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RETROSPECTIVE ANALYSIS OF ADVERSE DRUG REACTION REPORTING FORMS ASSOCIATED WITH PENICILLIN FAMILY ANTIBIOTICS (PCNE-DRP 9.0) BASED ON DRUG-RELATED APPROACH

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A widespread use of β-lactam antibiotics such as penicillins in practical medicine, and its authorized use in special categories of patients (e.g. children, pregnant and lactating women, the elderly) requires a critical investigation of their safety as well as the obligatory risk assessment before conducting antibacterial pharmacotherapy.
The aim of the work was the conduction of a retrospective study of adverse reactions cases, the identification and analysis of drug-related problems (DRP) associated with the use of penicillin family antibiotics.
Materials and methods. The objects of the study were adverse drug reactions (ADR) associated with the use of penicillin family antibiotics in inpatient and outpatient facilities, as well as the cases of self-treatment, which were recorded in the official ADR reports and then inputted in the regional (Republic of Crimea) database of spontaneous reports called ARCADe (Adverse Reactions in Crimea, Autonomic Database). The covered period is 2009–2018. The analysis of DRP was carried out using the 9.0 version of the qualification system DRP PCNE (Pharmaceutical Care Network Europe Foundation).
Results. The data analysis of ADR *reporting forms* has revealed that Amoxicillin clavulanate and Amoxicillin were the most frequent cause of ADR. A high incidence of penicillins ADR in pediatric patients (from 0 to 18 years) – 142 cases – has been found. The clinical manifestations of reactions included drug hypersensitivity reactions (309 cases), dyspeptic disorders (28 cases) and disorders of the central nervous system (5 cases). The incidence of serious ADR was 113 cases (33% of the total number of ADR in the study), which indicates a rather high risk of developing severe ADR for penicillins, resulted in a significant decrease in the quality of patients' lives.
Conclusion. The detection of DRP using the PCNE V9.0 approach is a useful and promising tool important to improve the quality of pharmacotherapy and their adherence to treatment. The highest DRP values which were observed for Amoxicillin clavulanate and Amoxicillin, may indicate a high frequency of irrational use of these drugs.
Keywords: penicillins, adverse reactions, drug-related problems, DRP, Amoxicillin clavulanate, Amoxicillin
List of abbreviations: DRP – drug related problems; ADR – adverse drug reactions; INN – international non-patented name

РЕТРОСПЕКТИВНЫЙ АНАЛИЗ КАРТ-ИЗВЕЩЕНИЙ О НЕЖЕЛАТЕЛЬНЫХ РЕАКЦИЯХ АНТИБИОТИКОВ ПЕНИЦИЛЛИНОВОГО РЯДА С ПРИМЕНЕНИЕМ МЕТОДА СИСТЕМЫ ПРОБЛЕМ, СВЯЗАННЫХ С ЛЕКАРСТВЕННЫМИ ПРЕПАРАТАМИ

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RESEARCH ARTICLE

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Широкое использование β-лактамных антибиотиков группы пенициллинов в практической медицине, официально допустимое их назначение особым категориям пациентов (дети, беременные и лактирующие женщины, лица пожилого возраста) требует серьезного отношения к изучению безопасности и оценке рисков при проведении антибактериальной фармакотерапии.

Целью работы было ретроспективное изучение случаев нежелательных реакций (НР), а также выявление и анализ проблем, связанных с применением лекарственных препаратов (*Drug-related problems*, DRP) группы пенициллинов.

Материалы и методы. Объектами исследования послужили случаи развития НР при применении группы пенициллинов в стационарных, амбулаторных учреждениях, а также при использовании препаратов в виде самолечения, т.е. карты-извещения о НР, зарегистрированные в региональной (Республика Крым) базе спонтанных сообщений ARCADe (*Adverse Reactions in Crimea, Autonomic Database*) за период 2009–2018 гг. Изучение и анализ DRP, проводились с использованием обновленной версии квалификационной системы DRP PCNE (*Pharmaceutical Care Network Europe Foundation*) V9.0.

