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Anaphylactic reaction to local administration of rifamycin SV

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Background and objective: Systemic reactions during anesthesia are commonly attributed to muscle relaxants, hypnotics, macromolecular solutions, latex, or parenteral antibiotics. After exclusion of these different components as causes, we were interested in the potential implication of rifamycin in the systemic reaction, which occurred during anesthesia, and in the immunologic mechanism by which it can trigger this reaction.

Methods: We report four cases of systemic reactions occurring after local administration of rifamycin. Three patients needed orthopedic surgery, and the fourth needed a urethrotomy. Severe systemic reactions occurred in all four patients when the surgeon washed the incision area with a rifamycin solution. All patients correctly responded to appropriate treatment and recovered. Skin tests were performed 2 months after the incident with the drugs used during anesthesia, latex, and rifamycin. To assess the relationship with a possible IgE-mediated mechanism, two *in vitro* tests were concomitantly performed to evaluate the cell reactivity to rifamycin: (1) determination of histamine release from peripheral basophils and (2) platelet cytotoxicity test, which explored the presence on platelets of specific IgE antibodies bound to the low-affinity receptor for IgE.

Results: Skin tests were performed with different drugs used during surgery, and results were only positive for rifamycin in the four cases, accompanied in two cases by a systemic reaction. Histamine release from basophils was positive in three of four patients. The platelet cytotoxicity test results were positive in all four cases.

Conclusion: It appears that rifamycin, used locally during surgery, is apt to trigger severe systemic anaphylactic reactions, which are linked to an IgE-related process. This situation is worth pointing out, especially in patients who undergo repeated orthopedic operations during which, at least in Europe, rifamycin is commonly used for the prevention of local sepsis. (*J ALLERGY CLIN IMMUNOL* 1995;95:1-7.)

Key words: Anaphylaxis, rifamycin, cutaneous tests, histamine release

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Abbreviation used

IDST: Intradermal skin test

Generalized reactions during anesthesia are usually well identified. Reported incidence of drug-induced anaphylaxis during anesthesia ranges from 1 in 1500 to 1 in 5000; among these only 50% are IgE-mediated. Muscle relaxants account for 70% and latex accounts for 12% of such reactions.¹ Other drugs such as hypnotics, analgesics, anxiolytics, plasma expanders, and systemic antibiotics are considered to be responsible for other undesirable reactions. Usually, the association of physical examination findings with results of skin tests performed a few weeks after an anaphylactic incident is sufficient for diagnosis. In a few cases the responsible allergen is not detected despite extensive investigations: this problem arose with latex when the prevalence of sensitization was lower. A similar reaction occurred with rifamycin after local application.

Rifamycins are a group of structurally similar, complex macrocyclic antibiotics produced by *Streptomyces mediterranei*. (Fig. 1 shows the Rifampicin and rifamycin chemical structures.) Rifampicin is widely used in tuberculosis therapy and is incriminated in 1.2% of all severe allergic reactions to drugs in the course of treatment for active tuberculosis.² However, the responsibility of rifamycin remains poorly documented: among rifamycins (rifamycin B, O, S, SV, and X), rifamycin SV is a semisynthetic antibiotic derived from natural rifamycin B. Its large spectrum of activity against gram-positive and gram-negative bacteria explains its wide use by surgeons for local application to infected surgical or cutaneous wounds.^{3,4} Side effects of rifamycins after local application are rare: some cases of allergic contact dermatitis have been described,⁵⁻¹⁰ and recently, the first mention of an anaphylactic reaction after local instillation of rifamycin SV was reported.¹¹ We report four representative cases of proven anaphylactic reactions after application of rifamycin SV to surgical wounds. The IgE-mediated mechanism has been evaluated by skin tests, histamine release tests, and secondly by a platelet cytotoxicity test.

