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ANALYSIS OF ADVERSE DRUG REACTIONS TO ANTIBACTERIAL AGENTS FOR SYSTEMIC USE IN CHILDREN

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ANALYSIS OF ADVERSE DRUG REACTIONS TO ANTIBACTERIAL AGENTS FOR SYSTEMIC USE IN CHILDREN IN UKRAINE

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The rational use of antibacterial agents (ABAs) for systemic use is crucial to the pediatric population, since every year the above-mentioned drugs are most often prescribed to children under two years old, and inappropriate use of ABAs at an early age contributes to an increased risk of comorbidities in children.

The study **aimed to** analyze the frequency of adverse reactions in children to ABAs (by J01 antibacterial drugs for systemic use) in Ukraine during the period of 2018–2023 and highlight those that have the highest rates of adverse reactions.

Materials and methods. During the study, methods of system analysis, passive pharmacovigilance, spontaneous reports, and methods of statistical data processing were applied. General trends in the development of manifestations of adverse reactions in the form of exponential trends were determined with the calculation of the validity value of approximation. There were analyzed 3207 spontaneous card reports (Form No. 137/o) received by the State Expert Center of the Ministry of Health of Ukraine on cases of adverse drug reactions (ADRs) of ABAs in children during the entire study for 2018–2023.

Results. Analysis of the incidence of ADRs revealed the highest rate in ceftriaxone – 998 cases of ADRs. Ceftriaxone, cefotaxime, azithromycin, and moxifloxacin had a declining tendency of the adverse effects, while levofloxacin had an upward trend. The obtained results justify the necessity of strict control over the usage of antibacterial drugs, that might reduce undesirable adverse reactions from their use.

Key words: pharmacovigilance, pediatrics, adverse drug reactions, antibacterial medicinal agents, drugs safety.

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АНАЛІЗ ПОБІЧНИХ РЕАКЦІЙ НА АНТИБАКТЕРІАЛЬНІ ЗАСОБИ ДЛЯ СИСТЕМНОГО ЗАСТОСУВАННЯ У ДІТЕЙ

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Було проаналізовано 3207 спонтанних карт-повідомлень (Форма № 137/о), що надійшли до Державного експертного центру МОЗ України, про випадки побічних реакцій (ПР) антибактеріальних засобів для системного застосування (АБЗ) у дітей протягом усього дослідження за період 2018–2023 рр.

Аналіз частоти виникнення ПР ЛЗ виявив найбільший показник у цефтріаксону – 998 випадків ПР ЛЗ. Цефтріаксон, цефотаксим, азитроміцин і моксифлоксацин виявили тенденцію до зниження частоти побічних ефектів, водночас стосовно левофлоксацину спостерігалась тенденція до зростання частоти. Отримані результати обґрунтовують необхідність жорсткого контролю щодо використання антибактеріальних засобів, що може знизити частоту побічних ефектів під час їх застосування.

Ключові слова: фармаконагляд, педіатрія, побічні реакції, антибактеріальні лікарські засоби, безпека ліків.

Introduction. The rational use of antibacterial agents (ABAs) for systemic use is crucial to the pediatric population, since every year the above-mentioned drugs are most often prescribed to children under two years old, and inappropriate use of ABAs at an early age contributes to an increased risk of comorbidities in children [1].

According to the modern literature, from 19% to 51% of cases of basic pharmacotherapy in children have adverse reactions to prescribed ABAs [2]. The anatomical and physiological features of the child's body significantly affect the metabolism of drugs used for pharmacotherapy in the pediatric population, namely the absorption of drugs, their distribution, pharmacokinetics, and immunological response to them. The presence and class of comorbidity contribute to complications seen in pediatric patients and adverse drug reactions [3; 4]. According to A.M. Butler et al., in the cohort of pediatric patients in the US study, between 31% and 36% received ABAs that cannot be used

for bacterial infections such as purulent acute otitis media, pharyngitis, and sinusitis. As a result, 30-day health care costs were generally higher among pediatric patients who received inappropriate ABAs, which ranged from $ 21 to $ 56 for bacterial infections. Annual costs in the US were highest for purulent acute otitis media ($ 25,3 million) and pharyngitis ($ 21,3 million) [5].

