One of the most important tasks of contemporary pharmacy is the search for new drugs characterized by high activity and safe to use. Unfortunately, the majority of drugs show some adverse drug reaction (ADR) or toxic effects, usually related to intake of an overdose, taking a drug for a too long time or hypersensitivity to a given drug components. Side effects can be often minimized by administering another pharmaceutical form of drug or an alternative drug from another chemical group. This solution is particularly important in treatment of the elderly whose enzymatic efficiency is reduced. An important element of correct hospitalization is to report and register all unwanted side effects of a given drug, which would eventually lead to a shortening of the treatment, reduction of its cost and help avoid the undesired effects in other patients. Each report on the undesired side effect of a given drug, which occurs at doses normally used in man. The character and intensity of the adverse drug reaction differ from very mild to highly serious. The widest range of side effects has been observed to accompany the use of cytostatics, antibacterics and antiinflammatory drugs. The most often developed maculaopapular rash, urticaria medicamentosa and Quincke’s edema. The other cases included erythroderma, anaphylactic shock, lichenoid exanthem, bullous eruption and Hoigne’s syndrome. The most probable factors producing these changes were concluded to be non-steroid antiinflammation drugs, antibiotics and other drugs from different pharmacological and chemical groups (carbamazepine, diltiazem, hydrocortisone, methtrotate and herbs). The frequency of occurrence of skin changes of particular type in age groups were also analyzed. The greatest number of skin changes in response to drug therapy was in the age group 41 – 60, while for the age group > 60 ADR revealed the greatest diversity in the clinical picture. The most probable explanation of these findings are the polypragmasy applied in the elderly patients and interdrug interaction as well as decreased efficiency of the organic clearances.

**Keywords:** drug hypersensitivity, ADR, antibiotics

In accordance with WHO definition (1), an ADR is a response to a medicine which is noxious and unintended and which occurs at doses normally used in man. In addition, a serious adverse event is defined as any event that is fatal, is life-threatening, is permanently or significantly disabling, requires or prolongs hospitalization and requires intervention to prevent impairment or damage (1). Frequently ADR may considerably complicate diagnostic approach and also may have a disadvantageous influence on the clinical outcome.

According to the research data of the last decades morbidity and mortality due to adverse drug reactions (ADR) have been recognized as a major health problem in many countries. It has been estimated, that ADR are the 4th to 6th largest cause for mortality in the USA. Various ADR result in death of several thousands of patients each year (75 000 up to 106 000) and many more suffer from ADR (1).

Furthermore, in the opinion of pharmacoeconomics experts, ADR impose a high financial burden on health care due to the hospital care of patients with drug related conditions. It is well known that some countries spend up to 15-20% of their hospital budget dealing with ADR complications (1). There are differences among countries regarding the occurrence of ADR and other drug-related problems. According to World Health Organisation (WHO), this may be due to differences in prescribing practices, genetics, diet, traditions, drug manufacturing processes,
drug distribution and the use of traditional and complementary drugs (for example herbal remedies) (1). The percentage of hospital admissions due to ADR is also estimated variously depending on the region of the world the data is obtained from. It has been estimated that approximately 11.5% hospital admissions are related to ADR in Norway, 13.0% – in France and 16.0% – in the United Kingdom (2-4). There is very limited information available on ADR in developing countries, however, it seems that the situation there is much worse than in Europe (1).

Undoubtedly the problem may be caused in some countries by the lack of legislation and proper regulations (ADR reporting) but also because of a large number of counterfeit products circulating on the market with no proper and scientifically supported information concerning their use and potential side-effects (1).

This study presents results of the analysis regarding frequency and type of ADR resulting in hospitalization in the Department of Dermatology, University of Medical Sciences in Poznań in the time period between 2000 and 2004.

EXPERIMENTAL

The paper describes investigation of 57 patients admitted to the Department of Dermatology during the time period between 2000 and 2004, in terms of diagnosis and clinical outcome resulting in hospitalization. We examined the database available in the Department of Dermatology and reviewed procedures used to characterize the possible causative factor of an ADR and also the clinical diagnosis.

