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Commentary

Metronidazole induced anaphylactic shock: a case report

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Abstract: Metronidazole-induced anaphylactic shock is an extremely rare drug reaction. We here reported the case of a 39-year-old man with severe anaphylactic shock caused by Metronidazole. The patient denied any history of food or drug allergies during initial medical assessments. However, he experienced a sudden cardiovascular collapse immediately after receiving intravenous Metronidazole. The patient underwent cardiopulmonary resuscitation and was returned to spontaneous circulation, being successfully managed as a case of anaphylactic shock.

Keywords: Hypersensitivity, Anaphylactic Shock, Metronidazole.

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Introduction:

Anaphylactic shock is a type-1 hypersensitivity reaction occurring after exposure to foods, drugs, or chemicals and can be accompanied by unfortunate consequences such as death. Among various drugs, antibiotics, especially cephalosporins and penicillins, cause the highest number of hypersensitivity reactions and anaphylactic shocks. Metronidazole, one of the antibacterial drugs belonging to the group of nitroimidazole derivatives, is mainly used in the treatment of anaerobic bacterial infections, as well as prophylaxis for surgical site infections. This drug rarely causes anaphylactic reactions[1].

Case description

A 39-year old man weighing 70 kilograms, with no history of allergy or drug reactions, was admitted to a medical center with a chief complaint of abdominal pain and fever. The patient's vital signs at the time of admission were as follows: blood pressure: 120/78 mmHg, respiratory rate: 18, pulse rate: 85 beats/minute, temperature: 38.5 Celsius. Based on medical examinations, the patient had an abdominal wall hernia in the umbilical area and was selected to undergo laparotomy. All pre-operative examinations were normal except for mild leukocytosis.

Five hundred milligrams (mg) of intravenous metronidazole at a rate of 5mg/minute (available as a ready-to-use 100 milliliter solution in a single dose bag) was prescribed as the surgical site

infection prophylaxis prior to surgery. Few minutes after the administration of about 15 mg of metronidazole, the patient developed a sudden arrhythmia, leading to pulseless ventricular tachycardia. Cardiopulmonary resuscitation was initiated immediately, according to the 2016 CLSI guidelines. The patient was successfully resuscitated after approximately 30 minutes, and the drug was not rechallenged anymore. At the time of this incident, the patient's blood count was within the normal range, without eosinophilia or lymphocytosis. Inflammatory markers were also normal, and he was apyretic, without any organ failure. His blood pressure was 115/67 mmHg with a pulse rate of 85 beats/minute; his oxygen saturation was 98%. Patient had been intubated and was transferred to the intensive care unit. Two days later, he was extubated with stable hemodynamic parameters. A clear temporal relationship was observed between Metronidazole administration and the onset of symptoms. The patient scored 6 on the Naranjo Adverse Drug Reaction Probability Scale, a ten-question scale developed to help standardize the assessment of causality for all adverse drug reactions. Based on the Naranjo Scale interpretations, the reaction presented by this patient was *probably* due to metronidazole. These results are shown in table 1.

Discussion

Anaphylaxis is a serious, acute and systemic hypersensitivity reaction resulting from the degranulation of mast cells or basophils. As a result of this reaction, preformed mediators, including histamine and tryptase are released. Such mediators are capable of affecting the cardiovascular, respiratory, gastrointestinal, and other organ systems. Two mechanisms can be considered for degranulation of mast cells: immune-mediated (IgE-mediated, anaphylactic) and nonimmune-mediated (chemically-mediated, anaphylactic) reactions[2]. Recently, anaphylactic reactions have received more attention compared with the past. However, their occurrence is still underestimated. In adults, anaphylactic reactions are often caused by analgesics and antibiotics[3].

The risk of drug-induced anaphylactic reactions usually increases with age and intravenous route of drug administration. Race is also an important factor, with African-Americans presenting with a higher prevalence of anaphylactic reactions[4].

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A literature review was performed in PubMed using the keywords “hypersensitivity reaction” and “Metronidazole;” the relevant results have been summarized in table2.

There have been several reports of hypersensitivity reactions to metronidazole in the literature. The reported reactions include: allergic contact dermatitis[5], persistent drug eruptions[6], respiratory crisis[7,8], systemic reactions[9-12], anaphylactic reaction[10], Stevens-Johnson syndrome/toxic epidermal necrolysis[13], severe generalized exanthematous pustulosis[14], and serum sickness reactions[15]. In most of these reports, the main symptoms of metronidazole hypersensitivity reactions were reported as cutaneous involvement and angioedema, which disappeared within a few hours of corticosteroid and antihistamine administration. Generally, the anaphylactic reaction is not a common phenomenon with metronidazole. In contrast to other reports, we have reported a severe anaphylactic reaction requiring cardiac resuscitation induced by this drug.