CASE REPORTS**Case 1**

In 1987, a 21-year-old man, without any personal or familial history of atopy, needed an osteotomy in his left

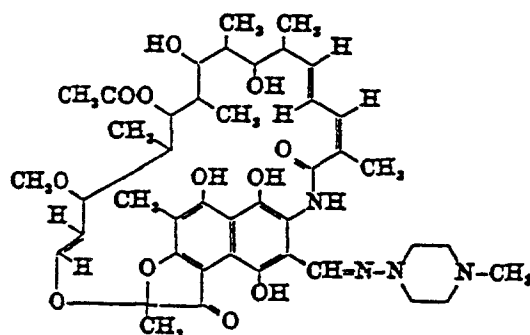
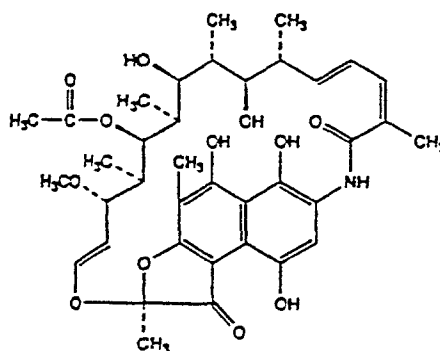
Rifampicin (C₄₃-H₅₈-N₄-O₁₂)Rifamycin (C₃₇-H₄₇-N-O₁₂)

FIG. 1. Structure of rifampin and of rifamycin.

knee. He previously underwent a total of 10 operations on both knees between 1982 and 1987 after a complex fracture of the legs. Anesthesia was induced with thiopental, vecuronium, and dextromoramide after premedication with midazolam. Ninety minutes after induction of anesthesia, just after the wound was sprayed with rifamycin SV and the tourniquet was released, the patient suddenly exhibited generalized erythema with angioedema. Hemodynamic perturbations occurred with tachycardia and circulatory collapse. After volume expansion and infusion of epinephrine, the situation rapidly improved: normal blood pressure was restored, and cutaneous signs disappeared. The diagnosis of anaphylactic shock was evident, but its cause was unclear. A diagnostic procedure was performed 6 weeks later: results of intradermal skin tests (IDSTs) with midazolam, thiopental, dextromoramide, and vecuronium were negative. The result of the prick test with latex was also negative. Wheal and flare reactions for histamine were measured at 7/15 mm and 10/19 mm, respectively, for the IDST. The result of a prick test with undiluted Rifocine, was positive at 7/20 mm, and results of IDST with Rifocine at concentrations of 50, 500, and 5000 μ l were positive for wheal and flare at 8/15, 10/19, and 18/40 mm, respectively. We performed prick tests with the

different constituents of Rifocine: ascorbic acid, sodium metabisulfite, sodium acetate, sodium bicarbonate, polyethylene glycol, and rifamycin. Only the result of the prick test with rifamycin was positive at 7 mm. Total serum IgE values were at 161 IU/ml (normal values in adults are less than 120 IU/ml). Five years later, although no more Rifocine had been administered, skin tests were performed again with exactly the same results. The result of the IDST with Rifocine at a concentration of 5000 μ g/ml was associated with pruritus and left leg urticaria. We concluded that this was an anaphylactic reaction after local administration of Rifocine, caused by a previous sensitization to rifamycin. Skin test results were reproducible 5 years after the incident in the absence of any additional drug introduction.

Case 2

A 46-year-old man, without any familial history of atopy but with a nocturnal cough, had undergone surgery for repair of a shoulder fracture in 1990 and 1991; surgery was performed on the left ankle at the same time. He needed an intervention for lumbar slipped disc. Anesthesia was induced with propofol, alfentanil, and pancuronium. The patient also received macromolecular solution. At the end of the surgical procedure just after the wound was washed, he exhibited a generalized erythema and circulatory collapse with tachycardia and ventricular extrasystoles. Volume expansion and administration of epinephrine were used to improve the hemodynamic state. To identify the responsible agent, the patient underwent a complete allergy assessment. Standard prick test results were positive for *Dermatophagoides farinae*, with total serum IgE at 248 IU/ml (normal range, below 120 IU/ml), and RAST value in response to *D. farinae* was 2.1. IDST results with propofol, alfentanil, pancuronium, and dextran were negative. The response to a prick test with latex was also negative. The result of histamine prick test was positive for wheal and flare at 6/12 mm, and the result of IDST was positive at 7/18 mm. The result of the prick test with undiluted Rifocine was positive for wheal and flare at 4/13 mm, and results of IDSTs at successive concentrations of 50, 500, and 5000 μ g/ml were positive for wheal and flare at 7/13, 8/16, and 12/35 mm, respectively. We concluded that this patient, who was atopic, demonstrated sensitization to rifamycin.