Результаты анализа карт-извещений о НР позволили выявить, что препаратами-«лидерами» по частоте развития НР являются амоксициллина клавуланат и амоксициллин. Стоит отметить высокую частоту развития НР на фоне применения пенициллинов у пациентов детского возраста (от 0 до 18 лет) – 142 случая. Клиническими проявлениями НР на антибиотики представленной группы были реакции лекарственной гиперчувствительности (309 случаев), диспепсические расстройства (28 случаев) и нарушения со стороны центральной нервной системы (5 случаев). Частота серьезных НР составила 113 случаев (33% от общего количества НР), что свидетельствует о достаточно высоком риске развития тяжелых НР при применении пенициллинов, сопровождающихся значительным снижением качества жизни пациентов.

Заключение. Выявление DRP при помощи метода PCNE V9.0 является важным и перспективным инструментом, необходимым для повышения качества фармакотерапии пациентов и улучшения их приверженности к лечению. Наиболее высокие показатели значений DRP наблюдались при применении амоксициллина клавуланата и амоксициллина, что свидетельствует о высокой частоте нерационального назначения данных препаратов.

Ключевые слова: пенициллины, нежелательные реакции, проблемы, связанные с лекарственными препаратами, DRP, амоксициллина клавуланат, амоксициллин

Список сокращений: DRP – проблемы, связанные с лекарственными препаратами; ЛС – лекарственные средства; МНН – международное непатентованное название; НР – нежелательные реакции; ПСС – причинно-следственная связь

INTRODUCTION

The history of the penicillin clinical use began in 1940 after the first experimental study of penicillin in mice, which confirmed a high antibacterial activity of this drug against staphylococci [1]. Currently, penicillin medicines are the basis of modern antibacterial chemotherapy and have an important place in the treatment of various infectious diseases [2].

A widespread use of β-lactam antibiotics in practical medicine, their officially authorized prescription for special categories of patients (children, pregnant and lactating women, the elderly) requires a serious attention to safety studies and risk assessment [3, 4]. A study of adverse drug reactions (ADR) of antibacterial drugs by Jung I.Y. et al. in South Korea, confirms the high frequency of ADR associated with the use of penicillins (16% of the total number of cases for chemotherapeutic agents). The main manifestations were allergic reactions and gastrointestinal disorders [5]. Numerous studies on the safety of the penicillin group also have been conducted on the territory of the Russian Federation [6, 7]. They made it possible to identify a high incidence of penicillin ADR, most often associated with ignoring patients' allergic anamneses, overdosage, and the non-compliance with the recommended frequency of administration.

THE AIM of the work was a retrospective study of ADR cases, as well as the identification and analyses of the drugs (penicillins) related problems (DRP) using the DRP PCNE V9.0 qualification system.

MATERIALS AND METHODS

The objects of the study were ADR developed after the use of penicillin medicines in inpatient or outpatient facilities, as well as the ones related to the use of the drugs for self-treatment. The ADR reporting forms recorded in the regional (Republic of Crimea) database of spontaneous reports called ARCADe (Adverse Reactions in Crimea, Autonomic Database) received in 2009–2018 period, were analyzed.

The detection of the cases of interest was carried out by the codes of the Anatomical and Therapeutic Chemical (ATC) classification of drugs proposed by World Health Organization [8].

During the analyses, the instructions for medical use of the State Drug Registers of the Russian Federation and Ukraine (for the cases registered before 2014 when the Republic of Crimea became the part of Russian Federation) were checked. In accordance with the ATC classification, penicillins are assigned the J01C – beta-lactam antibiotics, penicillins.

The seriousness of ADR was established in accordance with the definition given in paragraph 51 of Article 4 of Federal Law No. 61-FZ dated April 12, 2010 "On the Circulation of Medicines" [9].

The assessment of the causal relationship was carried out in accordance with the recommendations of the WHO Uppsala monitoring center [10]. According to this classification, 6 degrees of a causal relationship are distinguished, and only the first 3 degrees (certain, probable, possible) refer to a high degree of causality and allow to interpret adverse events as "adverse drug reactions".

