



WHAT CAN WE EXPECT FROM DRUG-INDUCED ALLERGY IN AN EMERGENCY DEPARTMENT?

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Abstract: Anaphylaxis is reported as a life-threatening clinical emergency, rising in incidence over the last years in relation to drug intake and it is characterized as being a systemic/generalized hypersensitivity reaction. Diagnosis can be overlooked by emergency physicians because anaphylaxis tends to vary in presenting forms and often might be under or wrongly diagnosed. In order to diagnose and treat it as an emergency condition, it is not necessary to find an agent as a cause nor to establish a clear mechanism but it becomes mandatory for further attitudes. We reviewed drug related allergic reactions admitted to the Emergency Room Department of Târgu-Mureș during 2019, creating an organized view around the incidence and underlying the foremost findings. From our search criteria, we thoroughly reviewed each chart, and noticed that the drugs most commonly involved in these reactions were antibiotics, non-steroidal anti-inflammatory and over the counter, the myorelaxant drugs.

INTRODUCTION

The incidence of allergic reaction presentation to an Emergency Department is rising, with various aetiologies, often identifying the cause being a challenge for the first responders and physicians, and due to non-specific, non-consistent sets of signs and symptoms. One of the first steps in the management of allergic reactions is to remove the allergen, if applicable. Epidemiological studies and data on allergic presentations specifically aimed at medical drug use are scarce. Drug hypersensitivity comprises an immune response to a substance (drug) following previous exposure to the same substance/drug or to an immunochemically related substance. In lack of previous exposure to the culprit substance, allergic reactions hardly develop before approximately 7 days of continuous use of treatment. Clinical manifestations of drug allergy include urticaria, angioedema, and/or systemic involvement, collapse, shock, death.(1) Anaphylaxis is defined as a life-threatening clinical emergency, increasing in incidence over the last years and it is characterized as being a systemic/generalized hypersensitivity reaction. Drug-induced anaphylaxis is more common throughout the adult population.(2) Either kind of mechanism (from all studied I-IV types, direct complement activation, direct histamine release, undetermined immunological pathways) can be implicated in drug allergic reactions, even a combination of these has been described.(3) As a paraclinical investigation, serum tryptase can be helpful, taking into consideration that values are often elevated when drug-induced, contrasting values from food-induced anaphylaxis.(2) Diagnosis can be overlooked by emergency physicians because anaphylaxis tends to vary in presenting forms.(4) In order to diagnose and treat it as an emergency condition, it is not necessary to find an agent as a cause nor to establish a clear mechanism but it becomes mandatory for

further attitudes. World Health Organization (WHO) defined as an adverse drug reaction (ADRs) every undesired, unintended, noxious type of effect due to a drug occurring at doses that are prescribed for the sole treatment, prevention, or diagnosis.(5) These types of ARDs are sub-classified into type A-predictable and type B-unpredictable reactions. Drug-related allergic reactions are included in type B reactions that are not determined by dosage intake, are independent of the drug's pharmacologic actions, often related to the patient's immunologic responsiveness.

AIM

This study aimed to investigate and consider the most frequent drug-related allergic reactions presenting to our Emergency Room, to raise awareness and facilitate with great accuracy the right diagnosis and anamnesis key points when possible. Thus, further investigations and recommendations may be conducted.

MATERIALS AND METHODS

This is a retrospective chart review study, carried out in the Emergency Department (ER) of the County Emergency Hospital of Târgu-Mureș for a period of one year (January-December 2019). The ER had a total of more than 83000 admissions for the year mentioned, directly serving a population of approximately 135000 people and a county of 535000 inhabitants. Being a university hospital, the ER is staffed 24/7 by emergency physicians and residents. For our retrospective study, we selected adult patients (excluding patients under the age of 17) with severe allergic reactions and anaphylaxis, focusing on drug-related reactions (clear or suspected), excluding causes of alimentary and insect reactions. The selection was made using the International Classification of

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Diseases (ICD-10, and more specifically L50.0, R21, R60, R57, T78.2, T78.3, T78.4), cross-referencing them with our inclusion criteria. After this selection was made, we single-handedly studied each admission chart, including the ambulance service's notes. For statistical calculations, Statistical Package for Social Sciences (SPSS, version 22, Chicago, IL, USA) was used. Data were considered as nominal or quantitative variables. Nominal variables were described as absolutes and relative frequencies (%) and the association between them was analysed by Pearson's Chi-square test or Fisher's Exact Test. We interpreted all tests against a $p=0.05$ significance threshold and statistical significance was considered for p -values below the significance threshold

RESULTS

Demographic data

We reviewed 99 charts of patients presenting to the ER with acute allergic reactions clear or suspected involving drugs. The mean age was 50.6 years, ranging from 17 up to 87 years old, with a standard deviation of 17.9. Females were comprising 55.6% of the group while males represented 44.4%. More than half of patients (59.6%) were coming from urban areas, while the rest resided in rural zones. The percentage of patients that had a positive history of any allergic event was 20.2%.