Antibacterial agents for systemic use are the drugs most commonly prescribed by physicians in the pediatric population. According to a study by M. Hufnagel et al., involving 17693 pediatric patients in 41 countries, 36.7% of children were prescribed antibiotics [6]. From which it follows that ABAs also provoke a higher frequency of adverse drug reactions (ADRs) in children, especially in hospitalized children, as it was found out in a cross-sectional study from Greece [7]. This is facilitated by both the peculiarities of these drugs (their high immunogenicity, in particular, allergenicity), and the significant frequency of medication errors (calculation of the single, daily and course doses; off-label drug use), and sometimes also the lack of adapted dosage forms for children. According to Italian scientists, the non-rational use of ABAs in the pediatric population can, among other things, not only cause an excessive economic burden on the healthcare system, but also contribute to the development of antibiotic resistance. Therefore, inappropriate use of ABAs in pediatric patients should be avoided in order to reduce the risks of ADRs, increased costs spent on pharmacotherapy, lifelong consequences, and the development of resistant organisms that provoke unexpected death [8].

Thus, in one of the studies conducted by S. Iftikhar et al., among 11892 pediatric patients, in 40.8% of cases, there were errors in the use of ABAs caused by incorrect dosage (19.9%), incorrect frequency (18.9%) or dual therapy with several ABAs (18.1%). Medication errors were most common in cases of lower respiratory tract infections, especially among children who had been in a healthcare facility for a long time [9].

A recent study in Serbia focused on the fact that antibacterial agents for systemic use are prescribed non-rationally [10]. According to a 2015 study by B. Bozic and M. Bajcetic, more than 85% of children in Serbia with a viral infection of the upper respiratory tract received an antibacterial agent for systemic use agent that does not meet treatment protocols [11].

There is a lack of data on the frequency of adverse reactions to ABAs used in children in Ukraine, which needs to be filled with appropriate research.

The study **aimed to** analyze the frequency of adverse reactions in children to ABAs (by J01 antibacterial drugs for systemic use) in Ukraine during the period of 2018–2023 and highlight those that have the highest rates of adverse reactions.

Materials and methods. The object of the study was notification cards (Form No. 137/o) on adverse reactions of medicinal agents received from the State Expert Center of the Ministry of Health of Ukraine from the National Database of Adverse Reactions of the Automated Pharmacovigilance Information System (APIS, in Ukrainian – AISF). Totally, it was analyzed 3207 spontaneous report cards on cases of ADRs to antibacterial agents for systemic use in children during the entire study for the period of 2018–2023. The manifestations of adverse drug reactions were analyzed, in particular, to group J01 antibacterial drugs for systemic use in the pediatric population. During the study, methods of system analysis, passive pharmacovigilance, spontaneous reports and methods of statistical data processing were applied, i.e., method of mass observations, grouping method, method of generalizing indicators and method of qualitative analysis. General trends in the development of manifestations of adverse reactions in the form of exponential trends were determined with the calculation of the validity value of approximation [12].

Results. Nevertheless, levofloxacin and moxifloxacin are contraindicated to the pediatric patients, the notification cards with ADRs to these fluoroquinolones were received by SEC MOH of Ukraine due to inappropriate use of the above-mentioned medicines in this cohort of population by physicians and pediatricians.

Analysis of the incidence of ADRs revealed the highest rate in ceftriaxone – 998 cases of ADRs (Fig. 1). Antibiotics in general had significantly more adverse reactions (84%) than synthetic antimicrobials (16%). Antibiotics included such medicines as ceftriaxone, amoxicillin, amoxilicin with clavulanic acid, azithromycin and cefotaxime. Linezolid, levofloxacin and moxifloxacin belonged to the group of synthetic antimicrobials. It is quite logical that ABAs are the leaders of this rating in the updated Standard of antimicrobial therapy (2023) [13] as linezolid, ceftriaxone and levofloxacin were assigned to group C (reserve group) under the WHO AWaRe classification (2021) [14].