Drug-related problems (DRP) are defined as "any circumstance or event related to drug therapy that actually or potentially prevents the patient from receiving the intended benefits of the pharmacotherapy" [11–19]. The study and analysis of DRP were carried out using the updated (9th) version of the DRP PCNE (Pharmaceutical Care Network Europe Foundation) qualification system, adopted on June 1, 2019 [20]. The appearance of a new

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classification category "Intervention Acceptance", as well as the update of the standard categories (P – problems, C – causes, I – interventions and O – the status of the problem or outcomes), is one of the characteristic features of this version of the PCNE system. Thus, Category "P" is divided into three groups: P1-effectiveness, P2 – safety, P3 – other. The causes of DRP, standardized by code "C", are classified as follows:

- C1 – Drug selection
- C2 – Drug form
- C3 – Dose selection
- C4 – Treatment duration
- C5 – Dispensing
- C6 – Drug use process
- C7 – Patient related
- C8 – Patient transfer related
- C9 –Other.

In Section I (planned interventions) interventions are divided into 4 classes: I1 – interventions at prescriber level; I2 – interventions at patient level; I3 – interventions at drug level; I4 – other interventions and activities. Options for the outcome of the intervention (code "A" – Acceptance) are as follows: the intervention is accepted (A1), the intervention is not accepted (A2) and there is lack of information about the acceptance of certain interventions (A3). Among the outcomes of DRP (code "O"), there are 3 main alternatives: the DRP problem is solved, partially solved or not solved.

The evaluation of the DRP analysis results was carried out by Matveev AV, Krasheninnikov AE, Egorova EA. Each case of ADR was evaluated by two researchers independently of one another, and in case of disagreement, the third opinion was taken into account (Koniaeva EI). Such an analysis makes it possible to identify the most likely causes of the development of ADR in each case [21]. The minimum amount of DRP characterizes a high degree of safety of pharmacotherapy, and high DRP values, on the contrary, indicate a significant risk of potential complications when prescribing the drug.

Clopper-Pearson method was used to calculate limits of confidence intervals.

RESULTS AND DISCUSSION

In order to study the ADR of the penicillin group drugs (J01C), 342 reports (2009–2018) were selected in the regional database ARCADe. It amounted to 5.01% (95% CI: 4.5–5.6%) of the total number of adverse reactions recorded during the covered period (6825 reports). Among all cases of ADR development due to the use of antimicrobial agents for systemic use (1771 cases), the frequency of ADR associated with the use of penicillins was 19.3% (17.5–21.3%), which indicates a high risk of adverse effects.

The analysis of 342 ADR reports of the pharmacological group "J01C" by the frequency in the context of its representatives, is of practical interest is (Table 1).

A significant predominance of amoxicillin ADR is most likely due to the high frequency of prescriptions of these drugs by doctors in outpatient and inpatient settings [22]. It is worth noting that European (2017) and WHO guidelines (2017) recommend the use of Amoxicillin and Amoxicillin-clavulanate as first-line drugs for infections of the lower and upper respiratory tract (mild and moderate severity), infections of the skin and soft tissues, as well as for infection of urinary system [23].

The analysis the patients' age categories with recorded ADR caused by penicillin family antibiotics, is also of scientific interest. In 142 cases (41.52% with 95%CI 36.2–46.9), ADR were observed in pediatric patients (from 0 to 18 years). The distribution analysis of ADR in children was carried out in accordance with Geppe NA' classification with the following results: 0–28 days old – 14 cases (4.1%; 2.3–6.8%); 29 days – 12 months old – 40 cases (11.7%; 8.5–15.6%); 1–3 years old – 34 cases (10; 7–13.6%); 4–7 years old – 19 cases (5.6%; 3.4–5.6%); 8–10 years old – 7 cases (2%; 0.8–4.2%) and 11–18 years old – 28 cases (8.2%; 5.5–11.6%). 200 records contained information about the development of adverse effects after penicillins administration in patients over 18 years old. The frequency of cases in this age group with subgroups is presented in Figure 1. A study of gender characteristics made it possible to determine that the majority of ADR were observed in female patients (196 cases, 57.3% with 95% CI 51.9–62.6%).

