

Severe anaphylaxis from rifamycin SV

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Background: Anaphylaxis to topical application of rifamycin SV, which is used topically in the fields of surgery and dermatology, is rare.

Methods: We report two cases of systemic reactions occurring after local administration of rifamycin (Rifocine, Gruppo Lepetit, Italy). Both of them needed repeated intermittent topical applications. Skin prick tests with Rifocine constituents were performed on our patients, and also on ten atopic and ten nonatopic subjects. Although an old investigative tool, Prausnitz-Küstner (P-K) test was also performed on one of the patient's spouses to show passive transfer and the IgE-mediated mechanism.

Results: Allergy assessment with skin tests on the patients were negative for aeroallergens, latex, and Rifocine constituents (except rifamycin SV). The patients' prick tests with rifamycin SV were positive, and the control subjects were negative. P-K testing was positive.

Conclusion: Two case reports support the existence of IgE-mediated reactions to rifamycin SV. IgE-mediated anaphylactic reactions from rifamycin SV appear to be extremely rare.

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INTRODUCTION

The exact frequency of adverse drug reactions to antibiotics is difficult to ascertain. The estimated overall incidence of hypersensitivity type reactions to these drugs is approximately 1% to 3%.¹

According to the Gell and Coombs' classification, drugs may produce allergic reactions by any of four types. It is likely that more than one mechanism may contribute to a particular reaction, but often one of them predominates. Anaphylaxis is an example of a type I hypersensitivity reaction and penicillin is its most frequent cause in humans.^{1,2} Anaphylaxis, however, due to topical application is considered to be extremely rare. This should likely apply to rifamycin SV that has been in use for years.

In this report, we discuss two patients who had experienced symptoms

of severe anaphylactic shock, caused by rifamycin SV, which was applied topically to infected traumatic wounds. The immunologic mechanism of the anaphylaxis was confirmed by skin test and P-K test.

CASE REPORTS

Patient Number 1

A 54-year-old paraplegic woman (as a result of a T₁₂ compression fracture from a traffic accident) was suffering from a gluteal pressure sore. This occurred because of inadvertent employment of an apparatus for gate support on infragluteal region described a hypersensitivity reaction soon after a dressing change. Interview with the patient revealed that she had been having dressing changes for 15 months. Since the fourth month of treatment, mild systemic reactions (such as peripheral tingling, warm sensation and prickling of lips and tongue) had been occurring within minutes after application of the drug. Generalized urticaria occurred in the course of time with dressings. Both duration and severity of the reactions had increased with time.

Generalized urticaria, angioedema, bronchospasm and hypotension occurred within minutes after local administration of Rifocine (rifamycin) on four occasions between January and May 1997. Urgent transportation to an emergency department with proper treatment given promptly saved her life every time. Although readministration of an agent that induces a hypersensitivity reaction is potentially dangerous, the possibility that the allergic reaction was caused by a drug used in cleansing the wound was ignored until April 1997. Since the patient and her medical care staff thought Rifocine could not be responsible for these symptoms because such symptoms due to Rifocine were quite rare, the dressing routine was continued, unfortunately. After the third reaction, allergy consultation revealed that causal agent was Rifocine and the patient and her spouse were warned about not to use this medication. The fourth reaction occurred because a nurse used the same medication despite the warning marked on the patient's chart.

Skin Prick Tests

The patient underwent a complete allergy assessment to identify the responsible agent. A diagnostic procedure was performed 2 weeks after the last reaction. Standard prick tests were applied with latex and 40 common aeroallergens in Turkey. Prick tests were also performed with the different constituents of Rifocine, to exclude the possible role of these substances present in the solution: rifamycin SV, sodium bicarbonate, ascorbic acid, potassium metabisulphite, disodium EDTA, lidocaine hydrochloride, polyvinyl pyrrolidone, and distilled water. Prick test with histamine (concentration: 1 mg/mL) was used as a positive control and saline solution as a negative control. The results (the greatest and smallest diameter of the wheal)

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were evaluated ten minutes later and expressed in millimeters. Skin prick tests with the constituents of Rifocine were also performed on ten atopic and ten nonatopic subjects. Serum immunoglobulin levels were also measured in all of the controls.

Allergy assessment with skin testing on the patient was negative for aeroallergens, latex, and Rifocine constituents (except rifamycin SV). The histamine prick test result was positive with a wheal of 5×4 mm and the prick test with rifamycin SV at concentrations of 10-fold dilution was also positive with a wheal of 10×6 mm (Fig 1). Because of a positive history of four anaphylactic reaction episodes, we performed rifamycin SV only at 10-fold dilution.