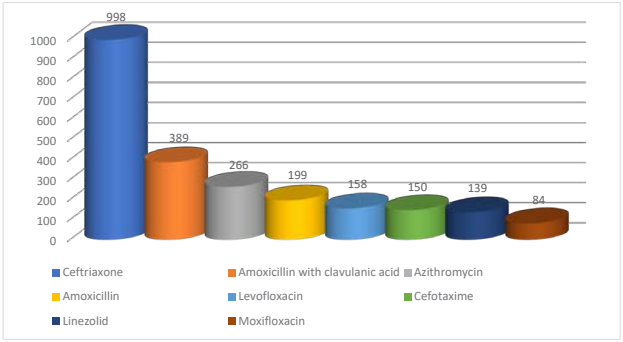

Fig. 1. Absolute indicators of the incidence of adverse reactions to antibacterial agents for systemic use in children by drugs for the period of 2018–2023

The absolute numerical indicator of the adverse reaction is not always a reflection of a reliable trend, therefore, for the sake of objectification, we considered the frequency index of the development of ADRs for the specified ABAs for a period of 6 years with the calculation of the value of the approximation reliability. This approach makes it possible to see significant trends in the pediatric cohort of patients receiving ABAs.

Among the specified class of ABAs, rates of incidence of ADRs to ABAs are presented on Table 1.

The trend of detection of ADRs to ceftriaxone among children for the period of 2018–2023 is mostly reliable, since the value of the approximation reliability ($R^2 = 0,8547$) of this trend is an acceptable value, since it is in the range from 0.5 to 0.8 (Fig. 2).

Table 1

Analysis of the frequency of detection of adverse reactions to the antibacterial drugs in children for 2018–2023

ABAs INN	Years of observation											
	2018		2019		2020		2021		2022		2023	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Ceftriaxone	296	41.05	278	35.74	127	24.80	123	31.70	67	20.42	107	22.19
Amoxicillin	46	6.30	45	5.79	35	6.83	20	5.15	18	5.48	35	7.23
Amoxicillin with clavulanic acid	53	7.30	96	12.36	63	12.30	48	12.37	32	9.75	97	20.04
Cefotaxime	42	5.80	52	6.69	19	3.71	14	3.60	8	2.43	15	3.01
Azithromycin	68	9.43	63	8.11	45	8.78	25	6.44	24	7.31	41	8.47
Linezolid	1	0.13	–	–	48	9.37	33	8.50	40	12.19	17	3.51
Levofloxacin	9	1.24	–	–	9	1.75	30	7.73	72	21.95	38	7.85
Moxifloxacin	–	–	–	–	74	14.45	3	0.77	3	0.91	4	0.83
Total	721		777		512		388		328		484	

The trend of detection of ADRs to amoxicillin among children for the period of 2018–2023 is not reliable, since the value of the approximation reliability (R^2 = 0,514) of this trend is close to the permissible value, as it approaches the range from 0.5 to 0.8, but is still not enough to be acceptable (Fig. 3).

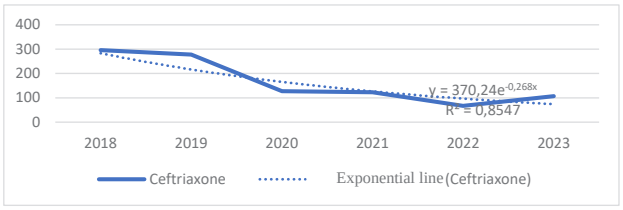

Fig. 2. The trend of detection of adverse reactions to ceftriaxone among children for the period of 2018–2023, line, trend equation and value of the approximation reliability

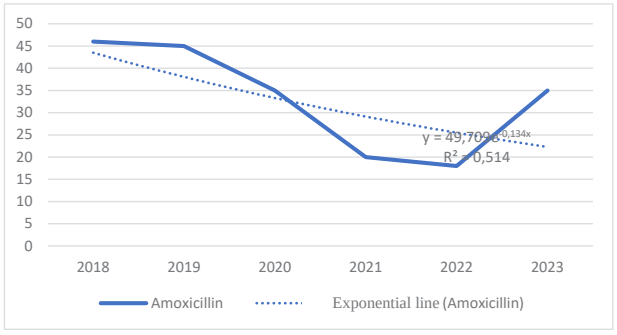

Fig. 3. The trend of detection of adverse reactions to amoxicillin among children for the period of 2018–2023, line, trend equation and value of the approximation reliability

Meanwhile, the trend of detection of ADRs to amoxicillin with clavulanic acid among children for the period of 2018–2023 is practically not reliable, since the value of the approximation reliability (R^2 = 0,0005) of this trend is not a reliable enough value, since it is in the range from 0 to 0.5 (Fig. 4).

