Article

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Abstract: (1) Background: National health system databases represent one of the most obvious sources of information about epidemiology of adverse drug reactions including drug-induced allergy and anaphylaxis. (2) Methods: Retrospective descriptive analysis of spontaneous reports with data on drug-induced anaphylaxis (SRsAs) extracted from Russian National Pharmacovigilance database (analyzed period 02.04.2019 - 21.06.2023). There were estimated percentages of SRsAs among SRs of drug-induced allergy (SRsDIAs), of pediatric, elderly and fatal SRsAs among total SRsAs. The structure of drugs involved in anaphylaxis was assessed among total SRsAs, pediatric and elderly SRsAs, and among fatal SRsAs. Patients demographic parameters were assesed. (3) Results: SRsAs were reported in 8.3% of SRsDIAs (2304/27,7), mean age of patients was 48.2 ± 15.8 years, 53.2% were females. Main causative groups of drugs were antibacterials for systemic use, ABs (44.6%), local anesthetics, (20.0%), and cyclooxygenase (COX)-inhibitors (10.1%). Fatal SRsAs were reported in 9.5% (218/2304), mean age of patients was 48.0 ± 16.7 years, 56.2% were females. Pediatric SRsAs accounted for 5.8% (133/2304), mean age 11.8±4.5 years, 51.9% were females. Elderly SRsAs were identified in 2.8% (65/2304), mean age was 73.0±5.3 years, 43.5% (27/65) were females. ABs were the leading causative agents in the elderly (40%), children (42.9%), and among fatal cases (50.0%). (4) Conclusions: Our study revealed relatively high proportion of anaphylaxis among SRs of drug-induced allergy. ABs were the most prevalent causative agents predominated especially in fatal SRsAs.

Keywords: drug-induced allergy; anaphylaxis; antibiotics; local anesthetics; cyclooxygenase (COX)-inhibitors

1. Introduction

Prevalence of severe allergic reactions, including anaphylaxis, is increasing worldwide with the most frequent elicitor groups including food, insect venom, and drugs [1-4]. Drug allergy may affect up to one third of patients in emergency departments [5]. The prevalence of self-reported drug allergy was estimated in a systematic review and meta-analysis of 53 studies (n - 26,306), which results revealed the value of 8.3% (range across studies 0.7-38.5%) [6]. Anaphylaxis is one of most severe forms of allergy, representing acute, potentially fatal reaction. A cross-sectional study based on a screening of medical records (from January 2015 to August 2017) identified the prevalence of anaphylaxis among emergency department admissions at the level of 0.00026%, and the pediatric population (age 1–16 years) was the most affected (60.9%). Anaphylaxis was triggered by drugs in 17.4% [7]. A retrospective 10-year study of practice in a tertiary hospital revealed drugs to be the most common cause of anaphylaxis in an emergency department (33%) [8]. Analysis of electronic health records from a large United States healthcare system described epidemiology of drug-induced

hypersensitivity reactions (HSRs): they were reported in 13.8% (377,474 out of 2.7 million patients), of which 53.1% were immediate type reactions, and 46.9% - delayed [9].

Anaphylactic reactions are among the most dangerous immediate type HSRs, and Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered as the most severe delayed-type HSRs [10]. Dhopeshwarkar N et al (2019) performed electronic health records analysis and revealed that 1.1% of patients report drug-induced anaphylaxis, and ABs, nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates were the main causative pharmacological groups [11]. Retrospective analysis based on the National Adverse Drug Reaction Monitoring System in China found the incidence of anaphylaxis to be 0.03%, and ABs, antineoplastic drugs, and contrast media were the most prevalent allergens [12]. ABs are also the most common triggers of delayed HSRs (SJS and TEN) [13, 14].

The aim of our study was to estimate proportion of SRsAs among SRsDIAs, proportion of pediatric SRsAs, elderly SRsAs, and fatal SRsAs among SRsAs, to detect the structure of drugs involved in anaphylaxis and to assess patients' characteristics (sex, age) using Russian National Pharmacovigilance database - Automatized Information System "Pharmacovigilance" (AIS).

2. Results

2.1. Analysis of SRsAs

A total of 27,727 SRsDIAs were detected in the electronic database during the study period (02.04.2019 - 21.06.2023). Of these, SRsAs accounted for 8.3% (n – 2304). Mean age of patients (SRsAs) was 48.2 ± 15.8 years (min - 1 day, max - 89 years), 53.2% (n - 1226) were females.

Analysis of outcomes among SRsAs revealed recovery in 90.54% (n - 2086), and death in 9.46% (n - 218).

SRsAs assessment revealed seven main pharmacological groups involved in anaphylaxis: ABs (44.6%, n - 1028), local anesthetics, LAs (20%, n - 460), COX-inhibitors (10.0%, n - 232), iodine-containing contrast medium, ICCM (6.6%, n - 153), cardiovascular (CV) drugs (6.2%, n - 143), central nervous system (CNS)-active drugs (1.5%, n - 35), and neuromuscular blocking agents, NMBAs (1.4%, n - 33). Other drugs accounted for 9.5% (n - 220).

2.1.1. Analysis of ABs Involved in Anaphylaxis

The mean age of patients with anaphylaxis due to ABs was 55.0±14.9 years (min – 1 day, max – 89 years), females were – 63.8% (n - 655). The number of SRsAs where ABs were causative agents was 1028 (46.7%), and beta-lactam antibiotics were the most prevalent group (87.74%, n - 902). Ceftriaxone was the most common among all ABs (63.3%, n - 687). The structure of ABs involved in anaphylaxis is shown in the Table 1. Lethal outcomes were reported in 109 cases of SRsAs caused by ABs (10.6%).

Table 1. The Structure of ABs involved in anaphylaxis.