All of the control subjects were females, and the age range was 36 to 53 years (mean 40.3 years). They were evaluated for Rifocine constituents by means of skin prick tests. All results were negative.

P-K Test

Informed consent was obtained from the patient and her spouse, and the P-K test was performed. Because of the possibility of transmission of bloodborne pathogens, the required screening tests (HIV, hepatitis, and HTLV viruses) were performed, and all were found negative. Serum was obtained from the patient, of which 0.1 mL was injected intradermally into the volar surface of the forearm of her spouse who had previously a negative skin reaction to rifamycin SV.^{3,4} Skin prick tests with rifamycin SV were performed at 24, 48, 72, 120, 168, 192, and 240 hours. The result of prick tests with rifamycin SV were positive with a wheal of 12×8 mm at 24 hours, 8×6 mm at 48 hours, 5×3 mm at 72 hours, 3×3 mm at 120 hours, 3×2 mm at 168 hours, and 2×2 mm at 192 hours. The result at 240 hours was negative. Skin prick test with rifamycin SV was also performed on the other forearm of the patient's spouse to investigate whether the reactions

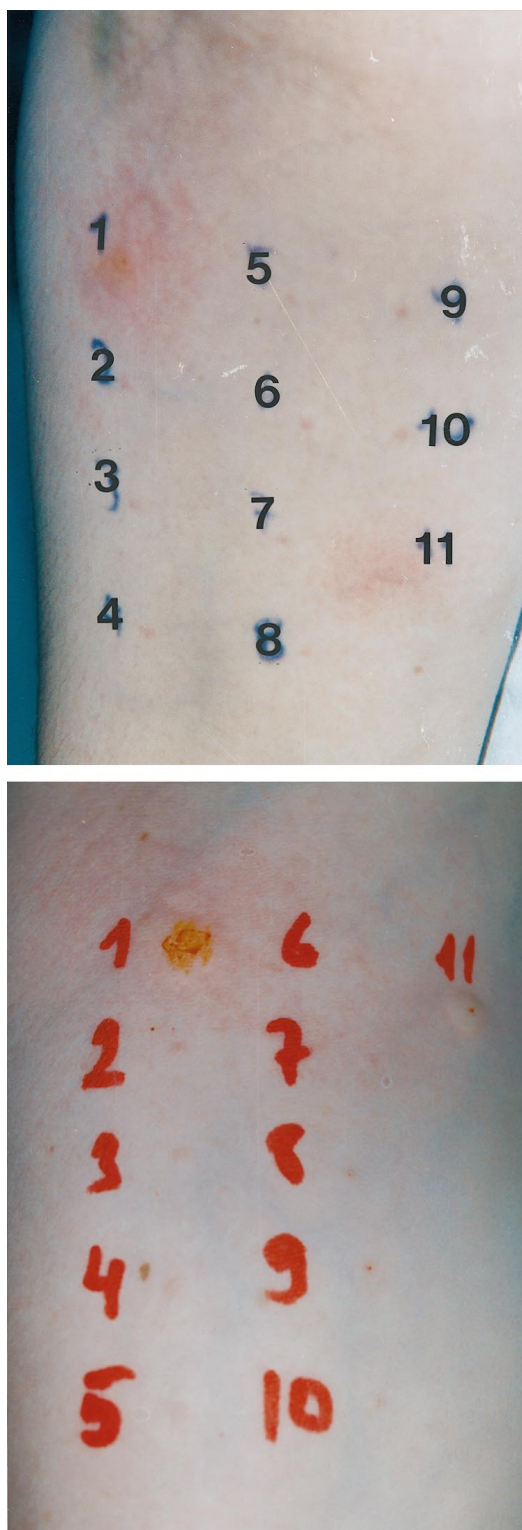


Figure 1. Skin prick tests (upper panel-patient 1 and lower panel-patient 2) with the different constituents of rifocine and latex. 1. rifamycin SV, 2. sodium bicarbonate, 3. ascorbic acid, 4. potassium metabisulphite, 5. disodium EDTA, 6. lidocaine hydrochloride, 7. polyvinyl pyrrolidone, 8. distilled water, 9. latex, 10. negative control, and 11. positive control.

were systemic or not. The result was negative.

Serum Immunoglobulin Levels

Serum immunoglobulin levels (IgG, IgM, IgA, and IgD) of the patient and spouse were normal, except total IgE which was 500 IU/mL (<100 IU/mL).