Case 3

A 69-year-old man without any history of familial or personal atopy underwent tibial osteotomy in 1987 and had surgery twice in 1992 for treatment of bilateral carpal tunnel syndrome. He needed an intervention for the rupture of the right biceps tendon and anterior acromioplasty. After premedication with midazolam, anesthesia was induced with propofol, atracurium, and fentanyl. Thirty-five minutes after induction, generalized

erythema occurred. In the next few minutes, the blood pressure fell from 130/8 to 60 mm Hg, concomitantly with perturbations of cardiac conduction. After volume expansion with 1000 ml of serum albumin and injection of 1 mg of epinephrine, the hemodynamic state improved and cutaneous erythema disappeared. Six weeks after the incident, allergy assessment with skin testing was negative for propofol, midazolam, fentanyl, and atracurium. The result of the prick test with latex was also negative, as were results of standard prick tests. The total serum IgE level was at 264 IU/ml. The histamine prick test result was positive for wheal and flare at 7/15 mm, and the IDST result was positive at 10/19 mm. Results of IDSTs with Rifocine at concentrations of 50, 500, and 5000 μ g/ml were positive for wheal and flare at 7/16, 13/20, and 13/30 mm, respectively; and the result of the prick test with undiluted Rifocine was positive for wheal and flare at 4/9 mm. We concluded that this was an anaphylactic reaction to local administration of Rifocine, caused by previous sensitization to rifamycin.

Case 4

A 34-year-old man was known to have asthma since the age of 6 years. His mother and one brother also have asthma. Another brother had atopic dermatitis. The patient claimed to be allergic to penicillin. He also had a history of multiple interventions: placement of hip prosthesis because of femoral head osteonecrosis in 1985, surgery for his left knee after a trauma injury in 1988, arthroscopy on the same knee in 1990, and repair of an inguinal hernia in 1991. He underwent a urethrotomy while under spinal anesthesia with lidocaine. Three days later, just before the removal of the urinary catheter, Rifocine was injected into the bladder. Immediately, a bronchospasm occurred; this was rapidly followed by a cardiac arrest, which was probably hypoxemic. Generalized erythema was detected at the same time. After tracheal intubation, mechanical ventilation, volume expansion, and administration of epinephrine and β_2 -agonists by aerosol for treatment of bronchospasm, hemodynamic status improved and the bronchospasm gradually disappeared. There was no neurologic lesion, and the patient was extubated after 24 hours. Results of skin tests, performed with a standard aeroallergens, were negative; and the total IgE level was at 139 IU/ml. The histamine prick test result was positive for wheal and flare at 6/18 mm, and the IDST result was positive at 10/23 mm. Results of IDSTs, performed with Rifocine at concentrations ranging from 50 to 5000 μ g/ml, were positive for wheal and flare at 15/25, 18/35, and 25/60 mm, respectively. The result of a prick test with undiluted Rifocine was positive at 8/17 mm. After an IDST at a concentration of 5000 μ g/ml, the patient exhibited a general reaction with pruritus, erythema, and urticaria on the upper part of the body. We concluded that this was an anaphylactic reaction after injection of Rifocine

TABLE I. Cutaneous test responses to histamine and rifamycin SV in four patients and two control series

Groups	Histamine		Rifamycin SV			
	Prick test W/F (10 mg/ml)	IDST W/F (10 mg/ml)	Prick test W/F (50 mg/ml)	(50 µg/ml)	Intradermal skin tests W/F (500 µg/ml)	(5000 µg/ml)
Patient No.						
1	7/15	10/19	7/20	8/15	10/19	18/40
2	6/12	7/18	4/13	7/13	8/16	12/35
3	7/15	10/19	4/9	7/16	13/20	13/30
4	6/18	10/23	8/17	15/25	18/35	25/60
Control						
Atopic patients	W: 5.5 ± 1.1 F: 18.0 ± 4.6	W: 10.5 ± 7 F: 28.2 ± 8.1	W: 0 F: 0	W: 0 F: 0	W: 0 F: 0	W: 0 F: 0
Nonatopic patients	W: 6.7 ± 1.8 F: 20.4 ± 8.1	W: 9.5 ± 4.2 F: 23.4 ± 7.5	W: 0 F: 0	W: 0 F: 0	W: 0 F: 0	W: 0 F: 0

Results are expressed in millimeters (mean of two opposite diameters of the wheal (W) and flare (F) reactions).

into the bladder of a patient previously sensitized to rifamycin.