ABs	N (Total - 1028)	%
Beta-lactams	*902*	*87.7*
Ceftriaxone	687	66.8
Cefotaxime	87	8.5
Cefazolin	39	3.8
Ampicillin sulbactam	17	1.7
Cefepime	15	1.5
Cefuroxime	10	1.0
Meropenem	10	1.0
Amoxicillin clavulanate	8	0.8
Cefoperazone sulbactam	7	0.7
Ertapenem	5	0.5

Cefoperazone	4	0.4
Ampicillin	4	0.4
Cefepime sulbactam	3	0.3
Amoxicillin sulbactam	2	0.2
Piperacillin tazobactam	2	0.2
Cephalexin	1	0.1
Cefixime	1	0.1
Other	*126*	*12.3*
Vancomycin	28	2.7
Ciprofloxacin	22	2.1
Levofloxacin	18	1.8
Metronidazole	14	1.4
Linezolid	7	0.7
Amikacin	7	0.7
Nitrofurantoin	7	0.7
Fosfomycin	5	0.5
Sulfamethoxazole trimethoprim	3	0.3
Tigecycline	3	0.3
Polymyxin B	2	0.2
Kanamycin	2	0.2
Amphotericin B	2	0.2
Gentamicin	1	0.1
Ofloxacin	1	0.1
Erythromycin	1	0.1
Clindamycin	1	0.1
Rifampicin	1	0.1
Isoniazid	1	0.1

2.1.2. Analysis of LAs Involved in Anaphylaxis

LAs were identified as a main cause of anaphylaxis in 20% of SRsAs (n - 460). The mean age of patients with anaphylaxis due to LAs was 44.3±14.9 years (min – 5 months, max – 84 years). Females were 53.7% (n - 247). The absolute leader was lidocaine (63.7%, n - 293). The structure of LAs is indicated in the Table 2.

Table 2. The Structure of LAs involved in anaphylaxis.

LAs	N (Total - 460)	%
Lidocaine	293	63.7
Procaine	68	14.8
Articaine	61	13.3
Ropivacaine	16	3.5
Bupivacaine	14	3.0
Mepivacaine	8	1.7

Among SRsAs caused by LAs lethal outcome was reported in 29 cases (6.3%).

2.1.3. Analysis of COX-Inhibitors Involved in Anaphylaxis.

The mean age of patients listed in SRsAs with COX-inhibitors as a main cause was 44.9±14.5 (min – 10, max – 81) years, and 62.1% (n - 144) were females.

The number of SRsAs with causative agents COX-inhibitors was 232 accounting for 10.07% of SRsAs. Among COX-inhibitors we did consider NSAIDs, acetaminophen, and metamizole. Acetaminophen inhibits COX in the brain structures with analgesic and antipyretic effects [15].

Acetaminophen was the cause of SRsAs in the vast majority of cases – 49 (21.1%). Nearly the same value was revealed for metamizole, another COX inhibitor without anti-inflammatory activity but with potent analgesic action [16]. It was detected in 48 cases (20.69%). Detailed information about COX-inhibitors involved in anaphylaxis is presented in the Table 3.

Table 3. The Structure of COX-inhibitors involved in anaphylaxis.

COX-inhibitors	N (Total - 232)	%
Acetaminophen	49	21.1
Metamizole	48	20.7
Ibuprofen	35	15.1
Diclofenac	29	12.5
Ketorolac	26	11.2
Acetylsalicylic acid	25	10.8
Ketoprofen	6	3.0
Celecoxib	5	2.2
Aceclofenac	3	1.3
Meloxicam	3	1.3
Lornoxicam	2	0.9
Nimesulide	1	0.4

Among SRsAs where COX-inhibitors were causative drugs lethal outcome was reported in 4 cases (1.72%).

2.1.4. Analysis of ICCM Involved in Anaphylaxis.

ICCM were causative agents in 6.6% of SRsAs (n - 153). The mean age of patients was 55.4±12.0 years (min – 8.5 months, max – 86 years), 47.1% (n - 72) were females. The structure of ICCM involved is presented in the Table 4. Lethal outcome was reported in 8 cases (5.2%).

Table 4. The Structure of ICCM involved in anaphylaxis.

ICCM	N (Total - 153)	%
Iopromide	97	63.4
Iohexol	39	25.5
Iomeprol	13	8.5
Iodixanol	2	1.3
Ioversol	1	0.7
Iopamidol	1	0.7

Lethal outcome was reported in 8 cases (5.2%).

2.1.5. Analysis of CV Drugs Involved in Anaphylaxis

SRsAs with CV drugs being causative agents accounted for 6.2% (n - 143) of SRsAs. The mean age of patients was 57.7±16.2 (min –19, max - 86), females were 76,9% (n-110). The highest frequency was reported for angiotensin-converting enzyme inhibitors, ACEIs (20.3%, n - 29), followed by beta-blockers (15.4%, n - 22) and calcium channel blockers (14.7%, n - 21). Table 5 contains data on the structure of CV drugs involved in anaphylaxis.

Table 5. The Structure of CV Drugs involved in Anaphylaxis.

CV drug	N (Total – 143)	%
ACEIs	*29*	*20.3*
Enalapril	17	11.9

Captopril	11	7.8
Perindopril	1	0.7
Beta-blockers	*22*	*15.4*
Bisoprolol	13	9.1
Metoprolol	5	3.5
Atenolol	3	2.1
Propranolol	1	0.7
Calcium Channel Blockers	*21*	*14.7*
Nifedipine	9	6.3
Amlodipine	8	5.6
Verapamil	4	2.8
Potassium-magnesium-asparaginate	*19*	*13.3*
Antiarrhythmics	12	8.4
Amiodarone	10	7.0
Digoxin	1	0.7
Propafenone	1	0.7
Diuretics	*11*	*7.7*
Furosemide	7	4.9
Spironolactone	3	2.1
Hydrochlorothiazide	1	0.7
Sartans (Losartan)	*8*	*5.6*
Statins	*6*	*4.2*
Rosuvastatin	4	2.8
Atorvastatin	2	1.4
Alpha-2 adrenergic receptor agonist (Clonidine)	*4*	*2.8*
Indirect oral anticoagulant (Warfarin)	*4*	*2.8*
Direct oral anticoagulants	*2*	*1.4*
Rivaroxaban	1	0.7
Apixaban	1	0.7
Unfractionated heparin	*2*	*1.4*
Antiplatelet drugs	*2*	*1.4*
Clopidogrel	1	0.7
Ticagrelor	1	0.7
Thrombolytic agent (Alteplase)	*1*	*0.7*

Among SRsAs due to CV drugs lethal outcome was detected in 13 cases (9.1%).