Patient Number 2

The patient was a 58-year-old woman without any history of familial or personal atopy, who developed diabetes mellitus at age 48 and was being treated with antidiabetic drugs. In addition, she had a chronic venous ulcer involving her right ankle for the past 32 years. She stated that the management of the wound had been carried out by intermittent dressings using Rifocine until 3 years ago when the anaphylactic symptoms, including generalized urticaria, wheezing, dyspnea, and hypotensive shock appeared immediately at the time of the last dressing change. This attack was treated with administration of epinephrine, β_2 agonist by nebulizer, and intravenous volume expansion. After this reaction, the drug was no longer used for her dressings. The main goal of the current admission to our hospital was to treat her nodular goiter. Her allergic reaction was noticed when she reported to her doctor the event she experienced 3 years before.

Skin Prick Tests

Skin tests were performed by the prick method (rifamycin SV used undiluted, and its constituents) and by the intradermal method (IDST) at concentrations of 80, 800, and 8000 μ g/mL. In addition, we also performed skin prick tests with 40 aeroallergens and latex. Prick tests (1 mg/mL) and intradermal tests (0.1 mg/mL) with histamine was used for the positive control.

Prick testing with aeroallergens and latex were negative. The histamine prick test result was positive with wheal at 7×6 mm, and also the result of IDST was positive at 12×12 mm. The result of the prick test with undiluted rifamycin SV was positive with a wheal at 14×10 mm (Fig 1). Results of IDSTs at concentrations of 80, 800,

and 8000 μ g/mL were positive for wheal of 12×12 mm, 16×14 mm, and 23×19 mm, respectively. Rifocine constituents (excluding rifamycin SV) did not elicit any positive reactions. At the time of IDSTs, this patient had a moderate systemic reaction with peripheral tingling, a warm sensation, generalized urticaria, and dyspnea.

DISCUSSION

Rifamycin SV is a semisynthetic macrocyclic antibiotic derived from natural rifamycin B.⁵ It has a large spectrum of bactericidal action on gram-positive and gram-negative microorganisms, especially *Staphylococcus aureus*. The rate of healing is considered to be significantly better than other forms of local antibiotics, so it is frequently preferred to treat infected surgical or traumatic cutaneous wounds in Turkey.

The adverse effects of rifamycin are few. Occasionally, it will produce a flulike syndrome in individuals who take the drug intermittently. There have also been reports of interstitial nephritis, thrombocytopenia, and hemolytic anemia. Side effects of rifamycin after local application are extremely rare^{1,5} but cases of allergic contact dermatitis have been described.^{6,7}

Until 1989, no anaphylactic reaction to rifamycin SV had been reported. Piazza⁸ in 1989, Mancuso and Masara⁹ in 1992, Cardot et al⁵ in 1995, and Laxenaire et al¹⁰ in 1996 reported cases of proven anaphylactic reactions after application of rifamycin SV to surgical wounds. Here, we report two cases who experienced severe anaphylactic shock after intermittent application of rifamycin SV. Our patients' histories indicated previous local administration of Rifocine. This explains the sensitization to this drug, ie, the more rifamycin SV applications were performed, the more sensitization and the more severe reactions that occurred.

Because of haptenic structure, skin testing with antibiotics is not only a reliable method of detecting allergy, but it also provides greater insight into the underlying mechanism. The relationship of anaphylactic reactions to

rifamycin SV was also confirmed by P-K test. These two processes suggest that this anaphylactic reaction occurred via an IgE-mediated mechanism.

To allow better assessment of the value of skin tests, it may be necessary to subsequently challenge patients under well-controlled circumstances with all agents producing negative and positive skin tests. Challenge with rifamycin SV was expected to cause serious anaphylactic reactions and was thus not done in this study. All of four reactions in the first patient can be considered as provocation.

P-K test positivity in our patient's spouse continued for eight to ten days. It was known that the half-life of serum IgE in human skin was approximately eight to fourteen days.¹¹ Our findings are consistent with the literature.

The role of atopy in predisposing a patient to an anaphylactic reaction during application of drugs is still being debated. Some patients are atopic¹²⁻¹⁴ and others nonatopic.^{1,15} Both of our patients were nonatopic (but one pt had elevated total IgE).

On the basis of clinical history and the results of skin tests and the P-K test, our diagnosis of these patients was IgE-mediated drug allergy to rifamycin SV. We also note the skin prick test with other suspected constituent did not elicit a positive response.

In conclusion, the development of the anaphylactic reactions due to topical application of rifamycin SV, although this is considered to be extremely rare, should be taken into consideration. This situation is worth pointing out, especially in patients who require the repeated topical applications of drugs for treatment of traumatic or surgical wounds.

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