RESULTS

In total, 57 patients were hospitalized because of ADR, which constituted 1% of all admissions to the Department of Dermatology at that time. The evaluated group consisted of 30 female patients (53%) and 27 male patients (47%). The age of hospitalized patients ranged from 9-79 years with mean of 44.5 years. In regard to particular age groups, patients age 41-60 pre-dominated (45%), and the least numerous age group were adolescents below 20 (12%) (Figure 1). Figure 2 presents the most frequent drug-related reactions: urticaria and angioedema (28%) and maculopapular exanthem (MPE) (28% of investigated group). Erythema multiforme constituted for 26.3% of all 57 admissions, while more infrequent reactions included: erythrodermia (8.8%), anaphylactic shock (3.5%), lichenoid exanthem (1.7%), bullous exanthem (1.7%) and Hoigne syndrome (1.7%).

Furthermore, number of admissions related to ADR was analyzed in comparison to all admissions to the Department of Dermatology in particular years between 2000 and 2004 (Figures 3 and 4). In 2000 there were 21 patients admitted due to ADR against 865 admissions related to other dermatoses, in 2001 – 10 patients due to ADR against 865 admissions, in 2002 – 15 patients due to ADR against 816 other admissions, in 2003 – 16 patients due to ADR against 835 admissions, and in 2004 – 16 patients due to ADR against 810 other admissions.
2002 – 5 admissions related to ADR against 1123, in 2003 – 10 ADR related admissions against 1029 and in 2004 – 11 patients were admitted because of ADR against 1000 admissions of other causes.

Statistical analysis of the obtained data revealed statistically significant difference between year 2000 and the last three years, which means that during the last three years, in comparison to the year 2000, there was statistically significant decrease in the number of admissions related to ADR in the Department of Dermatology.

Special attention was drawn into groups of medications being a potential cause of ADR in examined 57 patients. Figure 5 presents results of the evaluation. The potential causative factor could be established in 55% of hospitalized patients. Predominating group of potential ADR eliciting medications were non-steroid anti-inflammatory drugs (NSAIDs) (33%), antibiotics (7%) and carbamazepine (7%). Less frequent cause of ADR was: hydrocortisone (2%), methotrexate (2%), herbal remedy (2%) and diltiazem (2%). These observations were based on the information obtained from the clinical case history of investigated patients.

Consecutive analysis regarded variety of ADR types in different age groups. In case of younger patients (less than 20 years of age) and in patients aged between 21 and 40 years, urticaria and angioedema predominated as well as erythema multiforme. The most varied clinical pictures could be observed in hospitalized patients between 41 and 60 years of age and also in patients over 60 years old. In this age group predominating ADR types included: maculopapular exanthem, urticaria and angioedema, erythema multiforme and erythrodermia (Figure 6).
DISCUSSION AND CONCLUSION

Drug hypersensitivity is an important and complex problem in our clinical practice. Etiopathogenesis of ADR has not yet been fully understood and it is well known that these reactions have taken over the role of “the great imitator” of various diseases which makes the diagnosis of drug hypersensitivity even more difficult (5).

In the 1960s several researchers reported, that ADR were either a major cause of, or an important factor leading to hospital admissions of many patients. These authors also indicated, that approximately 5% of the patients admitted to the hospital because of various reasons presented an ADR and that 3/4 of these patients were admitted specifically because of an adverse reaction (6-10).

Contemporary literature data invariably indicate ADR as a significant and up-to-date issue. The incidence of hospital admissions due to ADR is estimated to be 1-16.8% and in case of pediatric patients it has been evaluated as 2 to over 4% (11-15).

An overwhelming part of the reports is obtained mainly from general medical wards, psychiatric wards, pediatric wards, and also from neurological, geriatric, surgical and intensive care units (15-18). There is practically no data originating in dermatological departments. In our study, an overall proportion of patients hospitalized in the Department of Dermatology between 2000 and 2004 due to ADR constituted of 1% of all admissions, which is consistent with general literature data. Moreover, according to our statistical analysis, there has been a significant decrease in the number of ADR related admissions to the Department of Dermatology during the last three years. This phenomenon may be mainly due to the alteration of the Department’s functioning profile, with no emergency service and only planned admissions. Furthermore, increasing knowledge and awareness of both general practitioners, managing mild cases of ADR and patients themselves, whose prompt reaction and admission to the physician allows to avoid severe consequences of drug hypersensitivity, may be another explanation.