2.1.6. Analysis of CNS-Active Drugs Involved in Anaphylaxis

SRsAs analysis revealed CNS-active drugs being causative agents in 35 (1.5%). The mean age of patients was 54.6±17.8 years (min –23, max - 82). The structure of drugs involved in anaphylaxis is indicated in the Table 6. Among the CNS-active drugs the highest prevalence was reported for synthetic opioid, fentanyl (57.1%, n - 20).

Table 6. The Structure of CNS-active Drugs involved in Anaphylaxis.

CNS-active drugs	N (Total - 35)	%
Fentanyl	20	57.1
Diazepam	4	11.4
Tramadol	4	11.4
Midazolam	3	8.6
Venlafaxine	1	2.9
Droperidol	1	2.9
Carbamazepine	1	2.9

Levetiracetam	1	2.9

Lethal outcome was reported in 5 cases (14.3%).

2.1.7. Analysis of NMBAs Involved in Anaphylaxis

NMBAs were detected as causative drugs in 1.2% of SRsAs (n – 28). The mean age of patients was 47.4 ± 14.3 years (min –22, max - 71). The highest prevalence was reported for rocuronium (n - 10) – 30.3%. NMBAs involved in anaphylaxis are presented in the Table 7.

Table 7. The Structure of NMBAs involved in Anaphylaxis.

NMBAs	N (Total - 28)	%
Rocuronium	10	35.7
Atracurium	8	28.6
Suxamethonium	5	17.9
Cisatracurium	5	17.9

Lethal outcome was detected in 28.6% (n-8) cases.

2.2. Analysis of Fatal SRsAs

The total number of fatal SRsAs was 218 (9.5%). Reports analysis revealed 56.2% were women, mean age was 48.0 ± 16.7 (min - 1 month, max - 86 years). Two cases of death were observed in pregnant women (1.4%), 17 cases in children (11.5%), and 65 (29.8%) – in the elderly. The leading causative groups were ABs (50%, n - 109), LAs (13.3%, n - 29), and CV drugs (6.0%, n - 13). The total structure of drugs detected in fatal SRsAs is shown in the Table 8.

Table 8. The Structure of Drugs involved in Fatal SRsAs.

Drug	N (Total - 218)	%
ABs	*109*	*50.00*
Ceftriaxone	68	31.2
Cefotaxime	13	6.0
Fosfomycin	5	2.3
Amoxicillin clavulanate	3	1.4
Levofloxacin	3	1.4
Ciprofloxacin	3	1.4
Cefazolin	3	1.4
Ampicillin sulbactam	2	0.9
Ertapenem	2	0.9
Amphotericin B	1	0.5
Meropenem	1	0.5
Tigecycline	1	0.5
Sulfamethoxazole trimethoprim	1	0.5
Vancomycin	1	0.5
Metronidazole	1	0.5
LAs	*29*	*13.3*
Lidocaine	19	8.7
Bupivacaine	7	3.2
Articaine	1	0.5
Procaine	1	0.5
Ropivacaine	1	0.5
CV drugs	*13*	*6.0*
Beta blockers	3	1.4

Bisoprolol	2	0.9
Metoprolol	1	0.5
ACEi (Enalapril)	3	1.4
Sartans (Losartan)	1	0.5
Calcium Channel Blockers (Amlodipine)	2	0.9
Antiarrhythmics (Amiodorone)	1	0.5
Statins (Rosuvastatin)	1	0.5
Antiplatelet drugs (Ticagrelor)	1	0.5
Alpha-2 adrenergic receptor agonist (Clonidine)	1	0.5
NMBAs	*8*	*3.7*
Rocuronium	4	1.8
Suxamethonium	2	0.9
Atracurium	1	0.5
Cisatracurium	1	0.5
ICCM	*8*	*3.7*
Iopromide	4	1.8
Iohexol	3	1.4
Iomeprol	1	0.5
CNS-active drugs	*5*	*2.3*
Fentanyl	2	0.9
Diazepam	1	0.5
Levetiracetam	1	0.5
Midazolam	1	0.5
COX-inhibitors	*4*	*1.8*
Diclofenac	2	0.9
Ibuprofen	1	0.5
Acetylsalicylic acid	1	0.5
Other drugs	*42*	*19.3*

The mean age of patients in fatal SRsAs depending on causative group of drugs is listed in the Table 9 together with sex distribution (%). The youngest age was reported in fatal SRsAs where LAs were causative drugs, the oldest – where CV drugs were the cause. Females predominated in all groups except fatal SRsAs with CV drugs, where 69.2% (n - 9) were males.
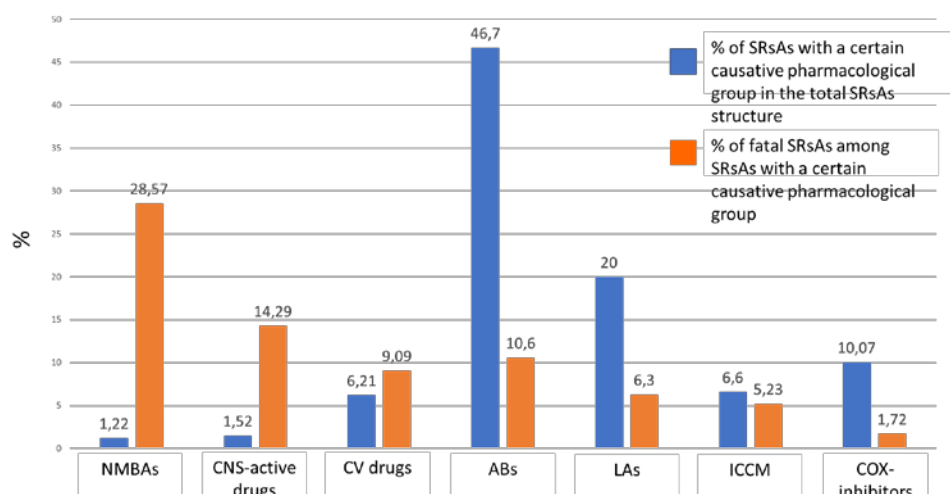
Table 9. Data on Age and Sex of Patients in Fatal SRsAs.