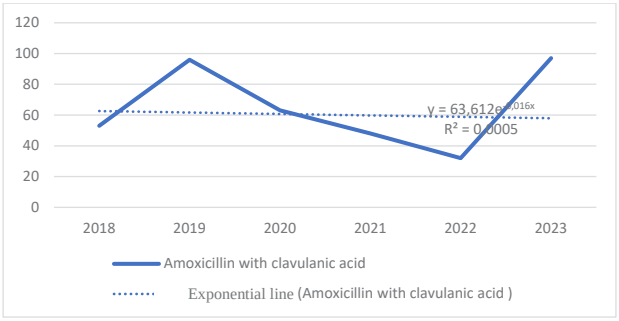

Fig. 4. The trend of detection of adverse reactions to amoxicillin with clavulanic acid among children for the period of 2018–2023, line, trend equation and value of the approximation reliability

The trend of detection of ADRs to cefotaxime among children for the period of 2018–2023 is mostly reliable, since the value of the approximation reliability (R^2 = 0,7162) of this trend is an acceptable value, since it is in the range from 0.5 to 0.8 (Fig. 5).

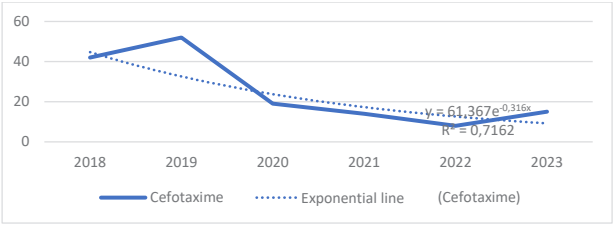

Fig. 5. The trend of detection of adverse reactions to cefotaxime among children for the period of 2018–2023, line, trend equation and value of the approximation reliability

At the same time, the trend of detection of ADRs to azithromycin among children for the period of 2018–2023 is also reliable, since the value of the approximation reliability (R^2 = 0,6974) of this trend is an acceptable value, since it is in the range from 0.5 to 0.8 (Fig. 6).

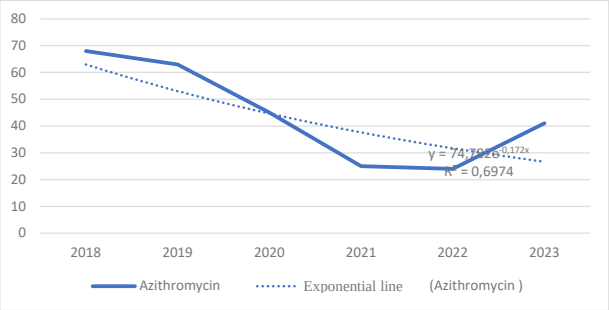

Fig. 6. The trend of detection of adverse reactions to azithromycin among children for the period of 2018–2023, line, trend equation and value of the approximation reliability

On the other hand, the trend of detection of ADRs to linezolid among children for the period of 2018–2023 is unreliable, since the value of the approximation reliability (R^2 = 0,0017) of this trend is not an acceptable value, since it is in the range from 0 to 0.5 (Fig. 7).

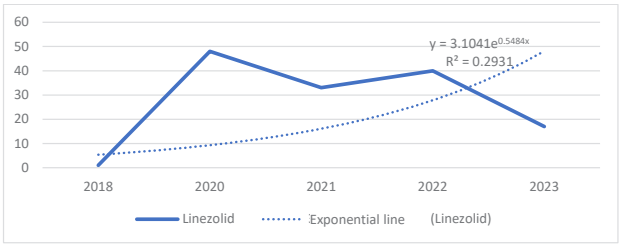

Fig. 7. The trend of detection of adverse reactions to linezolid among children for the period of 2018–2023, line, trend equation and value of the approximation reliability

In addition, the trend of detection of ADRs to levofloxacin among children for the period of 2018–2023 is reliable, since the value of the approximation reliability (R^2 = 0,3804) of this trend is an acceptable value, since it is in the range from 0.5 to 0.8 (Fig. 8).