In the present study, analysis of the ADR type and clinical picture revealed that the most frequent reactions were MPE and urticaria together with angioedema. In line with our results, Bigby et al. (19) reported that MPE accounts for approximately 95% of all drug-induced cutaneous eruptions. Clinically these exanthems usually present as erythematous macules and papules which often are initially localized within the trunk and subsequently spread to the extremities in a symmetrical fashion (20-23). MPE etiopathogenesis is complex and still remains unclear. Immunohistochemical studies have shown that the cell infiltrate in drug-induced MPE is mainly composed of CD3+ cells (40-70%), with a predominance of CD4+ cells (22-23). There is a possibility that drug-specific CD4+ cells expressing cytotoxic granule proteins such as perforin and granzyme B are critically involved in vacuolar alteration and destruction of basal keratinocytes (22-23). In case of drug-induced urticaria and angioedema, their patomechanism may be associated with type I hypersensitivity reaction mediated by IgE antibodies, although other mechanisms leading to direct and non-specific liberation of histamine or other inflammatory mediators are also common for this type of ADR (24). Urticaria and angioedema are associated in about 50% of cases and they can be complicated by a life threatening anaphylaxis, which is however much more often related to insect stings (59%) than to a drug allergy (18%) (24, 25). In our study anaphylactic shock accounted for 3.5% of analyzed hospital admissions (2 patients) and in both cases was caused by beta-lactam antibiotic.

The relationship between age and ADR-induced hospitalization is not clear and literature data concerning this matter is often contradictory. Hurwitz (26) reported a median age of 60 among British patients admitted because of ADR. Swedish authors (27) obtained similar results: the average age among ADR admissions was 66. Moreover, in South African study by Cooke et al. (28), the mean age was even higher at 72, with no admissions of patients below age 57. Data from Caransos et al. (12) and from Levy et al. (29) indicated a significantly higher number of ADR-related admissions in patients over 60 compared with those less than 60 years of age. On the other hand, McKenney and
Harrison (6), Ives et al. (16) and Levy et al. (29) did not record such a difference. Colt and Shapiro (13) similarly found no difference between those older and younger than 65 years.

In the present study, patients above 60 years of age accounted for 18% of all subjects admitted to the Dermatology Department because of ADR, however, the most numerous age group included patients between 41 and 60 years (45%). It is worth emphasizing, that in these age groups ADR demonstrated the highest diversity in relation to the clinical picture, including MPE, urticaria and angioedema, erythrodermia, erythema multiforme, anaphylaxis, bullous exanthema and Haigne syndrome, whereas in younger patients urticaria, angioedema and erythema multiforme predominated. Undoubtedly, further research to assess the role of patient’s age in frequency and clinical pattern of a drug-induced illness is required.

There are many studies evaluating and characterized drugs or drug categories implicated as causing hospital admissions. In the present study, potential causative drugs could be indicated in case of 55% examined patients. Predominating groups of causative medications included NSAIDs (33%), antibiotics (7%) and carbamazepine (7%). Presented results are in agreement with observations made by Caranasos et al. (12), Ives et al. (30), Ghose et al. (14), Colt and Shapiro (13) and Trunet et al. (18), who also indicated mentioned groups of drugs as accounting for the majority of drug hypersensitivity cases.

According to Roujeau (24), NSAIDs, but also angiotensin-converting enzyme (ACE) inhibitors are the two most frequent causes of drug-induced, non-IgE-mediated urticaria and angioedema. Angioedema occurs in 2-10 per 10 000 new users of ACE inhibitors, a rate estimated as higher than the risk associated with penicillins (about 1 per 10 000 courses) (25). In other authors’ (31) opinion, drugs deserving particular attention include also: central nervous system agents, hormones and synthetic substitutes and antineoplastic agents, although their association with skin and mucosal membranes as target organs may be less significant than with drugs mentioned before.

In conclusion, present study provides some new information concerning the frequency and clinical presentation of ADR in patients admitted to the Department of Dermatology, which is important especially in regard to sparse literature data originating within this speciality. It seems that in comparison to other common dermatoses, ADR were a rare cause of admission, and during the last three years number of patients presenting symptoms of drug hypersensitivity has significantly decreased. However, since the skin is the most frequent target of drug reactions and since drug hypersensitivity presentation is so highly variable, there is a permanent need for thorough ADR monitoring and research concerning engagement of a variety of factors in ADR etiopathogenesis. In our future studies we are planning to perform specific diagnostic procedures in terms of detailed characterization of possible causative medications responsible for ADR.

REFERENCES