Causative Group of Drugs	Age		Females
	Mean (SD)	Min; Max	% (N)
ABs	48.2 (16.1)	15 months; 85 years	53.8 (50)
LAs	39.4 (14.4)	5 months; 68 years	55.1 (16)
CV drugs	62.6 (10.6)	48 years; 86 years	30.8 (4)
ICCM	74.0 (8.2)	65 years; 86 years	62.5 (5)
NMBAs	37.0 (12.7)	22 years; 61 years	75.0 (6)
COX-inhibitors	50.7 (0.4)	50 years; 51 years	75.0 (3)
CNS-active drugs	45.6 (7.7)	32 years; 55 years	60.0 (3)
Other drugs	51.4 (15.2)	1 month; 80 years	57.8 (41)

SD – standard deviation.

The highest proportion of fatal SRsAs was revealed in SRsAs, where NMBAs and CNS-active drugs were causative agents notwithstanding the fact that SRsAs caused by these pharmacological groups accounted for only 1.2 and 1.5% in the total structure, respectively (Figure 1).

Figure 1. Prevalence (%) of fatal ARs among pharmacological groups compared with the structure of pharmacological groups involved in ARs.

2.3. Analysis of Pediatric SRsAs

Pediatric SRsAs (reports of patients ≤ 18 years) accounted for 5.8% (n - 133) of the total SRsAs structure. The mean age was 11.8± 4.5 years (min – 1 day, max – 18 years), females were 51.9% (n - 69). Outcome analysis revealed recovery in 87.2% (n - 116), and death in 12.8% (n - 17).

The most prevalent groups of drugs involved in anaphylaxis in children were ABs (42.9%, n - 57), LAs (12.8%, n - 17), and COX-inhibitors (6.0%, n - 8). Other drugs accounted for 38.3 (n - 51).

ABs were the leading causative pharmacological group in children and the absolute majority of reactions (87.7%) were due to ABs (Table 6). The mean age of children with anaphylaxis due to ABs was 16.0 ± 12.6 years (min – 1 day, max -18 years), females were 51.2% (n-29).   The structure of ABs involved in anaphylaxis in children is given in the Table 10.

Table 10. The Structure of ABs involved in Anaphylaxis in Children.

ABs	N (Total - 57)	%
Beta-lactams	*50*	*87.7*
Ceftriaxone	29	50.9
Cefotaxime	7	12.3
Cefazolin	5	8.8
Ampicillin sulbactam	4	7.0
Cefepime	2	3.5
Cefoperazone sulbactam	1	1.8
Meropenem	1	1.8
Amoxicillin clavulanate	1	1.8
Other	*7*	*12.3*
Vancomycin	4	7.0
Metronidazole	2	3.5
Linezolid	1	1.8

Lethal outcome due to ABs was reported in 8 cases (14.0%, 8/57), mean age was 7.4± 5.4 (min – 15 months, max – 16 years), males were 85.7% (n - 6). Ceftriaxone was detected in 7 cases, amoxicillin clavulanate – in 1.

Among LAs the leading agent was lidocaine, responsible for 52.9% of cases (Table 11). The mean age of children in SRsAs with LAs was 9.9±4.6 (min – 5 months, max – 17 years), males were 64.7% (n - 11). Fatal SRsAs included only lidocaine (3/17, 17.6%), mean age was 10.0±3.3 (min - 5, max -13) years, males were 66.7% (n - 2).

Table 11. The Structure of LAs involved in Anaphylaxis in Children.

LAs	N (Total - 17)	%
Lidocaine	9	52.9
Articaine	6	35.3
Mepivacaine	2	11.8

There were only 8 SRsAs with COX-inhibitors in pediatric population (acetaminophen – 50% (n - 4), ketorolac – 25% (n - 2) and metamizole – 25% (n – 2)). The mean age was 15.0±2.0 (min - 10, max - 18) years, females were 62,5% (n-5). There were no lethal outcomes among SRsAs with COX-inhibitors as causative agents in children.

2.4. Analysis of SRsAs in the Elderly

SRsAs of patients ≥65 years accounted for 2.8% (n - 65). The mean age was 73.0±5.3 (min - 65, max - 89) years, females were 43.5% (n - 27). Outcomes analysis revealed recovery in 53.8% (n - 35), and death in 46.2% (n - 30).

The most common causative pharmacological groups were ABs (40%, n - 26), CV drugs (20%, n - 13), and ICCM (12.3%, n - 8). The structure of drugs involved in anaphylaxis in the elderly is demonstrated in the Table 12.

Table 12. The Structure of Drugs involved in SRsAs in the elderly.

