequency of aspirin-induced asthma is attributable to our detailed verification of epidemiological diagnoses. The challenge tests performed in Krakow confirmed hypersensitivity in 75% of cases (i.e. three in every four patients who agreed to participate in this study). Due to the fact that many patients living in distant parts of Poland could not and/or did not want to visit the Department of Medicine in Krakow to undergo the aspirin challenge tests, the verification of diagnoses was mainly based on detailed history of the patients, the type of drugs taken by them and the analysis of patients' medical documentation. In the later part of the assessment, we found that six patients tolerate NSAIDs well; in another seven patients the diagnosis of asthma was not confirmed. In other, earlier epidemiological studies, the reported occurrence of aspirin-induced asthma oscillated between 3% and 9% [35–37].

The analysis of our studies indicates that patients with drug hypersensitivity require a more intense, statistically significant anti-asthmatic treatment ($p = 0.0009$). However, no statistically significant differences were found in the use of anti-asthmatic drugs. On the other hand, in the subgroup of 11 patients with diagnosed aspirin-induced asthma, 45% used corticosteroids intravenously during disease exacerbation, whereas there were only 4% of such people in the control group. By comparison, in the AIANE study [23] 25% of asthma patients required intravenous injection of corticosteroids to stop an attack of dyspnea.

We agree with other authors in the observation that hypersensitivity to analgesics is a predisposition to a more severe form of the disease [38]. As for disease severity, the comparison of the study population with a control population revealed that moderate and severe asthma occurred more frequently in the group with hypersensitivity symptoms. In the chi-square test this difference verged upon statistical significance. The fact that more drugs are used to better control the symptoms in a way indicates the level of disease severity. By analysing the effect of multiple factors on disease severity, we proved, using the logistic regression

model, that hypersensitivity to drugs triples the likelihood of a more severe form of the disease. Moreover, using the same statistical model, we proved that aspirin sensitivity combined with dyspnea (aspirin-induced asthma) increases this risk almost 30 times. Also, the age of the people surveyed had some influence on disease severity. The older the patient, the more severe the disease.

Conclusions

The frequency of aspirin-induced asthma occurrence in the Polish adult population is 0.1%. In the group of adult asthma patients, this frequency is 1.9%. Hypersensitivity reactions to non-steroidal anti-inflammatory drugs occur in 12.9% of adult asthma patients in Poland. Patients with aspirin-induced asthma have statistically significant, more severe clinical course of the disease when compared to aspirin-tolerant asthma patients. In the former group, the risk of severe asthma is almost 30-fold higher.

Acknowledgements

The authors would like to thank the participants in the Polish Multicenter Study of Allergic Diseases Epidemiological Study in Poland in the years 1998–2000 (PMSEAD Study) for assistance in the implementation of the survey: Jerzy Liebhart, Józef Małolepszy, Urszula Gładysz (Wroclaw Coordinating Group); Sabina Chyrek-Borowska, Zenon Siergiejko, Anna Rogalewska, Wiesław Szymański (Bialystok); Andrzej Dziedziczko, Ewa Banach-Wawrzynczak, Jacek Tlappa (Bydgoszcz); Michał Kurek, Teresa Małaczyńska, Elżbieta Grubska-Suchańska, Andrzej Lademan (Gdansk); Janusz Milanowski, Ewa Trebas-Pietras (Lublin); Piotr Kuna, Anna Elgalal, Izabela Kupryś (Lodz); Jerzy Alkiewicz, Anna Bremborowicz, Witold Młynarczyk, Wojciech Silny (Poznan); Ryszard Kurzawa, Iwona Sak (Rabka); Jerzy Kruszewski, Danuta Chmielewska, Wacław Droszcz, Elżbieta Zaraz (Warszawa); Andrzej Boznański, Renata Jankowska, Maria Nitter-Marszalska, Grażyna Machaj, Maria Wrzyszcz, Wanda Balińska (Wrocław); Edmund Rogala, Barbara Rogala, Radosław Gawlik (Zabrze).