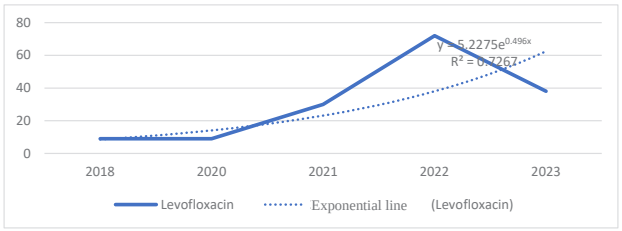

Fig. 8. The trend of detection of adverse reactions to levofloxacin among children for the period of 2018–2023, line, trend equation and value of the approximation reliability

The trend of detection of ADRs to moxifloxacin among children for the period of 2020–2023 is mostly reliable, since the value of the approximation reliability (R^2 = 0,8726) of this trend is an acceptable value, since it is in the range from 0.5 to 0.8 (Fig. 9). It's worth noting that there were detected no ADRs to moxifloxacin in 2018 and 2019.

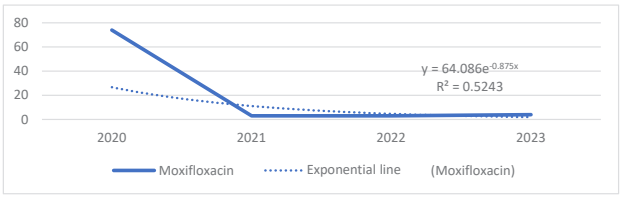

Fig. 9. The trend of detection of adverse reactions to moxifloxacin among children for the period of 2020–2023, line, trend equation and value of approximation reliability

Summarizing the above-mentioned indicators, it should be noted that the linear trends of detection of ADRs to ceftriaxone, amoxicillin, cefotaxime, azithromycin and moxifloxacin had a general downward tendency. This can be explained by the fact that since 2021, the requirements for dispensing prescription drugs have been strengthened, and the stewardship of antimicrobial drugs in healthcare facilities has been introduced. And the position of a clinical pharmacist (pharmacist) has been introduced into the pharmacotherapeutic teams in the infection control departments. On the other hand, the trend of detection of ADRs to levofloxacin indicates an increase in these indicators. In the updated Standard of medical care "Rational use of antibacterial and antifungal drugs for therapeutic and prophylactic purposes", Order of the Ministry of Health of Ukraine No. 1513 dated 23.08.2023, levofloxacin is assigned to the reserve group.

Compared to the data of a similar study conducted during 2008–2013 and published in 2019 in Brazil, the most widespread in the 3330 cases of adverse events among children detected during this period were adverse reactions to antibacterial agents for systemic use, in particular to vancomycin (352 cases of adverse reactions, which accounted for 9.08% of the total number of all detected ADRs to all groups of drugs according to the ATC classification) [14]. In contrast, in our study, only 9 cases of ADRs were detected to vancomycin in 2018, which was 1.2%, 14 cases of ADRs in 2019, which was 1.8%, 7 cases of ADRs in 2020, which was 1.4%, 11 cases of ADRs in 2021, which was 2.8%, 3 cases in 2022, which was 0.9%, and 9 cases of ADRs in 2023, which accounted for 1.9% of the total number of detected ADRs to J01 antibacterial drugs for systemic use. At the same time, during the entire period of our study, only 53 cases of ADRs to vancomycin were detected, which accounted for only 1.7% of all cases of ADRs to J01 antibacterial drugs for systemic use.

According to Brazilian scientists, the second place was taken by ceftriaxone (217 cases of adverse reactions, which were 5.6%) compared to 998 cases of ADRs, which was 31.1% of the total number of detected ADRs to J01 antibacterial drugs for systemic use in our study in Ukraine. Also, among the pediatric population of Brazil, oxacillin ranked 3rd (211 cases of adverse reactions, which were 5.45%) [15]. However, during our study, no ADRs for oxacillin were detected at all, as this drug is not registered in Ukraine at the moment.