Drug	N (Total - 65)	%
ABs	*26*	*40.0*
Ceftriaxone	23	35.4
Amoxicillin clavulanate	2	3.1
Cefixime	1	1.5
CV-drugs	*13*	*20.0*
Antiarrhythmic (Amiodarone)	3	4.6
Unfractionated heparin	2	3.1
Beta-blockers (Bisoprolol)	2	3.1
Calcium Channels Blockers	3	4.6
Amlodipine	2	3.1
Nifedipine	1	1.5
Diuretics	2	3.1
Furosemide	1	1.5
Hydrochlorothiazide	1	1.5
Thrombolytic agent (Alteplase)	1	1.5
ICCM	*8*	*12.3*
Iopromide	4	6.2
Iohexol	3	4.6
Iomeprol	1	1.5
COX-inhibitors	*5*	*7.7*
Diclofenac	3	4.6
Lornoxicam	1	1.5
Metamozole	1	1.5
NMBAs	*4*	*6.2*
Rocuronium	2	3.1
Atracurium	1	1.5
Cisatracurium	1	1.5
LAs	*2*	*3.1*
Bupivacaine	1	1.5

Procaine	1	1.5
Other drugs	*7*	*10.8*
Prednisolone	1	1.5
Iron formulations	2	3.1
Ethyl-methyl-hydroxypyridine succinate	1	1.5
Venlafaxine	1	1.5
Oxaliplatin	1	1.5
Pentoxifylline	1	1.5

Among the records with lethal outcomes in the elderly 53.3% (16/30) were reported in females. The majority of fatal SRsAs revealed ABs as causative agents (the only drug was ceftriaxone) – 31.4% (n - 16). ICCM were reported in 15.7% (n - 8), pentoxifylline - in 3.9% (n - 2), amiodarone - in 2.0% (n - 1), bupivacaine - in 2.0% (n - 1), and cisplatin - in 3.9% (n - 2).

3. Discussion

Our results revealed anaphylaxis in 8.3% of SRsDIAs registered in the AIS "Pharmacovigilance" database (2304/27,727) during the study period 02.04.2019 - 21.0 6.2023. Fatal SRsAs were reported in 9.5% (n - 218). There were close age and sex characteristics in the records of survived and died patients according to the SRsAs analysis (48.2 ± 15.8 years, females - 53.2% vs. 48.0 ± 16.7 years, females - 56.2%).

Based on the results of an 8-year post hoc analysis on the MEREAFaPS Study database (2012–2019) the mean age of population with anaphylaxis was 55.7 ± 17.7 years, and females were 52.4% [17]. The mean age of patients with drug-induced anaphylaxis in China was determined as 47.6 years (Beijing Pharmacovigilance Database analysis), and 52.7% were females [18]. Analysis of records with drug-induced anaphylaxis in Poland, West Pomerania, revealed the mean age of population to be 40.5 years, and 54.4% were females [19]. Female dominance in the structure of patients with drug-induced anaphylaxis (57.9%) was also proved by the results of an analysis of electronic health records (EHRs) of a large United States healthcare system [11] and by the results of a Tunisian retrospective study (males/female ratio was 0.6)), in the last study patients were younger than in most of other published works: the mean age was 33.52 years [20]. An analysis of drug-induced anaphylaxis in a Vietnamese Pharmacovigilance Database revealed 51.8% patients between 20 and 60 years old, 53.2% were female [21]. Korean Health Insurance Review and Assessment Service (HIRA) database analysis (period - January 2011to December 2019) indicated that the mean age of patients with drug-induced anaphylaxis was 52 years, 55.2% were female [22].

ABs are among the most common triggers of drug-induced anaphylaxis. Their leading role was proved both by retrospective and prospective studies [8, 24, 25]. Our results revealed ABs to be the main cause of anaphylaxis in all age groups (44.6% (n - 1028) in total SRsAs, 42.9% (n - 57) in pediatric SRsAs, and 40.0% (n – 26) in the elderly), and among fatal SRsAs (50% (n - 109)). According to our study the absolute leader among ABs causing anaphylaxis was ceftriaxone.

Zhao Y et al (2018) revealed ABs to be the main group in the structure of drugs involved in anaphylaxis (39.3%), followed by traditional Chinese medicines (11.9%), radiocontrast agents (11.9%), and antineoplastic agents (10.3%) [18]. Among all the drugs analyzed cephalosporins were leading agents, accounted for 34.5% [18].

Based on the FDA Adverse Event Reporting System (FAERS) analysis drug-induced anaphylaxis was reported in 0.27% of all adverse drug events (47,496/17,506,002), and causative drugs included ABs (14.87%)), monoclonal antibodies (13.06%), and COX-inhibitors (NSAIDs and acetaminophen – 8.83%). Anaphylaxis deaths were associated with ABs, radiocontrast agents and intraoperative agents, and the rate of fatal cases was 6.28% (2984/47,496) [23].

Pagani S et al (2022) defined the leading role of ABs in ARs development (53.78%), and penicillins were the most prevalent (66.67%) followed by cephalosporins (21.10%), and fluoroquinolones (8.56%) [17]. Penicillins were the cause of ARs in 50% according to the data of Wong A et al (2019), and sulfonamides and cephalosporines were other common causes [9].

Cephalosporins are proved to be common triggers of ARs in adults and children [26 - 29], and a 3rd generation agent including ceftriaxone were among main inducers of allergic reactions reported in hospitals of South Korea [30]. Analysis of the Korean Adverse Event Reporting System (KAERS) and HIRA database revealed incidence rates for hypersensitivity reactions including anaphylaxis to cefaclor, other 2nd generation cephalosporins, and 3rd generation cephalosporins to be 1.17/10,000 persons (0.38/10,000 persons), 3.57/10,000 persons (0.38/10,000 persons), and 5.82/10,000 persons (0.61/10,000 persons), respectively [31]. Another Korean study revealed five common medication risk factors for drug-induced anaphylaxis including cephalosporine cefaclor, ICCM (iopromide, iohexol, iomeprol), and tolperisone [22]. Cephalosporines were defined as the most common ABs causing ARs based on the results of China Hospital Pharmacovigilance System analysis [12]. Third generation cephalosporines were determined as the main cause of drug-induced anaphylaxis based on the results of a Vietnamese Pharmacovigilance Database [21].

