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ENGLISH VERSION: THE STUDY OF PREVALENCE OF HYPERSENSITIVITY TO B-LACTAM ANTIBIOTICS AMONG THE POPULATION OF UKRAINE*

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Allergic reactions to β-lactam antibiotics are the most common cause of adverse drug reactions, mediated by specific immunological mechanisms. The aim of this research was to determine the prevalence of hypersensitivity to β-lactam antibiotics among the population, by examining anamnestic data and conducting allergological examination to increase the safety of antibiotic therapy and improve the pharmacoeconomic profile of treatment.

Key words: β-lactams, hypersensitivity, skin tests, drug allergy.

Drug allergy is a pathological reaction to medications, based on immunological mechanisms [1, 2]. At present, the range of applied β-lactam antibiotics has changed and benzylpenicillin is no longer the most common representative agent of this group: other drugs have taken its place. In Spain, France and the United States, ampicillin and cephalosporins are currently more often prescribed, and these drugs are the main cause of allergy [3].

Most patients with the allergic history of penicillin or β-lactam antibiotics (BLAs) are misdiagnosed in 90% about the allergic reaction to penicillin, due to the fact that symptoms, associated with the patient's disease, are obscured as allergy [4].

The prevalence of reported allergy to penicillin is estimated at 9 to 12% [5,6]. Meanwhile, its prevalence in hospitalized patients can reach up to 15% [7]. The frequency of allergic reactions to penicillins varies from 0.7 to 10%, with the frequency of anaphylactic reactions ranging from 0.015 to 0.004% [7].

In Ukraine, today there is no special system for registering the drug allergy (DA), and accordingly there is no precise information on the number of hypersensitivity reactions to medications, as well as the types of reactions and their consequences. In addition, there is no evidence on the effectiveness of their treatment at both in- and outpatient stages. It should be noted that in Ukraine, the over-the-counter drug sale is also implemented. At the same time, the increase in the number of DA has lately attracted attention in the developed countries as well.

The aim of the research was to determine the prevalence of hypersensitivity to β-lactam antibiotics among the population by studying the anamnestic data and conducting allergic examination to improve the safety of antibiotic therapy and enhance the pharmacoeconomic profile of treatment.

Materials and methods

In order to achieve aim of the research, 81 women and 119 men were enrolled in a clinical study. The examined patients underwent prick and intradermal tests to determine the prevalence of hypersensitivity to β-lactam antibiotics. The study was conducted on the basis of the city clinical hospital over the period from 2016 to 2017.

Prior to the launch of the study, written consent was obtained from each patient for participation in scientific research and carrying out procedures. The decision of the commission on bioethics of city clinical hospital No.1 was also obtained (abstract of minutes No. 17 as of 02.04.2016).

To conduct prick tests, we used solutions with the following concentrations: benzylpenicillin sodium salt 0.5 mg / ml, ceftriaxone 5 mg / ml, amoxicillin clavulonate 20 mg / ml. The second stage of the diagnostics was carried out with the help of diagnostic preparations benzylpenicilloyl poly-L-lysine (PPL), a mixture of minor determinants of penicillin (SMD), clavulanic acid (DIATER, Spain).

The prick test procedure was conducted as follows: a drop of histamine solution (positive control) is applied to the skin of the inner surface of the forearm, underneath – a drop of water for injections (negative control), downwards – the solution of the studied allergen (benzylpenicillin sodium salt, ceftriaxone, amoxicillin clavulonate). After that, the skin is pierced through the drop with a special lancet. The result of the reaction is evaluated using standard criteria. The formation of a blister more than 3 mm in diameter with the surrounding erythema 20 minutes after the test is regarded as a positive reaction (Romano A. Et al., 2005). In addition, testing the drugs requires to assess the results of prick tests 24 hours after the test.

The intradermal test was conducted as follows: the antibiotic solution is injected intracutaneously into the skin of the inner surface of the forearm. The results are assessed in 20 minutes. The reaction is considered positive if the diameter of the formed element exceeds 2 diameters of the injection papule or exceeds the diameter of the injection papule by 3 mm. When evaluating the reaction after 24 hours and later, the reaction is considered positive if an infiltrated erythematous element develops [3].

The reaction results were registered with a contour on a transparent adhesive tape.

Results and discussion

In the course of the study, we 200 examined patients who were treated at the hospital of a therapeutic profile. The patients' age was 56.2 ± 3.6 years. The duration of the underlying disease is 8.49 ± 5.68. Patients were diagnosed according to ICD-10.

The structure of the basic morbidity includes: diseases of the respiratory system – 6%, diseases of the cardiovascular system – 75.5%, diseases of the gastrointestinal tract – 10.5%, diseases of the urogenital system – 2%, diseases of the musculoskeletal system – 3%, diseases of the blood system – 6% (Fig. 1).