In addition, among all groups of drugs according to the ATC classification in Brazil, ADRs were also caused by such ABAs as cefepime (59 cases of ADRs, which

were 1.52%) compared to 49 cases of ADRs in our study in Ukraine, which accounted for 1.5% of the total number of detected ADRs for J01 antibacterial drugs for systemic use, amoxicillin (53 cases of ADRs, which were 1.37%) compared to 199 cases in our study in Ukraine, which were 6.2%, meropenem (43 cases of ADRs, which were 1.11%) compared to 16 cases of ADRs in our study in Ukraine, which were 0.5%, ampicillin (42 cases of ADRs, which were 1,08%) compared to 37 cases in our study in Ukraine, which were 1.2%, benzylpenicillin (41 cases of ADRs, which were 1.06%) compared to 5 cases in our study in Ukraine, which were 0.2%, cefuroxime (39 cases of ADRs, which were 1.01%) compared to 58 cases in our study in Ukraine, which were 1.8%, metronidazole (30 cases of ADRs, which were 0.77%) compared to 18 cases in our study in Ukraine, which were 0,6%, piperacillin and tazobactam (29 cases of ADRs, which were 0,75%), imipenem and cilastatin (28 cases of ADRs, which accounted for 0.72% and clindamycin (28 cases of ADRs, which were 0.72%) [15]. For the period of 2018–2023, the last three above-mentioned ABAs did not provoke any ADRs in our study in Ukraine among children.

Following a study by scientists from the United States, Yu. Kalvin et al., after implementing antimicrobials stewardship programs at two health care facilities, prescribing of all classes of antimicrobials decreased, as well as costs per 1000 patient-days. At the same time, the implementation of antimicrobial stewardship programs in health care facilities with the involvement of clinical pharmacists/pharmacists contributed to a reduction in health care costs by $ 228353 during the study period, which lasted 12 months (the study was conducted in two health care facilities with antimicrobials stewardship, and three health care facilities in the control group with antimicrobials use rates, that were slightly above average). Cost reduction can be achieved in different healthcare settings using the above-mentioned model, while healthcare costs increase in the absence of control over the use of antimicrobials [16].

Conclusions

1. Among the antibacterial drugs, antibiotics more often cause adverse effect in children than synthetic antibacterial agents – 84% vs 16% respectively.
2. Among antibiotics during the period of 2018–2023, the leading positions in terms of quantity are occupied by ceftriaxone (998 cases of adverse reactions, which are 31.1% of all adverse reactions to antibacterial agents for systemic use), amoxicillin with clavulanate (389 cases, which are 12.1%) and azithromycin (266 cases, which are 8.3%). The inhibitor-protected amoxicillin/clavulanate is 2 times more likely than amoxicillin without clavulanate to cause adverse reactions in children — 389 cases of adverse reactions versus 199 cases, respectively.
3. The approximation values we calculated allowed us to identify reliable trends in the frequency of adverse reactions in the pediatric population. Ceftriaxone, cefotaxime, azithromycin, and moxifloxacin had a tendency to decline, while levofloxacin had an upward trend.
4. A comparative analysis revealed a similar trend in Brazil, in particular, high rates of adverse reactions to the antibiotics ceftriaxone and amoxicillin, which are among the top five, and antibacterial drugs, as well as in Ukraine, cause the highest frequency of adverse reactions among children.
5. The trends we have identified actualize the strengthening of control over the circulation of antibacterial drugs, the restriction of the clinical use of their individual representatives (ceftriaxone, azithromycin, fluoroquinolones in children) and not only in order to restrain antibiotic resistance, but also to reduce undesirable adverse reactions from their use.
6. Widespread implementation of antimicrobials stewardship can be a real lever of influence on the safety of antibiotic therapy in children and help to reduce adverse reactions and antibiotic resistance among children. International experience shows that it is expedient to involve clinical pharmacists/pharmacists in the stewardship of antimicrobials, which can reduce the rate of adverse reactions and optimize healthcare costs.

The authors declare that there is no conflict of interest.

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