LAs in our study were reported in 20.0% of SRsAs (n - 460). They were ranked second in the list of causative agents among total SRsAs, pediatric SRsAs, and among fatal SRsAs. LAs are typically considered to be anaphylaxis triggers prevalent in dentistry practice [32], though the risk of true IgE-mediated allergy was shown to be lower than 1% [33 - 37]. Amide local anesthetics are less involved in hypersensitivity reactions compared with ethers, and among amides lidocaine is known to be the most associated with severe allergic reactions. Other amides are safer in this respect, though published data demonstrated their ability to cause anaphylactic shock, that was shown for mepivacaine [38] and bupivacaine [39]. French Pharmacovigilance Database System analysis revealed a twentyfold growth of reports on anaphylactic reactions involving local anesthetics from 1985 to 2020 year, and lidocaine was reported to be the most common cause (81.49%) [40]. Leading role of lidocaine in severe HSRs and in anaphylaxis development in dental practice was stated in the work by Matveev AV et al (2020) [41]. Anesthetics (first, lidocaine, second – bupivacaine) were reported among top eight pharmacotherapeutic groups involved in anaphylaxis based on results of Vietnamese Pharmacovigilance Database analysis [21].

NSAIDs are a common cause of hypersensitivity [25] responsible for a significant proportion of anaphylaxis in clinical practice of tertiary care hospitals and emergency departments [8, 21, 24, 42]. Our data revealed COX-inhibitors (NSAIDs, acetaminophen and metamizole) to be the third causative group among total (10.1%, main drug - acetaminophen) and pediatric SRsAS (6.0%, main drug - acetaminophen), and the fourth - among elderly SRsAs (7.7%, main drug - diclofenac). Fatal SRsAs analysis revealed COX-inhibitors only in 1.8% (two cases - diclofenac, one case - ibuprofen). In the USA NSAIDs (ibuprofen and naproxen) were the second cause of anaphylactic reactions (13.0%) after ABs (61%) [11], while in Poland NSAIDs were the main causative pharmacological group (acetylsalicylic acid, ketoprofen, metamizole and ibuprofen) [19]. These results are supported by the FAERS database analysis (study period 1999 to 2019) by Yu RJ et al (2021), which revealed acetaminophen and NSAIDs (acetylsalicylic acid, celecoxib, diclofenac) among top 50 drugs causing anaphylaxis [23]. Based on the analysis of a Vietnamese Pharmacovigilance Database NSAIDs were found to be a second pharmacological group involved in drug-induced anaphylaxis [21]. Published data indicate that in children NSAIDs are a second significant pharmacological group causing anaphylaxis after ABs [43]. Our results revealed acetaminophen to be the leader among COX-inhibitor in total SRsAs and pediatric SRsAs., and no fatal cases involving acetaminophen were detected. EudraVigilance Database analysis (2007–2018) found that acetaminophen-induced anaphylaxis was most common at age group 18–64 years, and among acetaminophen-induced ARs anaphylaxis was the second cause of death after hepatic failure with shock [44]. A systematic review of 85 studies reporting hypersensitivity reactions to acetaminophen revealed that acetaminophen hypersensitivity reaction prevalence among children was 10.1% (95% confidence interval 4.5-15.5) [45]. A retrospective analysis of 159 validated spontaneous reports in children (database of German Federal Institute for Drugs and Medical Devices) revealed another COX-inhibitor, ibuprofen, to be the main drug responsible for anaphylaxis development [46].

According to our results ICCM were identified in 6.6% of SRsAs (n - 153), with the most common agents iopromide and iohexol. ICCM were on the third place among causative drugs in the elderly

SRsAs (12.3%). This group of agents is known to mediate severe hypersensitivity reactions which may lead to a lethal outcome [47, 48]. ICCM group was reported to be a leader among drugs involved in anaphylaxis due to the results of 13-year period analysis of Japanese Adverse Drug Event Report (JADER) database [49]. Based on the results of a 10-year study in China, total radiocontrast agents accounted for 11.9%, ICCM - for 9.5% [18]. Pagani S et al (2022) demonstrated association of anaphylaxis with radiology contrast agents in 6.92% [17]. Nguyen KD et al (2019) reported contrast media to be on the fourth place among all pharmacological groups caused drug-induced anaphylaxis [21]. FAERS database analysis reported iohexol, iopamidol and iopromide among top 50 drugs involved in anaphylaxis [23]. Published studies suggest that anaphylaxis due to radiocontrast medium is more common in older age and on repeated drug exposure [50].

Our study reported CV-drugs to be the fourth significant group involved in anaphylaxis in total SRsAs (6.2%, n - 143) with next most common groups: ACEIs (enalapril, captopril, perindopril), beta-blockers (bisoprolol, metoprolol, atenolol), and calcium channel blockers (nifedipine, amlodipine, verapamil). In the elderly CV-drugs were the second group caused anaphylaxis (20%, n - 13). ACEIs and beta-blockers are known causes of anaphylaxis in clinical practice [51]. A systematic review and meta-analysis of observational studies stated that beta-blockers and ACEIs increase the severity of anaphylaxis (beta-blockers, odds ratio [OR] 2.19, 95% confidence interval [CI] 1.25-3.84; ACEIs, OR 1.56, 95% CI 1.12-2.16) [52]. Anaphylaxis severity was shown to be increased with ACEIs intake along with presence of such factors as mastocytosis, and high fever prior to anaphylaxis [53]. Published studies based on pharmacovigilance databases revealed less significance of CV-drugs in anaphylaxis compared with our results. FAERS analysis reported no CV-agents among top-50 drugs causing anaphylaxis [23]. Vietnamese Pharmacovigilance Database analysis revealed cardiac therapy agents on the 22nd place among drugs involved in anaphylaxis [21], a 10 year retrospective analysis of the Beijing Pharmacovigilance Database reported cardiovascular medications accounted for 0.9% of drug-induced anaphylaxis [18].