Table 1 – Frequency of ADR reporting forms on penicillins

INN	TC-code	Amount of reporting forms, abs. value	Percentage of reporting forms in the total amount of ADR cases (95% CI)
Monocomponent drugs			
Amoxicillin	J01CA04	111	32.5 (27.5–37.7)
Ampicillin	J01CA01	14	4.1 (2.3–6.8)
Benzylpenicillin	J01CE01	11	3.2 (1.6–5.7)
Benzathine benzylpenicillin	J01CE08	2	0.6 (0.1–2.1)
Combinations			
Amoxicilline clavulanate	J01CR02	186	54.4 (48.9–59.8)
Amoxicilline sulbactam	J01CR01	18	5.3 (3.1–8.2)

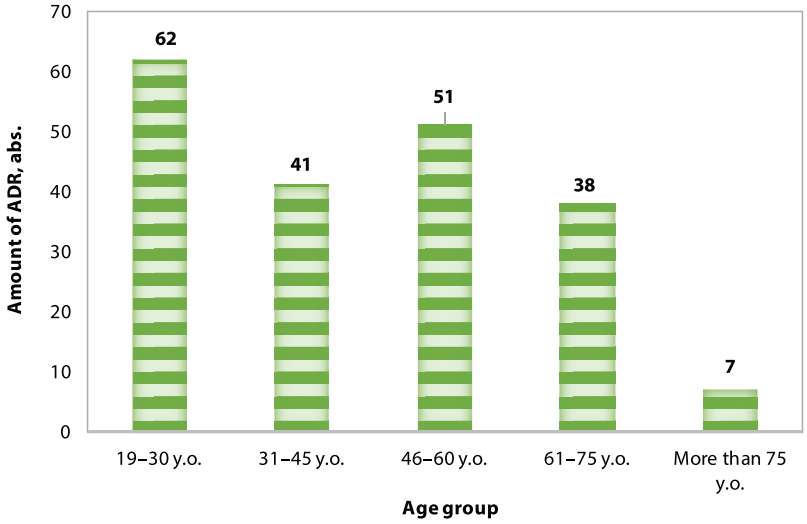
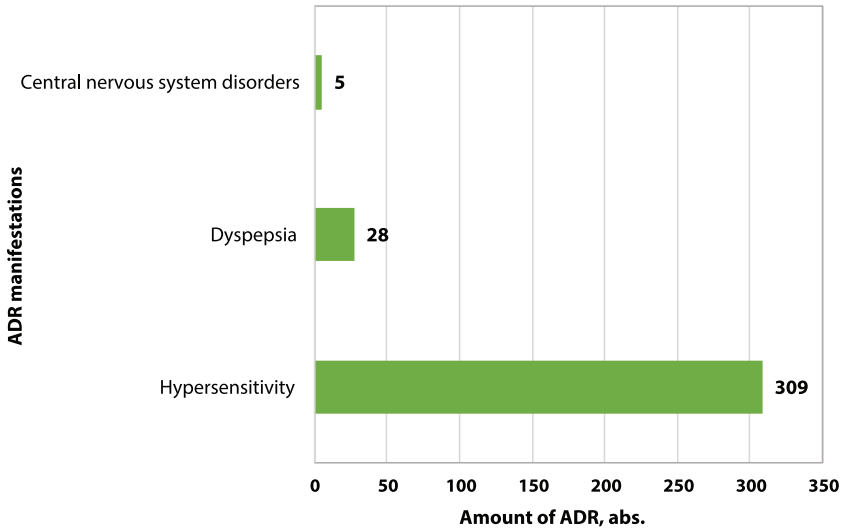