Involved causative agents

During the gathering of our data, we found that in 90.9% of cases, a probable causative agent was identified by the on-call ER physicians based on the premise that other allergic causes were ruled out. The list of causative agents can be found in table no. 1, with a leading top three blamed agents such as antibiotics 23.2% (comprising of 78.2% beta-lactam antibiotics, 8.69% macrolide antibiotics, both 4.34% for imidazole derivat and fluoroquinolones, as well as one instance of the unidentified class of antibiotic), non-steroidal anti-inflammatory drugs (NSAIDs) with 22.2% of cases (inclusion consisting of acetaminophen also), and on the third place regarding frequency 17.2% we found over the counter muscle relaxants (94.11% of cases tolperisone was ingested, and chlorzoxazone for the remaining percentage). In one instance, proton pump inhibitors were associated with tolperisone ingestion. Overall, proton pump inhibitors (PPIs) were used by 8 patients out of 99, with the noticeable outcome as 50% of proton pump users developed angioedema versus 27.4% for those without PPIs.

Table no. 1. The percentage of causative agents

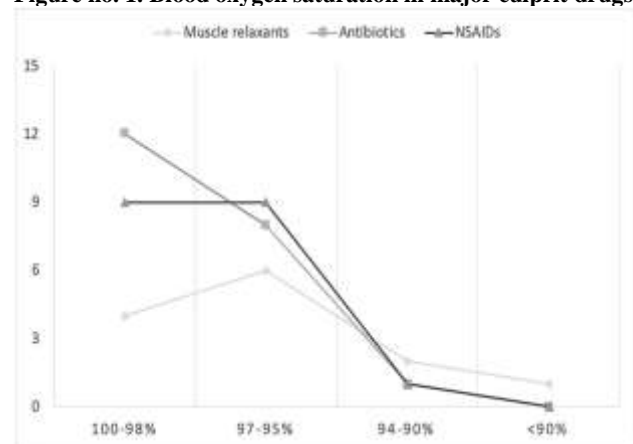
Causative agents	% of patients
Antibiotics	23,2
NSAIDs	22,2
Myorelaxants	17,2
Unidentified	9,1
Opioid cough medication	4
Plant based cough medication	3
Furazolidone	3
Metamizole	2
Topical steroids	2
Prolactin inhibitors	2
Opioids	2
Angiotensin II receptor blockers	2
Intravenous contrast dye	1
Antiemetics	1
Calcium blockers	1
Antifungal	1
Topical analgesics	1
Antispasmodics	1
Plant-based medicine/supplements	1

Clinical manifestations

Different clinical features were present upon admission to the ER Department, from simply generalized

rashes involving the skin and/or mucosa to imposing respiratory, cardiovascular and central nervous system symptoms (figure no. 2). Cutaneous manifestations were present in 70 patients comprising of urticaria, skin rashes, and/or erythema. The occurrence of pruritus was 76.8%, while respiratory complaints such as dyspnoea were reported in 34.3% of cases. Blood oxygen saturation (figure no. 1) was available for 89 patients and 28.08% had values under 97%, the lowest values being registered after intake of tolperisone or Hederæ Helicis Folium (ivy leaf cough medicine). The lowest blood pressure value was in relation to tolperisone use. Swallowing difficulties as described by patients were reported in 30 instances, and visible lingual edema was noted in 5 cases, while glottis edema in 1 case, and genital edema in 2 patients. Gastrointestinal manifestations were present in 1.01% of cases. Other clinical presentations such as hyperthermia, hypothermia, lipothymia, and dysphonia were below 2%.