METHODS

Skin tests

Skin tests were performed successively by the prick method (rifamycin used undiluted) or by the intradermal method (IDSTs) at concentrations of 50, 500, and 5000 µg/ml. Prick tests (1/100) and IDSTs (1/100) with histamine (concentration = 10 mg/ml) represented positive controls. In addition, evaluation of atopy was performed by skin tests with current airborne allergens (*D. pteronyssinus*, pollens, cat dander). All of the drugs used during anesthesia were also used in IDSTs. Skin tests were performed on our four patients and also on 10 atopic and 10 nonatopic subjects. For one patient, the components of Rifocine were tested separately: rifamycin SV, ascorbic acid, sodium metabisulfite, ethylenediamine, sodium tetracetate, propylene glycol, monosodium carbonate, and distilled water. Prick tests and IDSTs were also performed with saline solution as negative controls. For those tests, the wheal and the flare were recorded by the Scotch tape technique 10 minutes after the performance of the test. The results are expressed in millimeters (average length of two opposite diameters).

Histamine release

Histamine release from human basophils was quantified by a radioimmunoassay (Immunotech Corp., Boston, Mass.). Venous blood collected in a heparinized tube was diluted (1:4) in histamine release buffer. One hundred microliters of diluted blood was incubated with 50 µl of Rifocine at different concentrations in round-bottomed microtiter plates. After 30 minutes of incubation

at 37° C and centrifugation at 4° C, supernatants were collected and stored at -20° C until they were tested. To increase the sensitivity of the dosage, histamine was acylated before the incubation with monoclonal antibodies fixed on the solid phase. After competition between histamine-iodine 125 and histamine (performed for 18 hours at 4° C), the specific bound radioactivity was determined by using a gamma counter (LKB, Uppsala, Sweden). Results were obtained from a standard curve and expressed as a percentage of the total histamine release obtained after lysis of cells. Sensitivity of the assay was 0.1 nmol. Peripheral blood leukocytes from three of four patients who were sensitive to rifamycin and from five healthy subjects were tested.

Antiparasite cytotoxicity by platelets

Another method used in the laboratory to test the potential involvement of specific IgE antibodies is represented by the platelet cytotoxicity test according to previous studies.¹⁴ Platelets recovered in each of the four patients were suspended in Eagle's minimal essential medium (MEM; Gibco, Grand Island, N.Y.) (15.107 platelets per well) and incubated in flat-bottomed microplates with 50 to 100 *Schistosoma mansoni* schistosomula with 10% heat-inactivated normal human serum, and Rifocine at different concentrations in a final volume of 200 µl. Platelets isolated from five healthy donors were treated in the same conditions as a control. After 24 hours at 37° C and 5% CO₂ in air, motionless and dark dead larvae were clearly distinguished from mobile and refractive living schistosomula by optical microscopy, which allowed us to define a percentage of antiparasite cytotoxicity. Each experiment was done in triplicate. Platelet aggregation was never observed during the test.

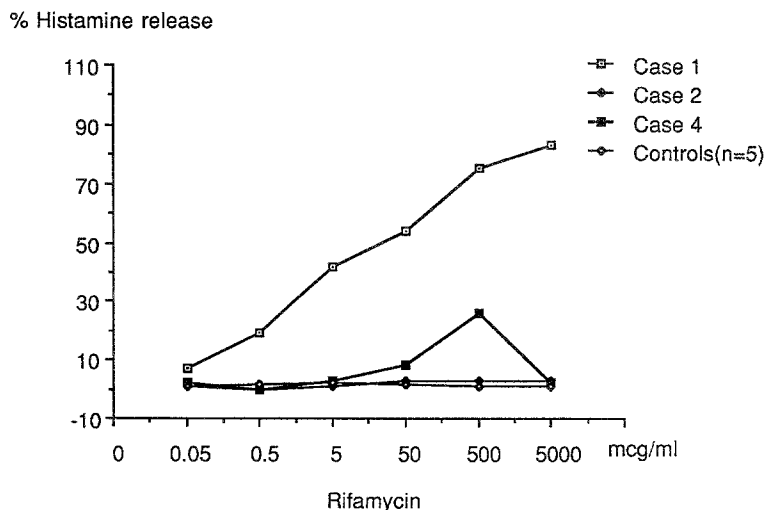


FIG. 2. Percentage of histamine release from basophils of patients allergic to rifampicin and controls.