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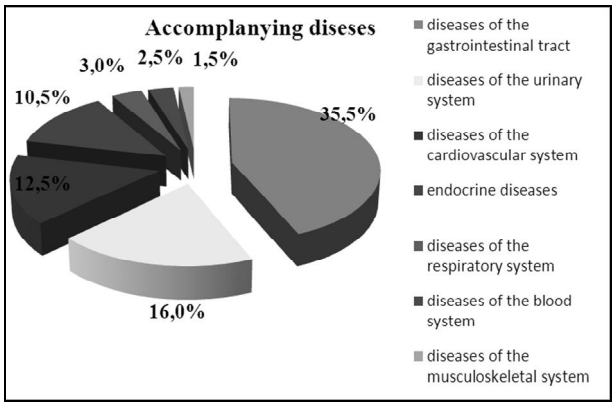

Figure 1. The structure of the basic morbidity of patients examined for hypersensitivity to β-lactams

The structure of concomitant diseases includes: diseases of the respiratory system – 3%, diseases of the cardiovascular system – 12.5%, diseases of the gastrointestinal tract – 35.5%, diseases of the urogenital system – 16%, diseases of the endocrine system – 10.5%, diseases of the musculoskeletal system – 1.5%, diseases of the blood system – 2.5% (Fig. 2).

After conducting the tests and collecting the history, we analyzed the obtained data. We found that out of 200 patients, 21 patients had a positive prick test. The table given below demonstrates the data on patients with a detailed history and tests results. In 9 patients, the anamnesis was not aggravated, but in conducting the tests there were 2 patients in whom the tests for histamine, water, benzylpenicillin sodium salt, ceftriaxone and amoxicillin clavulonate were positive and therefore no intradermal tests were performed. In 7 patients, a positive intradermal test was observed only for amoxicillin clavulonate in 1 patient, for benzylpenicillin sodium salt and ceftriaxone – in 2 patients, only for benzylpenicillin sodium salt – in 1 patient, for benzylpenicillin sodium salt, ceftriaxone and amoxicillin clavulonate – in 3 patients.

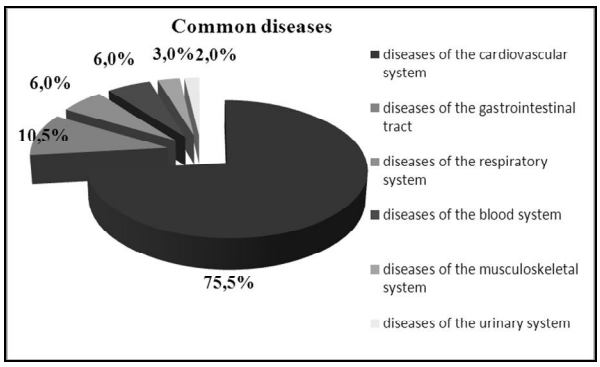

Figure 2. The structure of concomitant diseases in patients examined for hypersensitivity to β-lactams

The remaining 12 patients from the table had an aggravated allergic history, despite the fact that almost all allergens were different. Analyzing the data of the, 8 people with an aggravated anamnesis who had negative prick tests and intradermal tests were observed. 1 patient had a positive test for benzylpenicillin sodium salt, ceftriaxone and amoxicillin clavulonate, 2 patients – for ceftriaxone, and 1 patient – for benzylpenicillin sodium salt and ceftriaxone.

Table 1
The results of intradermal tests in patients examined for hypersensitivity to β-lactams

Patients	Benzylpenicillin sodium salt	Ceftriaxone	Amoxicillin clavulonate	Allergic history
Patient N., age: 29	_	_	+	_
Patient N., age: 65	+	+	+	cereals, honey, dust, fluff, ambrosia, arginine glutamate, Novocaine (procaine hydrochloride)
Patient L., age: 71	+	+	_	_
Patient P., age: 71	+	+	_	_
Patient S., age: 63	_	_	_	mulberries, vitamin B12 (methylcobalamin), Biseptol (sulfamethoxazole, trimethoprim), tetracycline hydrochloride, diacardine retard (diltiazem hydrochloride).
Patient V., age: 61	_	_	_	iodine
Patient Kh., age: 66	_	_	_	ambrosia
Patient T., age: 39	_	_	_	B12 group vitamins (methylcobalamin), Novocaine (procaine hydrochloride), sage grass
Patient A., age: 44	_	+	_	ambrosia
Patient S., age: 53	+	+	_	Benzylpenicillin sodium salt, tetracycline hydrochloride
Patient K., age: 34	_	_	_	azithromycin
Patient G., age: 33	_	_	_	Retarpen (benzathine benzylpenicillin)
Patient Ch., age: 41	_	_	_	**positive prick test, intradermal test was not conducted**
Patient Sh., age: 78	+	_	_	_
Patient D., age: 66	_	_	_	**positive prick test, intradermal test was not conducted**
Patient K., age: 59	+	+	+	**-**
Patient B., age:80	+	+	+	**_**
Patient S., age:56	+	+	+	**_**
Patient T., age: 23	_	+	_	spring rhinorrhea
Patient S., age: 20	_	_	_	Levofloxacin hemihydrate
Patient Ya., age: 63	_	_	_	Analgin (metamizole)

Allergic reactions to β-lactam antibiotics (β-lactams) are a common cause of adverse drug reactions, mediated by specific immunological mechanisms [3].