Figure 1 – The frequency of penicillins ADR in age categories of adult patients



Note: CNS – central nervous system

Figure 2 – The distribution of penicillin family antibiotics ADR according to their clinical manifestations

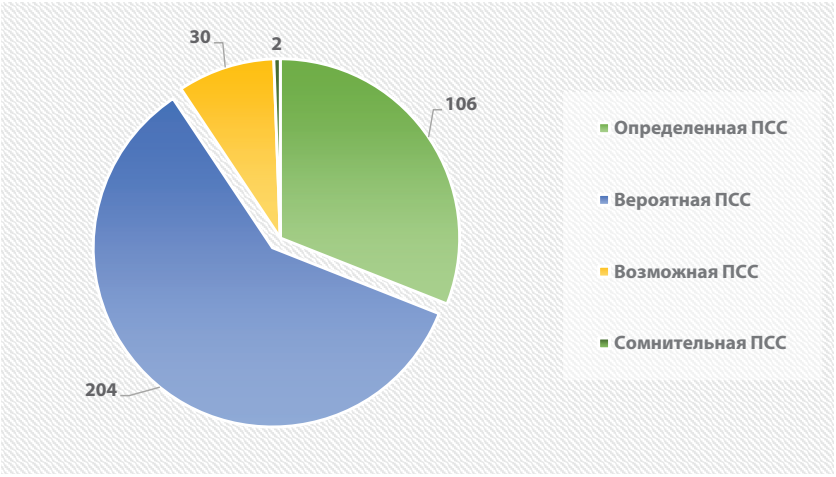


Figure 3 – Distribution of ADR cases by the type of casual relationship according to the WHO-UMC approach

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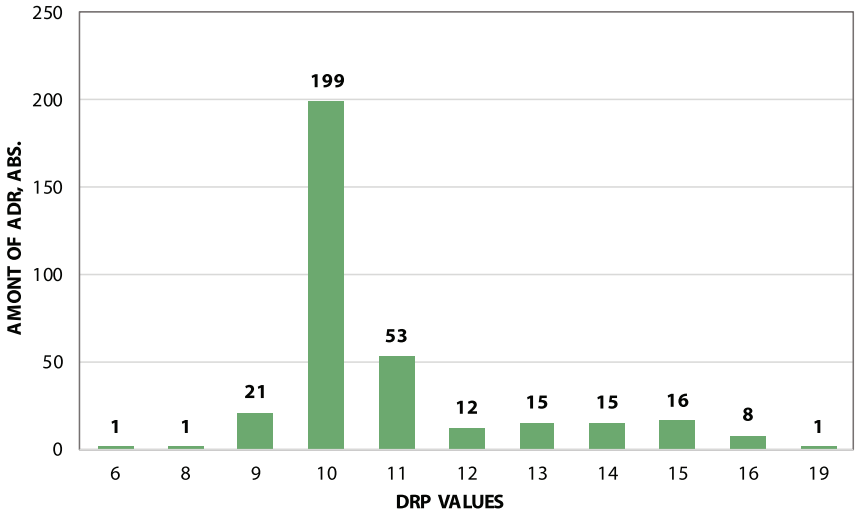

Figure 4 – Distribution of ADR cases by the quantity of total DRP value

Table 2 – Median (max:min) indices, DRP values in cases of ADR in the administration of penicillin family antibiotics according to standard qualification grades