RESULTS

Skin tests

Twenty subjects, 10 allergic and 10 nonallergic, were evaluated for sensitivity to rifampicin (Rifampin) by means of IDSTs. All results were negative at concentrations from 50 to 5000 pg/ml. In the four patients who had systemic allergic reactions during surgical procedures, results of IDSTs with rifampin SV were positive at the concentration of 50 μ g/ml from 7 to 15 mm. At 5000 μ g/ml, reactions ranged from 12 to 25 mm. Two patients had a mild systemic reaction with pruritus, erythema, and urticaria at the time of skin testing. One patient was evaluated 5 years after the anaphylactic incident with the same results (Table I). Diluents did not elicit any positive reaction. The results are summarized in Table I.

Histamine release

The first patient (case 1) exhibited a marked histamine release from basophils in contact with rifampin SV, with a maximum of 83% for the concentration of 5000 μ g/ml. The fourth had a positive response at 26% for a concentration of 500 μ g/ml. The second patient had a negative response with no detectable histamine release. The third patient was not tested (Fig. 2). Negative controls showed no detectable histamine release. These data are shown in Fig. 2.

Antiparasite cytotoxicity by platelets

Results of antiparasite cytotoxicity tests are shown in Fig. 3. Spontaneous cytotoxicity of plate-

lets without allergen was 4.5%, 16%, 7.5%, and 9.5%. Cytotoxicity values in the four cases for a rifampin SV concentration of 100 μ g/ml were 70%, 61.5%, 93%, and 60%, respectively.

DISCUSSION

Anaphylactic reactions during anesthesia have already been extensively described. Most of them are related to muscle relaxants, plasma expanders, dextrans, and latex. In all situations recovery of anamnestic data, verification of previous operations, the exact beginning of the anaphylactic reaction during anesthesia, and skin tests are necessary to identify the responsible agent.¹⁵ In this way skin tests represent a sensitive and easily accessible method for screening these patients. However, the use of chemicals for skin testing may result in irritant reactions that may be interpreted incorrectly; thus, adequate controls must be tested simultaneously. Allergic reactions to muscle relaxants are responsible for more than 50% of anaphylactic incidents during anesthesia: quaternary ammonium ions are involved in a number of mechanisms that mediate these allergic reactions.¹⁶ Natural rubber has been found to produce contact dermatitis and contact urticaria in up to 6.2% of employees in operating units.¹⁷ However, it may also cause rhinitis, asthma, and anaphylaxis.¹⁸ Dextrans are polysaccharides with an average molecular weight ranging from 40,000 to 70,000 d, and they are currently used to reduce the incidence of perioperative thromboembolic mortality and morbidity. They may be responsible for severe anaphylactic reactions but seem to be

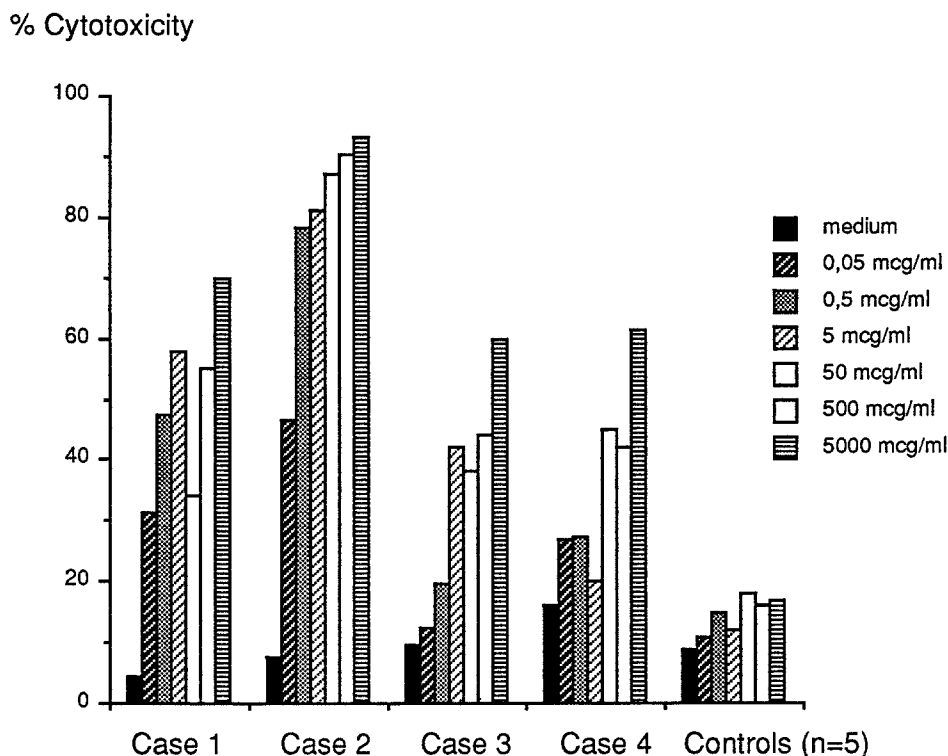


FIG. 3. Platelet cytotoxicity from patients sensitized to rifamycin (compared with a group of five control subjects).