When conducting skin tests, it is necessary to consider cross-reactivity. Skin tests often demonstrate cross-reactivity between β-lactam antibiotics (penicillins, cephalosporins) [3].

The following clinical case report will illustrate this tendency: Patient T., aged 18, a medical student, was admitted to the pulmonology department with complaints of breathing difficulty, swelling of the mucous membranes of the lips, the appearance on the skin of single red lesions that were accompanied by itching and burning, productive cough, fever up to 39°C, slight shortness of breath at rest, sweating, general weakness.

From the anamnesis of the disease, it is known that the patient had community-acquired right-sided lower lobe pneumonia, which was treated by the family doctor. After administering the prescribed levofloxacin, 500 mg (1 tablet), in 20 minutes the patient started to complain of breathing difficulty, swelling of the mucous membranes, the appearance of single red eruptions on the skin, which were accompanied by itching and burning. The ambulance service took the patient to the emergency room of the city clinical hospital.

From the anamnesis of life, it is known that he had chickenpox as a child. Allergic history has not been previously aggravated.

Data of the objective examination: the patient's condition of moderate severity. The skin of the face, trunk, upper and lower extremities are covered with maculopapular rash. The labial mucosa is swollen. Peripheral lymph nodes are not enlarged.

Respiratory rate is 20 per 1 min., on percussion: dullness of the pulmonary sound on the right in the lower part, on auscultation: crepitus on the right, moist rales on the right.

Blood pressure: 120/80 mm Hg, pulse: 90 beats per 1 min; borders of the heart are within the age norm. Heart sounds are loud, rhythmic.

The tongue is covered with white coating. Abdomen on palpation is soft, painless. Costovertebral angle tenderness symptom is negative on both sides.

Blood test data: RBC – 4.8 x 10^{12} / l, hemoglobin – 146 g / l, color index – 0.91, platelets – 350 x 10^{9} / l, WBC – 17.0 x 10^{9} / l, ESR – 12 mm / h, WBC count: stab – 10%, segmented –74%, eosinophils – 12%, lymphocytes – 14% monocytes – 3%. ECG: HR – 90 per 1 min., sinus rhythm. Electrical axis of heart is not deviated. X-ray of thoracic organs: local amplification, thickening of the pulmonary pattern in the lower lobe on the right. Conclusion: right-sided lower lobe pneumonia.

From the above presented, it is possible to make a preliminary diagnosis: community-acquired right-sided lower lobe pneumonia, grade III, RF 0. Immediate-type hypersensitivity reaction to levofloxacin. Considering this situation, for the selection of antibiotic treatment, the patient underwent the prick and intradermal tests with the following drugs: benzylpenicillin sodium salt 0.5 mg / ml, ceftriaxone 5 mg / ml, amoxicillin clavulonate 20 mg / ml. The results of the tests were negative. The patient was prescribed empirical treatment of community-acquired pneumonia: ceftriaxone 1.0 intravenously, in dropper once a day for 5 days, azithromycin 500 mg, 1 tablet once a day for 3 days.

Due to the similarity in the structures, there is cross-reactivity between different penicillins and even between penicillins and cephalosporins [8, 9, 10]. A common feature in the structure is a four-membered β-lactam ring, which is articulated with a five-membered thiazolidine ring in penicillins and a six-membered dihydrothiazine ring in cephalosporins. Penicillins have one side chain (R1), whereas cephalosporins – two (R1 and R2). When R1 and R2 of the side chains are replaced, different antibiotics are obtained. These changes, although minor, can be recognized by the immune system as different ones with the corresponding clinical consequences [11].

Conclusions:

1. Allergy to β-lactams, in particular, to penicillin, is often reported by patients, but in most cases this has not been proven. Therefore, patients who have been allergic to β-lactams are given prick tests and intradermal tests to confirm the diagnosis. In case of proven allergy, the patient is provided with precise recommendations on the use of this group of drugs.

2. To date, the use of β-lactam antibiotics is safe because it has few side effects, a wide spectrum of action and a low price for a course of treatment. It should be noted that doctors of different specialties unreasonably ignore this group of drugs.

3. Unlike β-lactam antibiotics, the group of cephalosporins has high risks of side effects that lead to allergic reactions. The presented clinical case report is an example of this tendency.

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