INN / DRP subcategory	Amoxicillin	Ampicillin	Benzyl-penicillin	Benzathine benzyl-penicillin	Amoxicilline-clavulanate	Amoxicilline-sulbactam
Category P – Problems						
P1. Effectiveness	0 (0:0)	0 (0:0)	0 (0:0)	0 (0:0)	0 (0:0)	0 (0:0)
P2. Safety	1 (1:1)	1 (1:1)	1 (1:1)	1 (1:1)	1 (0:1)	1 (1:1)
P3. Other	0 (0:2)	0 (0:2)	0 (0:0)	0 (0:0)	0 (0:2)	0 (0:1)
Category C – Causes						
C1. Drug selection	0 (0:3)	0 (0:1)	0 (0:2)	0 (0:0)	0 (0:3)	0 (0:1)
C2. Drug form	0 (0:0)	0 (0:0)	0 (0:0)	0 (0:0)	0 (0:1)	0 (0:0)
C3. Dose selection	0 (0:2)	0 (0:2)	0 (0:0)	0,5 (0:1)	0 (0:3)	0 (0:2)
C4. Treatment duration	0 (0:0)	0 (0:0)	0 (0:0)	0 (0:0)	0 (0:0)	0 (0:0)
C5. Dispensing	0 (0:2)	0 (0:0)	0 (0:0)	0,5 (0:1)	0 (0:1)	0 (0:0)
C6. Drug use process	0 (0:1)	0 (0:1)	0 (0:0)	0 (0:0)	0 (0:2)	0 (0:1)
C7. Patient related problems	0 (0:1)	0 (0:1)	0 (0:0)	0 (0:0)	0 (0:1)	0 (0:1)
C8. Patient transfer related problems	0 (0:1)	0 (0:1)	0 (0:1)	0 (0:1)	0 (0:1)	0 (0:1)
C9. Other	1 (0:1)	1 (0:1)	1 (1:1)	1 (1:1)	1 (0:1)	1 (1:1)
Category I – Interventions						
I1. Interventions at prescriber level	2 (0:2)	2 (1:2)	2 (1:2)	2 (2:2)	2 (0:2)	2 (2:2)
I2. Interventions at patient level	1 (0:2)	1 (1:2)	1 (0:2)	1,5 (1:2)	1 (0:2)	1 (1:1)
I3. Interventions at drug level	1 (0:1)	1 (1:1)	1 (1:1)	1 (1:1)	1 (0:1)	1 (1:1)
I4. Other interventions and activities	1 (0:1)	1 (1:1)	1 (1:1)	1 (1:1)	1 (0:1)	1 (1:1)
Category A – Acceptance						
A1. Intervention is accepted	1 (0:2)	1 (1:1)	1 (1:1)	1 (1:1)	1 (0:1)	1 (1:1)
A2. Intervention is not accepted	0 (0:0)	0 (0:0)	0 (0:0)	0 (0:0)	0 (0:1)	0 (0:0)
A3. Other	0 (0:1)	0 (0:0)	0 (0:0)	0 (0:0)	0 (0:1)	0 (0:0)
Category O – Outcomes						
O. Status of problem	0 (0:1)	0 (0:1)	0 (0:1)	0,5 (0:1)	0 (0:1)	0 (0:1)
O1. Solved	1 (0:1)	1 (0:1)	1 (0:1)	0,5 (0:1)	1 (0:1)	1 (0:1)
O2. Partially solved	0 (0:0)	0 (0:0)	0 (0:0)	0 (0:0)	0 (0:0)	0 (0:0)
O3. Not solved	0 (0:1)	0 (0:1)	0 (0:1)	0,5 (0:1)	0 (0:2)	0 (0:1)

Table 3 – Total Median (Max:min) values in cases of ADR caused by individual members of penicillin family antibiotics according to standard qualification grades

INN	Category «P»	Category «C»	Category «I»	Category «A»	Category «O»	Sum of DRP values
Amoxicillin	1 (1:3)	2 (1:6)	5 (2:6)	1 (1:2)	1 (0:2)	10 (8:16)
Ampicillin	1 (1:3)	2 (2:5)	5 (4:6)	1 (1:1)	1 (1:2)	10 (10:15)
Benzylpenicillin	1 (1:1)	2 (2:4)	5 (3:6)	1 (1:1)	1 (1:2)	10 (10:11)
Benzathine benzylpenicillin	1 (1:1)	3 (2:4)	5,5 (5:6)	1 (1:1)	1,5 (1:2)	11 (10:14)
Amoxicilline-clavulanate	1 (1:3)	2 (1:9)	5 (2:6)	1 (0:2)	1 (0:2)	10 (6:19)
Amoxicilline-sulbactam	1 (1:2)	2 (2:5)	5 (5:5)	1 (1:1)	1 (1:2)	10 (10:14)

The development of penicillin ADR most often occurred after the oral administration (265 cases, 77.5% with 95%CI 72.7–81.8%) and less often after the parenteral administration (intravenously – 52 cases, 15.2% (11.6-19.5%); intramuscularly – 25 cases, 7.3% (4.8–10.6%)).