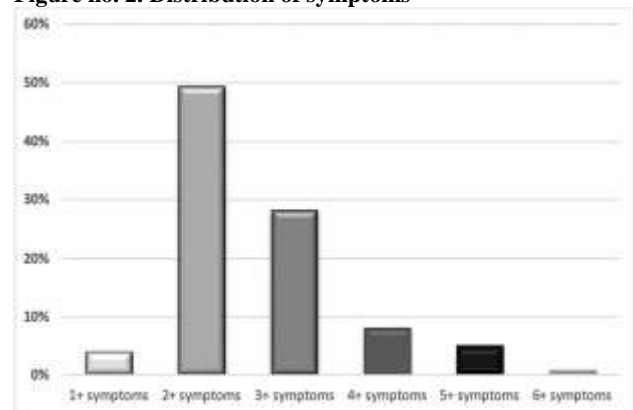
Figure no. 1. Blood oxygen saturation in major culprit drugs



Emergency Room management

Treatment was administered to all patients admitted to the ER, 82.8% receiving intravenous (i.v) hydrocortisone, 22.2% i.v methylprednisolone sodium succinate, 63.3% i.v histamine H_2 receptor antagonist (ranitidine), 62.6% oral selective inverse agonist of peripheral histamine H_1 receptor (loratadine). More than half of cases received i.v. saline solution (59.5%). Adrenaline was administered to 8 patients, and bronchodilator (either adrenaline, salbutamol, or fluticasone nebulization) therapy was used in 7% of cases. Ringer solution and calcium gluconate were used less than 5% of the times. No significantly statistical p -values were found in relation to the causal agent and course of treatment followed.

Figure no. 2. Distribution of symptoms



Patient outcomes

Twelve percent of cases were admitted for further

observation or to an intensive care unit. These patients were slightly older (age ranging from 45 to 82), 66% had one or more comorbidities, and one patient had a history of allergy but not in relation to the known causative agent of the current hospitalization. Leading drugs for admittance were muscle relaxants, antibiotics, and NSAIDs. For the remaining percentage of patients that were discharged from the ER after a few hours of monitoring a recommendation for an allergy, follow-up was given, and sometimes over the counter, antihistaminic pills were prescribed for the following days.

DISCUSSIONS

Probable causative agents could have been identified in almost all cases if ER patient history were to be taken more comprehensively. Due to overcrowding of the Emergency Room Departments, the immediate concern of physicians is to pinpoint the right diagnosis and administer a correct treatment, leaving further investigations to an allergology service.

Allergic reactions or anaphylaxis? To establish the diagnosis of anaphylaxis, neither the presence of cardiovascular collapse, shock, or cutaneous manifestations are required to meet these criteria. Anaphylaxis does not have to be caused by an identifiable agent or be mediated by a specific mechanism. The term “anaphylaxis” is favoured over some terms used in former times, for instance, “systemic allergic reaction,” “anaphylactoid reaction,” or “pseudoanaphylaxis.”(6) In the last years, different variations on the exact definition of anaphylaxis emerged, but in essence, they confirm all of the above.

In our emergency department service, serum tryptase investigation is rarely taken into consideration, on one hand, due to financial issues and on the other hand due to lack of knowledge and/or sub-staffing and overworked medical personnel. Serum tryptase among other investigations (urinary histamine metabolites/leukotriene E4) could be proven useful in diagnosing other disorders such as mast cell activation syndromes that present recurrent clinical manifestation of mast cell mediator release, involving from two or more organ systems (may present even as anaphylaxis), often having medication as a trigger.(7)

Very little data was available regarding patients' allergology follow-up, less than 10% of cases returning to our hospital for further investigations, or at the recommendation of other physicians due to their reluctance towards prescribing/administering further drugs, even those unrelated to the ER admission. Less severe cases of hypersensitivity to muscle relaxant drugs that seek medical attention in a later stage, such as a presentation to allergology service, confirm our findings.

Calcium gluconate solution has also been utilized to decrease capillary permeability in allergic reactions (8), but with scarce scientific evidence, usually being administered in our ER as a fall-back treatment.

In our country, although efforts are being made in this direction, patients still have easy access to all sorts of drugs without needing a physician's prescription, including antibiotics, NSAIDs, muscle relaxants. Thus, a continuous rise in the occurrence of allergic case presentations to the ER Department involving various medications and combinations of these seems to be plausible. Muscle relaxant hypersensitivity (especially to tolperisone) appears to be the most unforeseen frequent finding. Ranitidine was administered to a number of 63 patients. Research data shows that associating H₂ blockers to H₁ antihistamine treatment in acute allergic reactions enhances additional benefit (9) in patient outcome and resolution of the condition, especially those involving the skin. Even in PPIs hypersensitivity, H₂ receptor antagonists can be administered,

being considered an alternative, and very few reports exist of a risk of allergic reactions to H₂ receptor antagonists.(10)

CONCLUSIONS

The prevalence of allergic reactions for both counter and prescribed drugs is rising. According to our finding, there is a slight emphasis on the occurrence of these states involving the intake of muscle relaxants. Self-medication is considered a co-factor in these findings. In addition, patient history is often not thoroughly documented in the emergency room, thus being a challenge in identifying these cases in order to raise awareness.

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