mediated by dextran-reactive antibodies, which are related to IgG class antibodies; this explains why in this situation, skin test results are usually negative.¹²

However, each drug or blood product administered in the perioperative period has the capacity to produce a life-threatening allergic reaction. Problems are usually associated with intravenous administration; the problems with locally applied products are fewer.¹³

During orthopedic surgery, the risk of postoperative infection is approximately 2% to 5%. It rises to 20% to 35% if the wound is contaminated; therefore, local administration of rifamycin SV 5% during and after operations has been used by some surgeons to prevent local sepsis.^{3,4} This particular interest in Rifocine 5% has many reasons; rifamycin SV has a large spectrum of bactericidal action on gram-positive and gram-negative microorganisms, especially *Staphylococcus aureus*. Its local action is furthered by a slow resorption rate, depending on vascularization, contact surface, administered volume, and frequency of administration. The rate of healing is considered to be significantly better than that associated with other forms of local antisepsis. It does not induce resis-

tance. Moreover, Rifocine 5% is locally well tolerated.

Although this was considered to be extremely rare, several case reports mentioned allergic contact dermatitis caused by topically applied products containing rifamycin SV. In the case of traumatic aggression and ulceration, loss of integrity of the skin might favor penetration and hence the induction of sensitization.⁸⁻¹⁰ Until the recent reports of Piazza¹¹ and Mancuso and Masara,¹⁹ no systemic reaction to rifamycin SV had been reviewed.

In this study four cases of anaphylactic reactions to rifamycin occurring during a surgical procedure are described. In all cases symptoms began at the end of the intervention, a long time after anesthetic drugs had been administered. For the first three patients, case history indicated previous local administration of Rifocine, explaining the sensitization to this drug. Skin tests were performed, successively by prick and intradermal methods. All results were positive, even triggering a mild systemic reaction during skin testing in two cases. Twenty patients devoid of any sensitization to rifamycin were tested in parallel without any de-

tectable reaction. To exclude the possible role of other substances present in the antibiotic solution, the first patient was cutaneously tested for all constituents of Rifocine: rifamycin SV, ascorbic acid, sodium metabisulfite, ethylenediamine, sodium tetracetate, propylene glycol, sodium monocarbonate, and distilled water. Only the result of the skin test for rifamycin SV was positive. The relationship of anaphylactic reactions to rifamycin SV was confirmed by *in vitro* tests: histamine release of basophils was positive in two thirds. The way rifamycin could be responsible for a basophil or mast cell degranulation via the FcεRI remains unknown. Nevertheless, the rifamycin molecule has a high absorption on plasmatic proteins (more than 80%). It could form a complex with plasma proteins and become a macromolecule that could trigger the bridging of IgE receptors and consequently induce the transduction signal to mast cells or basophils. A second test demonstrates the participation of IgE in these patients; it is the cytotoxicity test of platelets. Previous studies have shown that the low-affinity receptor for IgE (FcεRII), present on platelets from patients with allergic disorders, could be stimulated either by anti-human IgE antibodies or the relevant allergen to generate cytotoxic mediators.¹⁴ It is known that the number of FcεRII-bearing platelets is increased in allergic patients²⁰ and that in patients with Hymenoptera venom hypersensitivity, the IgE-mediated stimulation of platelets was reduced after rush desensitization.²¹ The cytotoxicity of platelets from our subjects was always significantly increased in the presence of rifamycin. The association of positive skin test results with positive histamine release and positive platelet cytotoxicity in the presence of rifamycin represented data indicating that the symptoms exhibited by the patients were IgE-dependent.

In conclusion, it appears that some patients undergoing a surgical procedure, particularly an orthopedic procedure, are susceptible to systemic anaphylactic reactions linked to a hypersensitivity mechanism caused by rifamycin SV, which is applied topically to prevent local sepsis. Besides muscle relaxants, hypnotics, plasma expanders, and latex, other pharmaceutical products, including topically applied antibiotics need to be tested, particularly if the anaphylactic reaction occurs late after the induction period of anesthesia and in case of repeated surgical orthopedic procedures.

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