Allergic reactions due to concomitant administration of multiple drugs in intravenous fluid in emergency departments in Turkey

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Abstract

The present study aimed to evaluate patients who were referred to adult allergy clinic due to allergic reactions after concomitant multiple intravenous-drug administrations in Emergency Department (ED). Between January 2017 and January 2019, patients admitted to our allergy clinic with hypersensitivity reactions to intravenous drugs administered in ED were included retrospectively. Fifty-seven patients who developed allergic reactions after intravenous drug administration in EDs were evaluated. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) were the most common cause of allergic reactions (n = 40, 70.2%). Skin Prick Tests (SPT) were positive in 6 (10.5%) patients. Drug Provocation Tests (DPT) were positive in 10 (17.5%) patients. No significant correlation was found between the total number of drugs in the intravenous fluid and the degree of allergic reaction (r = -0.145, p = 0.282). There was no statistically significant difference between the degree of allergic reaction and history of atopic disease (p = 0.579). In conclusion, concomitant administration of multiple drugs in intravenous fluids may increase the risk of allergic reactions.

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Introduction

The Emergency Department (ED) is the unit where first aid is applied to emergent patients.[1] Non-emergency patients also frequently apply to ED. Increases in the number of ED admissions impede the work flow of ED[2] and are increasing all over the world.[3-5] The increasing demand for ED is affected by the health-care systems of the countries, the socio-demographic characteristics of the societies, and the increasing health needs.[6,7] Because the recent regulations in the health-care system in Turkey, all patients presenting to ED must be admitted and examined even if their condition is not emergent. Due to these wrong health policies, patients who applied to the ED in Turkey have an expectation to have intravenous drug treatment even if they are treated orally. Therefore, drug administrations in intravenous fluids have increased in ED in Turkey and a recent study in Turkey showed that patients had a strong desire to receive intravenous treatment when admitted to the ED.[8]

The risk of drug allergy increases if the rate of consumption, frequency and amount of drug increase.[9] Subcutaneous or intravenous drug administrations increase risk of allergic reactions. Oral drug intake has been shown to be safer than parenteral administration. It has been shown that the risk of allergic reaction increases in cases of long-term high-dose drug administration and concomitant administration of multiple drugs.[9-11] Recently, a large number of patients who developed an allergic reaction due to concomitant administration of multiple drugs in intravenous fluid in ED applied to our allergy outpatient clinic.

The present study aimed to evaluate patients who were referred to adult allergy clinic due to allergic reactions after concomitant multiple intravenous-drug administrations in ED.

Materials and Methods

Study design

Between January 2017 and 2019, patients admitted with hypersensitivity reactions to intravenous drugs administered in ED were included retrospectively. The study protocol was approved by Ethics Committee (no: 2020/04-23). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Participant selection and data collection

Demographic data, comorbidities, medical treatments in ED, degree and treatment of allergic reactions, Skin Prick Tests (SPT), Intradermal Tests (IDT) and Drug Provocation Tests (DPT) results were obtained from the medical records of the patients. The definition and severity of Type 1 systemic hypersensitivity reactions following drug infusion were determined according to the modified classification of Rueff *et al.*[12] (Table 1).

Diagnosis of drug allergy

The diagnosis of drug allergy was based on history, physical examination findings, SPT, IDT and DPT. SPT and IDT were performed on the volar side of the forearm. Skin tests were evaluated 20 minutes after applying the culprit drug, with positive (histamine) and negative (saline) controls. Neither SPT nor IDT were performed on patients who had received antihistamines in the last seven days and who had had dermographism. In SPT, an induration diameter of 3 mm and over was accepted as positive. In IDT, an induration diameter of 3 mm or more was considered positive. DPT was performed in a single-blind manner by increasing the dose at intervals of 15-30 minutes. All DPTs were performed under the observation of an allergy specialist. DPT was not performed with culprit drugs if patients had a history of severe allergic reactions and/or anaphylaxis.

Statistical analysis

Statistical analysis was performed using SPSS 20 software (IBM). The distribution of numerical data was evaluated by Kolmogorov-Smirnov test. If numerical data were normally distributed, mean and standard deviation were used, if they were not normally distributed, the median (minimum-maximum) was used. Frequency distributions were used for categorical data. Spearman correlation analysis was used to calculate the direction and severity of the relationship between two categorical variables. Pearson chi-square test was used to evaluate the relationship between two categorical variables.