Skin testing remains an essential tool to diagnose or confirm the presence of an allergic disease in individuals with hypersensitivity reactions. Skin prick test (SPT) is a safe and minimally invasive skin testing method, used to diagnose type I (IgE-mediated) allergies based on medical history and clinical signs. This method detects allergies to foods, drugs, or inhalants; its results provide sufficient evidence for allergenicity and can help confirm the diagnosis of a suspected type 1 allergy[9,10]. The results of our study have not been confirmed by SPT. The majority of allergic contact dermatitis cases with topical metronidazole for treating rosaceous acne[12] as well as fixed-drug eruptions, have been verified by Positive Patch tests (PTs). According to the results obtained by patch tests (and other testing methods), there is a possibility of an allergic cross-reaction between metronidazole and other imidazoles, such as ketoconazole, miconazole, clotrimazole, and albendazole[7], Therefore, the patient presented was advised to avoid taking any of these drugs.

There were important differences between our case and cases addressed in other reports; these include an immediate reaction after the infusion of Metronidazole and the incidence of a sudden hypotension and arrhythmia, leading to pulseless ventricular tachycardia. Additionally, our case was the first report of anaphylactic reaction with Metronidazole, requiring cardiopulmonary resuscitation.

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Drug reactions can be managed in three ways: avoiding the offending drug, prescribing premedication, and desensitization. Possible desensitization mechanisms include mitigating the mast cells and basophil response to the allergen and decreasing the production of inflammatory mediators. The risks and benefits of the desensitization method should both be considered and the patient should be involved in any decision-making process, crucial to the patient[16].

Table 1. Adverse drug reaction probability scale (Naranjo scale)

Question	Yes (score)	No (score)	Do Not Know	The present case's score
1.Are there previous conclusive reports on this reaction?	**+1**	**0**	**0**	**+1**
2. Did the adverse event appear after the suspected drug was administered?	**+2**	**-1**	**0**	**+2**
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	**+1**
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	**0**
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	**+2**
6. Did the reaction reappear when a placebo was given?	-1	+1	0	**0**
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	**0**
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	**0**
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	**0**
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	**0**
	Patient calculated scores: 6 (probable)			

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Table 2. clinical cases regarding metronidazole induced hypersensitivity reactions

Author /year	Patient demographics	Underlying Disease	History of drug allergy	Administration route of Metronidazole	Symptoms	Reaction severity	patient outcome
Aruanno/ 2020	45 y/o, m	gastrointestinal dysbiosis	No history	Oral tablet	labial angioedema and itching widespread erythematous maculopapular rash	Did not required cardiopulmonary resuscitation	**Recovery without sequela**
A Prieto/ 2005	34 y/o, f	trichomonal vaginitis	history of Fixe drug eruption due to sulphonamides	Topical	pruritic, erythematous, blistered lesions,	Did not required cardiopulmonary resuscitation	**Recovery without sequela**
Añíbarro B/1997	19 y/o, f	toothache	facial angioedema and rhinoconjunctivitis due to horse hair sensitization	Oral tablet	nasal and ocular itching, rhinorrhea, sneezing, and watery eyes	Did not required cardiopulmonary resuscitation	**Recovery without sequel**
ML Kurohara/1991	31 y/o, f	vaginal Trichomonas	No history	Oral tablet	hives over her entire body, shortness of breath	Did not required cardiopulmonary resuscitation	**Recovery without sequel**
Weart CW/1983	32 y/o, f	vaginitis	Tetracycline allergy	Oral tablet	Arthralgia, myalgia, fever, chills, pruritic rash, leukopenia	Did not required cardiopulmonary Resuscitation	**Recovery without sequela**
Chwee Ying Tang/ 2013	69 y/o, f	laparoscopic cholecystectomy	No history	Intravenous	pruritus and erythema	Did not required cardiopulmonary Resuscitation	**Recovery without sequela**
Naveen Kumar/2013	67 y/o, m	Diarrhea	history of an itchy, erythematous oval lesion after taking of Metronidazole	Oral tablet	itchy lesions	Did not required cardiopulmonary Resuscitation	**Recovery without sequela**
Fernández-Jorge B/2008	45 y/o, f	rosacea	No history	Intravenous	acute, itchy, vesicular and erythematosus eruption around the mouth	Did not required cardiopulmonary Resuscitation	**Recovery without sequela**
T Asensio/2008	51 y/o, f	Gingivostomatitis	No history	Oral tablet	sneezing, rhinorrhea, perioral paresthesia, and upper airway angioedema followed by generalized pruritic erythematous lesions	Did not required cardiopulmonary Resuscitation	**Recovery without sequela**

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Abbreviation: y/o: years old; m: male; f: female;

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