The total number of SRsAs with causative agents being CNS-active drugs in our study was 35 (1.5%) with the leading role of fentanyl, diazepam, and tramadol. Published clinical studies revealed relatively low incidence of fentanyl-associated anaphylaxis [54, 55], mainly cases are reported [56 - 59]. Low frequency of anaphylaxis is also known for benzodiazepines [60], though diazepam is considered to be more common cause of allergy compared with midazolam [61]. Pagani S et al (2022) indicated a frequency of anaphylaxis due to tramadol equal to 0.32%, 2/608 [17], and literature analysis revealed only several cases of tramadol-induced anaphylaxis [62 - 64]. From the other hand, some studies based on pharmacovigilance database analysis revealed a significant role for several drugs affecting CNS. FAERS database analysis reported fentanyl, midazolam, propofol, and sufentanyl among top-50 drugs involved in anaphylaxis [23], Vietnamese Pharmacovigilance Database analysis indicated analgesic opioids and psychostimulants were on the 18th and 19th positions among groups involved in anaphylaxis [21].

NMBAs in our study accounted for 1.43% (n - 33), and the most prevalent were rocuronium and suxamethonium. NMBAs are the most frequent allergens responsible for acute hypersensitivity reactions during anaesthesia [65 - 67], and leading causative agents for perioperative anaphylaxis [68]. A French pharmacovigilance survey from 2000 to 2012 revealed suxamethonium and rocuronium to be the most common NMBAs causing ARs [69]. Atracurium, rocuronium, and succinylcholine were listed among top 50 drugs involved in anaphylaxis based on FAERS analysis [23].

According to fatal SRsAs analysis most of cases were due to ABs (and beta-lactams among ABs), which is in complete accordance with published data. Beta-lactam antibiotics, muscle relaxants, and injected radiocontrast medium were the main triggers of fatal drug anaphylaxis based on analysis made by Turner PJ et al (2017) [70] and the higher prevalence of ABs among drugs involved in total ARs and fatal ARs is also proved by the vast majority of reported studies in adults and children [11, 17, 18, 23, 43, 71, 72].

Published data indicate that drug-induced anaphylaxis is associated with more lethal cases than food-induced and venom-induced [73]. Actuality of the problem is supported by increasing number

of fatal cases reported in modern studies. A systematic review of 46 observational studies reported increased frequency of deaths due to drug-induced anaphylaxis during the study period (IRR per year, 1.02; 95% CI, 1.00-1.04), and the highest rates were detected for Australian region [74]. Jerschow E et al (2014) stated a significant increase in fatal drug-induced anaphylaxis over 12 years (from 0.27 (95% CI, 0.23-0.30) per million in 1999 to 2001 to 0.51 (95% CI, 0.47-0.56) per million in 2008 to 2010 (p< 0.001) [75]. Fatal SRsAs percentage reported in our study (9.5%) exceeds published values. FAERS database analysis revealed 6.28% (2,984/47,496) reports of anaphylaxis followed by death [23], Brazilian Hospital Information System – 5.8% [76], Beijing Pharmacovigilance Database – 3.3% (39/1,189) [18], Vietnamese Pharmacovigilance Database analysis - about 2.3% (111/4,873) [21]. The rate of fatal drug-induced anaphylaxis in Spain was 1.02% [77], and   Latin American anaphylaxis registry revealed that only 0.3% of cases were fatal [78].

Our study has some limitations. First, retrospective design of the study based on the analysis of SRsAs entered in the AIS "Pharmacovigilance" made it impossible to evaluate the effect of concomitant medications and comorbidities, laboratory tests performed, and to estimate risks of anaphylaxis in different populations.

It is worth to note, that the number of SRsAs reported in our study was based on the analysis of spontaneous reporting records and thus cannot completely reflect the prevalence of anaphylaxis in a real clinical practice. Reported proportions of drugs involved in anaphylaxis described in our study may be determined not by their true safety profile, but by a frequency of their prescribing. E.g.: an absolute leader determined in our study was ceftriaxone, and it is one of the most prescribed drugs to treat various infectious diseases worldwide, ranging from 2.5% of therapeutic prescriptions in Northern Europe to 24.8% in Eastern Europe; also it is the most prescribed AB for a surgical prophylaxis (34.4% of ABs prescriptions in Eastern Europe, 24.8% in Southern Europe,   23.6% in West and Central Asia, and 19.7% in Northern Africa) [79]. A promising approach to assess real world prevalence of ARs due to a drug may be based on a parallel assessment of a drug consumption rates.

4. Materials and Methods

4.1. Data Source

Federal Service for Surveillance in Healthcare (Roszdravnadzor) is responsible for drug safety and effectiveness monitoring in the Russian Federation. Spontaneous/voluntary adverse reaction (AR) reporting is regulated by legislation in the Russian Federation. All reports are directed to the AIS "Pharmacovigilance" database which is a national pharmacovigilance database. It was established in 2008 and its structure, functioning and management comply with ICH E2B (R3) standard [80]. AIS "Pharmacovigilance" uses MedDRA version 25.0 as a reference tool [81]. Drugs are identified by brand name and international nonproprietary names (INN), which are both selected automatically by reporters when they fill out the official reporting form. Drug categories are determined in accordance with ATC classification. Causality assessment is made in AIS "Pharmacovigilance" by built-in WHO algorithm and Naranjo algorithm. Signal detection is performed using built-in quantitative statistical methods (proportional reporting ratio, PRR; reporting odds ratio, ROR; reduced rank regression, RRR). AIS "Pharmacovigilance" receives ARs reports on all drugs registered and approved for use in the Russian Federation, and cases occurred abroad. SRs may come from medical professionals, pharmaceutical companies, patients, and their representatives. In June 2023 the total number of individual case safety reports in AIS was >2 100 000 and no cases of reports made by patients, or their representatives were presented. Most of reports were generated by healthcare workers (mainly from hospitals).