Results

Fifty-seven patients who developed allergic reactions after intravenous drug administration in EDs were evaluated. The mean age of the patients [13 (22.8%) male, 44 (77.2%) female] was 36.21±11.85 years. The most common comorbid disease was hypertension (10.5%). Thirty-seven (64.9%) patients had atopic disease. The most common comorbid atopic diseases were asthma (24.6%) and chronic urticaria and angioedema (24.6%). The most common cause of ED admissions was upper respiratory tract infection (56.1%). Nineteen (33%) patients had a family history of atopy and 8 (14%) patients had a family history of drug allergy. Demographic data and baseline characteristics of the patients are shown in Table 2. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) were the most common intravenously administered drugs in EDs and were the most common possible causes of allergic reactions (n = 40, 70.2%). Other common intravenously administered drugs were cephalosporins (n=13, 22.8%), vitamin B (n=11, 19.3%), ranitidine (n=11, 19.3%), metoclopramide (n=10, 17.6%), and vitamin C (n=8, 14%). In terms of the drugs that cause allergic reactions, the degree and treatments are shown in Table 3.

SPT and IDT were performed on 14 (24.6%) patients with at least one drug. SPT for these 14 patients were negative. IDT were positive in six (42.8%) patients. DPT with culprit drugs were performed on 10 (17.5%) patients and were positive in four (40%) of them. The results of the diagnostic tests are shown in Table 4.

The relationship between the total number of drugs in the intravenous fluid and the degree of allergic reaction was investigated, and no significant correlation was found between the two variables ($r = -0.145$, $p = 0.282$). The degree of allergic reaction was compared in patients with and without a history of atopic disease. There was no statistically significant difference between the two groups ($p = 0.579$).

Discussion

In the current study, in which we evaluated allergic reactions due to multiple drug infusions in serum in ED, the most frequently used drugs were NSAIDs, cephalosporins, vitamin B and ranitidine. Most of these patients could have been treated orally. A drug carries a higher risk of allergic reactions when administered intravenously than when it is administered orally; therefore, oral drug intake is safer than parenteral drug intake,[13] especially in patients with a history of atopic disease and/or drug allergy. In such instances, drugs should be given orally if there is no indication for intravenous treatment. The risk of allergic reaction increases as the consumption rate, frequency and amount of the drug increase. In addition, when more than one drug is administered in the same intravenous fluid, the risk of drug allergy increases, since the risk of cross-reaction may occur.[9]

Table 1. Classification of severity of Type 1 systemic hypersensitivity reactions.

Classification	Symptom
Grade I	Common skin symptoms (flushing, diffuse urticaria, angioedema)
Grade II	Moderate-severe respiratory, cardiovascular and/or gastrointestinal symptoms
Grade III	Anaphylactic shock, loss of consciousness
Grade IV	Cardiac arrest, apnea

In recent years, there has been an increase in ED admissions in Turkey due to an incorrect policy known as 'health transformation.' Most of these patients, who mainly had upper respiratory tract infections and/or myalgia, did not need emergency medical care and could have been treated in primary health-care centers.[14] A study in Turkey showed that the most commonly diagnosed disease in EDs is upper respiratory tract disease.[15] In our study population, the most common indication for intravenous treatment was also upper respiratory tract infection. NSAIDs were the most common intravenously administered drugs in EDs and were the most common causes of allergic reactions.

Multiple drug administration in intravenous fluid is also frequently observed in EDs in our country. The most important reason for this is the increase in the expectations of patients from physicians to administer multiple drugs in intravenous fluid in the ED. Most of these patients could be treated with orally available drugs. Frequent and high-doses administration of multiple drugs in intravenous fluids increase the possibility of allergic reactions.[13,16] The risk of cross-reactions increases when more than one drug is administered in the same intravenous fluid. In addition, as the molecular size of the drugs increases, their allergenicity increases. Due to the administration of more than one drug in the same intravenous fluid, drugs may bind to each other and haptenization of drugs may occur, which increases the allergenicity of drugs.[9-11,16,17] Cross-reactions between beta-lactam antibiotics (penicillins, amoxicillin, and cephalosporins) are frequently observed in the lit-

Table 2. Demographic data and baseline characteristics of patients.