A study of the clinical manifestations of adverse reactions that occur in patients against the background of the administration of penicillin family antibiotics, revealed an absolute predominance of drug hypersensitivity reactions of varying severity (urticaria, pruritus, skin hyperemia – 298 cases (87.1%; 83.1–90.5%), angioedema – 9 cases (2.6%; 1.2–4.9%), anaphylactic shock – 2 cases (0.6%; 0.1–2.1%)). The distribution of the remaining cases of ADR by their clinical manifestations is presented in Figure 2. In 28 cases (8.2%; 5.5–11.6%) against the background of the administration of penicillin family antibiotics, the patients had various dyspeptic disorders (nausea, bloating, diarrhea, spastic pains). Disorders of the central nervous system (5 cases; 1.5% 95%CI 0.5–3.4%) were manifested in the forms of dizziness, darkening in the eyes, weakness and tinnitus.

An important step in the drug safety analysis, is the identification and assessment of the cases of serious ADR that require the doctor to timely withdraw the drug, hospitalize the patient and / or conduct emergency pharmacotherapy. In the case of the studied group of drugs, the frequency of serious reactions was 113 cases (33%; 28.1–38.3%), which indicates a rather high risk of developing severe ADR, accompanied by a significant decrease in the quality of patients' lives The distribution of such cases in accordance with the criteria of their severity, was presented by the following results: death – 1 case (0.3%; 0-1.6%), threat to patient's life – 8 cases(2.3%; 1–4.6%), temporary disability – 50 cases (14.6%; 11–18.8%), hospitalization or extension of its term – 54 cases (15.8%; 12.1–20%). The patient's death (1 y.o.) occurred as a result of the development of an anaphylactic shock (face cyanosis, respiratory and cardiac arrest) against the background of the administration of Amoxicillin-clavulanate suspension for an acute respiratory disease. It is worth notifying that, simultaneously with the suspected drug, the child was prescribed a syrup containing Phenylephrine, Salbutamol and Bromhexine, as well as Hephenadine tablets (5 mg). In most cases, the development of angioneurotic oedema posed a threat to the lives of patients and required emergency pharmacotherapy with glucocorticoid and anti-allergic drugs.

The analysis of drug correction cases to stop ADR clinical manifestations is of further interest. Despite a high incidence of non-serious events, the administration of drugs to relief ADR was necessary in the absolute majority of cases – 293 (85.7%; 81.5–89.2%). In remaining 49 cases (14.3%; 10.8–18.5%), ADR did not require additional pharmacotherapy. Among the pharmacological groups prescribed for the correction of ADR, antiallergic agents for oral and external use, glucocorticoids (Dexamethasone, Prednisolone) and sorbents prevailed.

An important step in safety assessing when using drugs, is to determine the causality between the ADR manifestations and the clinical and pharmacological characteristics of the drug [10]. One of the algorithms for determining the causal relationship is the WHO-UMC algorithm proposed by specialists of the WHO Center for Drug Safety Monitoring (Uppsala, Sweden).

The results obtained for causality, make it possible for doctors to correctly assess the current clinical situation and timely take the necessary treatment and preventive measures. The results of the causality analysis are presented in Figure 3. It is worth paying attention to the predominance of a certain and probable type, which indicates a high risk of developing adverse reactions due to the use of penicillins.