References

1. Gomes E.R., Demoly P. Epidemiology of hypersensitivity drug reactions. Curr. Opin. Allergy Clin. Immunol. 2005; 5: 309–316.
2. Faich G.A. Adverse-drug-reaction monitoring. N. Eng. J. Med. 1986; 314: 1589–1592.
3. Johansson S.G., Hourihane J.O., Bousquet J. et al. EAACI (the European Academy of Allergology and Cinical Immunology) nomenclature task force. A revisited nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 2001; 56: 813–824.
4. Stevenson D.D., Sanchez-Borges M., Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. Ann. Allergy Asthma Immunol. 2001; 87: 177–180.
5. Widal F., Abrami P., Lermoyez J. Anaphylaxie et idiosyncrasie. Press Medical 1922; 30: 189–192.
6. Samter M., Beers R.F. Jr. Intolerance to aspirin: clinical studies and consideration of its pathogenesis. Ann. Intern. Med. 1968; 68: 975–983.
7. Stevenson D.D., Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. J. Allergy Clin. Immunol. 2006; 118: 773–786.
8. Szczeklik A., Niżankowska-Mogilnicka E., Sanak M. Hypersensitivity to aspirin and others NSAIDS'. In: Kay A.B., Kaplan A.P., Bousquet J., Holt P.G. (ed.). Allergy and allergic diseases. Blackwell Publ. London 2008; 1966–1980.
9. Grzelewska-Rzymowska I., Szmidt M., Rożniecki J. Pokrzywka z nadwrażliwością na aspirynę; studium kliniczne. Pneumonol. Alergol. Pol. 1993; 61: 25–28.
10. James J., Warin R.P. Chronic urticaria: the effect of aspirin. Br. J. Dermatol. 1970; 82: 204–205.
11. Mastalerz L., Setkowicz M., Sanak M., Szczeklik A. Hypersensitivity to aspirin: common eicosanoid alterations in urticaria and asthma. J. Allergy Clin. Immunol. 2004; 113: 771–775.
12. Zembowicz A., Mastalerz L., Setkowicz M., Radziszewski W., Szczeklik A. Safety of cyclooxygenase 2 inhibitors and increased leukotriene synthesis in chronic idiopatic uriticaria with sensitivity to nonsteroidal anti-inflammatory drugs. Arch. Dermatol. 2003; 139: 1577–1582.
13. Hedman J., Kaprio J., Poussa T., Nieminen M.M. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. Int. J. Epidemiol. 1999; 28: 717–722.
14. Vally H., Taylor M.L., Thompson P.J. The prevalence of aspirin intolerant asthma (AIA) in Australian asthmatic patients. Thorax 2002; 57: 569–574.
15. The International Study of Asthma and Allergies in Childhood (ISSAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet 1998; 351: 1225–1232.
16. Ellwood P., Asher M.I., Beasley R., Clayton T.O., Stewart A.W., ISAAC Steering Committee. The international study of asthma and allergies in childhood (ISAAC): phase three rationale and methods. Int. J. Tuberc. Lung Dis. 2005; 9: 10–16.
17. Asher M.I., Keil U., Anderson H.R. et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur. Respir. J. 1995; 8: 483–491.
18. Maziak W., Behrens T., Brasky T.M. et al. Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Munster, Germany. Allergy 2003; 58: 572–579.
19. Peat J.K., Haby M., Spijker J., Berry G., Woolcock A.J. Prevalence of asthma in adults in Busselton, Western Australia. BMJ 1992; 305: 1326–1329.
20. Burney P., Malmberg E., Chinn S., Jarvis D., Luczyńska C., Lai E. The distribution of total and specific serum IgE in the European Community Respiratory Health Survey. J. Allergy Clin. Immunol. 1997; 99: 314–322.
21. Chinn S., Burney P., Jarvis D., Luczyńska C. Variation in bronchial responsiveness in the European Community Respiratory Health Survey (ECRHS). Eur. Respir. J. 1997; 10: 2495–2501.
22. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). Eur. Respir. J. 1996; 9: 687–695.
23. Szczeklik A., Niżankowska E., Duplaga M. et al. on behalf of the AIANE Investigators. Natural history of aspirin-induced asthma. Eur. Respir. J. 2000;16: 432–436.
24. Marquette C.H., Saulnier F., Leroy O. et al. Long term prognosis for near fatal asthma. A 6-year follow-up study of 145 asthmatic patients who underwent mechanical ventilation for near-fatal attack of asthma. Am. Rev. Respir. Dis. 1992; 146: 76–81.
25. Picado C., Castillo J.A., Montserrat J.M., Agusti-Vidal A. Aspirin-intolerance as a precipitating factor of life-threatening attacks of asthma requiring mechanical ventilation. Eur. Respir. J. 1989; 2: 127–129.

26. Małolepszy J., Liebhart J., Wojtyniak B., Pisiewicz K., Płusa T. Występowanie chorób alergicznych w Polsce. Alergia Astma Immunologia 2000; 5 (supl. 2): 163–169.
27. Liebhart J., Malolepszy J., Wojtyniak B., Pisiewicz K., Plusa T., Gladysz U. Prevalence and risk factors for asthma in Poland: results from the PMSEAD Study. J. Investig. Allergol. Clin. Immunol. 2007; 17: 367–374.
28. Schubert B., Grosse Perdekamp M.T., Pfeuffer P., Raith P., Brocker E.B., Trautmann A. Nonsteroidal anti-inflammatory drug hypersensitivity: fable or reality? Eur. J. Dermatol. 2005; 15: 164–167.
29. Kalyoncu A.F., Karakaya G., Sahin A.A., Baris Y.I. Occurrence of allergic conditions in asthmatics with analgesic intolerance. Allergy 1999; 54: 428–435.
30. Naesdal J., Brown K. NSAID-associated adverse effects and acid control aids to prevent them: a review of current treatment options. Drug Saf. 2006; 29:119–132.
31. Langman M.J. Epidemiology of non-steroidal anti-inflammatory drug damage to stomach and duodenum. Ital. J. Gastroenterol. Hepatol. 1999; 31 (suppl. 1): 2–5.
32. Tenenbaum J. The epidemiology of nonsteroidal anti-inflammatory drugs. Can. J. Gastroenterol. 1999; 13: 119––122.
33. Peura D.A. Prevention of nonsteroidal anti-inflammatory drug--associated gastrointestinal symptoms and ulcer complications. Am. J. Med. 2004; 117 (supl. 5A): 63S–71S.
34. Kasper L., Sladek K., Duplaga M. et al. Prevalence of asthma with aspirin hypersensitivity in the adult population of Poland. Allergy 2003; 58: 1064–1066.
35. Chafee F.H., Settipane G.A. Aspirin intolerance. I. Frequency in an allergic population. J. Allergy Clin. Immunol. 1974; 53: 193–199.
36. Settipane G.A., Chafee F.H., Klein D.E. Aspirin intolerance. II. A prospective study in an atopic and normal population. J. Allergy Clin. Immunol. 1974; 53: 200–204.
37. Giraldo B., Blumenthal M.N., Spink W.W. Aspirin intolerance and asthma. A clinical and immunological study. Ann. Intern. Med. 1969; 71: 479–496.
38. Barnes P.J., Woolcock A.J. Difficult asthma. Eur. Respir. J. 1998; 12: 1209–1218.