Age (mean ± SD)	36.21±11.85
Distribution of age, years	n (%)
18-25	12 (21)
26-40	23 (40.4)
41-65	20 (35.1)
66 and older	2 (3.5)
Gender	
Male/Female	13 (22.8)/44 (77.2)
Atopic disease	37 (64.9)
Comorbiditiy	
Asthma	14 (24.6)
Chronic urticaria/angioedema	14 (24.6)
Drug allergy	14 (24.6)
Allergic rhinitis	11 (19.3)
Hypertension	6 (10.5)
Diabetes mellitus	4 (7)
Goiter	4 (7)
Bee allergy	4 (7)
Cardiovascular disease	2 (3.5)
Chronic obstructive pulmonary disease	2 (3.5)
Gastroesophageal reflux	1 (1.8)
Family history of atopic disease	19 (33.3)
Family history of drug allergy	8 (14)
Reason for admission to the emergency room	
Upper respiratory tract infection	32 (56.1)
Myalgia/back pain	10 (17.6)
Gastrointestinal symptoms (abdominal pain, diarrhea, nausea, vomiting)	8 (14)
Headache	6 (10.5)
Poisoning	1 (1.8)
Eozinofil count (/mm^3) (median)	183.3 (normal range: 0-500)
Total IgE (IU/mL) (mean ± SD)	223.87 ± 262.98 (normal range: 0-170)

Table 3. Culprit drugs for allergic reactions, degree and treatment of allergic reaction.

Total number of drugs in intravenous fluid	n (%)
1	
2	21 (36.8)
3	18 (31.6)
4	7 (12.3)
5	6 (10.5)
8	4 (7)
1	(1.8)
Drugs administered intravenously	
NSAIDs	40 (70.2)
Cephalosporins	13 (22.8)
Vitamin B	11 (19.3)
Ranitidine	11 (19.3)
Metoclopramide	10 (17.6)
Vitamin C	8 (14)
Hyoscine-N-butylbromide	8 (14)
Penicillin	6 (10.5)
Paracetamol	5 (8.8)
Thiocolchicoside	5 (8.8)
Proton pump inhibitor	2 (3.5)
Allergic reaction type	
Type 1	56 (98.2)
Type 4	1 (1.8)
The degree of Type 1 allergic reaction	
Grade 1	22 (38.6)
Grade 2	21 (36.8)
Grade 3	13 (22.8)
Treatment of allergic reaction	
Antihistamine	36 (63.2)
Systemic corticosteroid	32 (56.1)
Oxygen	15 (26.3)
Adrenalin	12 (22.1)
Beta 2 agonist	10 (17.6)
Hospitalization	4 (7)
Admission to intensive care unit	1 (1.8)

Table 4. IDT and DPT results.

	Result n (%)	Positive Drugs n (%)
IDT	Positive: 6 (42.8) Negative: 8 (57.2)	H2 receptor blocker (ranitidine): 3 (21.4) Proton pump inhibitor: 1 (7.1) Cephalosporins:1 (7.1) NSAIDs: 1 (7.1)
DPT with the culprit drug	Positive: 4 (40) Negative: 6 (60)	NSAIDs: 3 (30) Paracetamol: 1 (10)

erature.[18] In addition, cross-reactions between NSAIDs drug groups are frequently observed due to COX-1 (cyclooxygenase 1) inhibition.[17] In our study, 63.2% of patients who developed an allergic reaction after intravenous treatment had two or more drugs in the intravenous fluid administered to them. However, in our correlation analysis, we did not find any significant connection between the number of drugs in the fluid and the severity of the allergic reaction.

In the current study, an inappropriate medical practice that we observed in the ED is the administration of drugs which are not indicated in the treatment of the patient's disease. We observed that non-indicated treatments, such as vitamins B and C, were administered intravenously to patients in EDs for upper respiratory tract infections, myalgia, back pain, and headache. This inappropriate treatment can, and did, cause allergic reactions. 19.3% of patients who developed an allergic reaction after intravenous treatment in the ED were given vitamin B, and 14% of these patients were also given vitamin C in intravenous fluids.

Diagnostic tests should be performed to confirm the diagnosis of drug allergy.[18] *In vitro* tests and valid skin tests should be performed for diagnostic purposes. When skin tests or *in vitro* tests are positive, this result indicates a hypersensitivity reaction. The positivity should be consistent with the clinical history of the patients. However, the sensitivity of these tests is low, and negative skin tests and in-vitro tests cannot completely exclude the diagnosis of drug allergy. Therefore, DPT, which is the gold-standard test, should be performed to confirm the diagnosis of a suspected drug allergy.[19,20] DPT should be performed according to the risk-benefit ratio for each patient. In patients with a history of serious allergic reactions, DPT with alternative drugs may be performed instead of with culprit drugs. In our study, DPTs were performed with safe alternative drugs due to risk of anaphylaxis in many of patients.

This study had some limitations. We could not perform SPT and IDT with culprit drugs in many patients (75.4%) as some drugs are not suitable for skin testing, some patients had dermographism and their previous allergic reaction was very severe, and skin tests presented a risk of anaphylaxis in others.

Conclusions

Concomitant administration of multiple drugs in intravenous fluids may increase the risk of allergic reactions. The rational use of medicine principle should be obeyed and oral treatment should be preferred if possible.

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