The second stage of the reporting forms analysis, was aimed at studying the problems related to the use of drugs (DRP). The calculation of the total DRP values for the cases of ADR, yielded the following results: DRP values between 5–8 were found in 2 cases (6 DRP – 1 case of HP, 8 DRP – 1 case), in 21 reporting cards the

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total number of DRP amounted to 9, and in 199 cases – 10 DRP. In the remaining 120 cases of ADR, the DRP values were higher than 10 (the minimum was 11 DRP, the maximum – 19 DRP), which may indicate the likelihood of an irrational choice of the drug, interaction of penicillins with other drugs, errors in the selection of individual doses or the frequency of administration. The frequency distribution of individual DRP values for penicillin family antibiotics is shown in Fig. 4. The calculation of the total number of DRP for all cases of ADR (3712 DRP) made it possible to determine the average number of DRP, which amounted to 10.85 per 1 patient.

A quantitative analysis of the problems associated with the use of various members of penicillin family antibiotics according to the main classification categories, is also of interest. The indicators of the minimum, maximum values and the DRP median for each of the drugs, are presented in Table 2.

The study of individual categories of the DRP system revealed the fact that for all the drugs under study, the maximum number of the drugs associated problems, was recorded in section "I" (Intervention). High DRP values, in this case, are due to the interventions performed by the doctor in the form of withdrawn the suspected drug and prescribing drugs for the ADR correction.

A detailed study of the results of DRP calculating according to the qualification category "C" (ADR causes) revealed the fact that the main reasons for the development of drug related problems, are various violations of the dosage regimen (low drug dose / low frequency, high drug dose / high frequency, unclear or incorrect recommendations on the dose regimen and frequency of administration). In accordance with the classification of DRP PCNE V9.0, the information on drug dosing violations is presented in section C3 – dose selection. The results of this section analysis of the classification, can be presented as follows: the dose of the suspected drugs was exceeded in 9 cases (2.6% of the total number of cases of penicillins ADR; 1.2–4.9%), the use of low doses of the drugs (below the minimum therapeutic doses) – in 6 cases (1.75%; 0.6–3.8%), the absence of indications of a dosage regimen or unclear instructions for use (for example, "1 tablet" without indicating the strength of the action) – in 19 cases (5.6% of cases; 3.4–8.5%). The main reasons for the development of penicillin related problems were individual hypersensitivity reactions, the manifestations of which were allergic reactions of varying severity.

The analysis of the final DRP values for individual members of penicillin family antibiotics showed that the maximum DRP value was observed in the administration of Amoxicillin-clavulanate (19 problems) and Amoxicillin monopreparations (16 problems) (Table 3). A study of these cases confirmed the irrational use of antibacterial drugs in acute respiratory viral infections with a violation of the dose regimen, which led to such high rates of DRP. The minimum DRP values (6 and 8 problems) were observed with the use of the same drugs. The corresponding cases of ADR have been associated with the development of allergic reactions against the background of their rational use.

Calculation of the median DRP showed the highest values for Benzathine benzylpenicillin, for the other drugs the median values were identical and amounted to 10 DRP / case, while the largest diapason between the minimum and maximum values of DRP was found for Amoxicillin-clavulanate (max: min – 6:19), and the smallest – for Benzylpenicillin (max: min – 10:11).

CONCLUSION

The results of the analysis of the ADR reporting forms revealed the fact that Amoxicillin-clavulanate and Amoxicillin are the "leaders" in the frequency of ADR development in the penicillin family antibiotics.

It is worth notifying that a high frequency of ADR against the background of penicillins administration in pediatric patients (from 0 to 18 years) is represented by 142 cases. The clinical manifestations of the antibiotics ADR were drug hypersensitivity reactions (309 cases), dyspeptic disorders (28 cases) and disorders of the central nervous system (5 cases). The frequency of serious adverse reactions was 113 cases (33% of the total number of ADR), which indicates a rather high risk of developing severe penicillins complications accompanied by a significant decrease in the quality of patients' lives.

The highest DRP values were observed against the background of Amoxicillin-clavulanate and Amoxicillin administration, the minimum DRP values were observed against the background of Benzylpenicillin preparations.

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AUTHOR'S CONTRIBUTION

All authors equally contributed to the research work.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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