4.2. Definitions

For this study, we used the following definitions [82]:
1.   "Adverse reaction - a response to a medicinal product, which is noxious and unintended. Adverse reaction may arise from use of the product within or outside the terms of the marketing
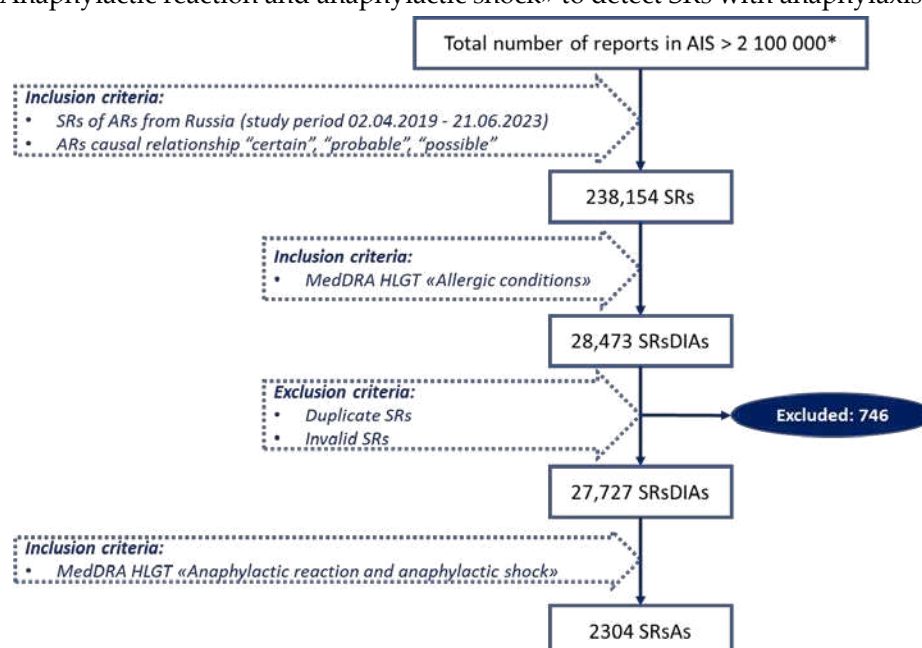
authorization or from occupational exposure. Use outside the marketing authorization includes off-label use, overdose, misuse, abuse and medication errors".

2. "Causality: In accordance with ICH-E2A, the definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected. For regulatory reporting purposes, as detailed in ICH-E2D, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse reaction. Therefore all spontaneous reports notified by healthcare professionals or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the reporters specifically state that they believe the events to be unrelated or that a causal relationship can be excluded".

3. "A spontaneous report is an unsolicited communication by a healthcare professional, or consumer to a competent authority, marketing authorisation holder or other organisation (e.g. regional pharmacovigilance centre, poison control centre) that describes one or more suspected adverse reactions in a patient who was given one or more medicinal products. It does not derive from a study or any organised data collection systems".

4.3. Study Design and Data Selection

Study design: a retrospective, descriptive study of SRs accumulated in AIS "Pharmacovigilance" database. Study period: 02.04.2019 - 21.06.2023.

Data selection was made using several steps described at Figure 2. First, from the total number of reports in AIS "Pharmacovigilance" SRs from the Russian Federation only were extracted with obligative inclusion criterion - high probability of a causal relationship ("certain", "probable", "possible"). Probability assessment was performed automatically in AIS "Pharmacovigilance" using built-in Naranjo algorithm. Second, using MedDRA high level group term (HLGT) «Allergic conditions» we defined the total number of SRs describing drug-induced allergy (SRsDIAs). Then we excluded duplicate and invalid reports getting exact number of SRsDIAs occurred in the Russian Federation. Validity was determined according to paragraph VI.B.2 of the EMA "Guideline on good pharmacovigilance practices" and paragraph 407 of the Eurasian Economic Union "Good pharmacovigilance practice", which state that information in a SR must contain at least 4 elements: identifiable reporter; identifiable patient; at least one suspected drug; at least one suspected ADR. If any of these 4 elements is absent, the report is considered invalid [82, 83]. Next step we used MedDRA HLGT – «Anaphylactic reaction and anaphylactic shock» to detect SRs with anaphylaxis (SRsAs).

Figure 2. Flowchart of SRsAs selection from AIS "Pharmacovigilance".

4.4. Drug Identification and Analyzed Categories

For this study, we used INN of suspected drugs, groups were distinguished according to the ATC classification. Drug identification did not distinguish between dosage forms or routes of administration.

Patient demographic information and data on causative drugs were extracted from the sample including SRsAs. All identified SRsAs were first analyzed. Then two age categories were defined: elderly (SRsA describing patients ≥65 years) and pediatric (SRsAs describing patients ≤18 years). The reported age was described in days, weeks, and years. Also, fatal SRsAs were estimated (SRsAs with a lethal outcome due to anaphylaxis).

4.5. Statistical Analysis

Descriptive statistics was used for all analyzed parameters; qualitative variables were described using absolute (n) and relative (%) values. All statistical analyses were performed using Microsoft Excel 2019. The percentage of SRsAs among SRsDIAs was estimated, mean age and sex differences were analyzed, the structure of causative drugs was detected.

5. Conclusions

SRs analysis performed in our work revealed anaphylaxis accounting for 8.3% of all drug-induced allergic reactions. In the structure of drugs involved leaders were ABs, LAs, ICCM, COX-inhibitors, CV drugs and CNS-active drugs. The number of pediatric SRsAs was almost twice as high as the number of SRsAs in the elderly (5.8% vs. 2.8%). Our results proved a higher prevalence of females with drug-induced anaphylaxis in all analyzed categories of SRsAs except the elderly (43.5%). Fatal SRsAs were reported in 9.5%, they were mainly caused by ABs, LAs, and CV-drugs. The highest percentage of deaths was observed in the elderly (46.2% (n - 30)), while in children it was 3.6 times less (12.78% (n – 17)). National pharmacovigilance databases and EHRs are important tools to assess the structure of drugs involved in various ARs including HSRs and to get information on demographic characteristics of patients [84], though a higher objectivity level of results may be obtained taking into account data on the actual drug consumption in real clinical practice.

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