

Anaphylaxis during rapid oral desensitization to rifampicin



Ekaterini Syrigou, MD, PhD^a, Dimitra Grapsa, MD, PhD^b,
Eugenia Nanou, MD^a, Maria Zande, MD^a,
Antonios Vassias, MD^b, Ioannis Gkiozos, MD, PhD^b, and
Konstantinos Syrigos, MD, PhD^b

Clinical Implications

- We herein report, for the first time in the English literature, a case of anaphylaxis during rapid oral desensitization to rifampicin in a male patient with active tuberculosis and a history of rifampicin-induced anaphylactic reactions.

TO THE EDITOR:

Rifampicin (also known as rifampin) is one of the most potent first-line antituberculosis drugs and an indispensable treatment option for isoniazid-resistant, rifampicin-sensitive tuberculosis (TB). Hypersensitivity reactions to rifampicin, mainly including fever, flu-like syndrome, rash, thrombocytopenia, acute renal failure, urticaria, and anaphylaxis, are considered rare but may occur among susceptible individuals and lead to premature discontinuation of the drug.¹

Drug desensitization is a well-established procedure that may temporarily modify a patient's immunologic response to the sensitizing agent, thus allowing for continuation of treatment.² Desensitization to rifampicin has been previously described in rare case reports, almost invariably with successful results.²⁻⁶ We herein report a case of anaphylaxis during rapid oral desensitization to rifampicin in a male patient with active TB and a history of anaphylactic reactions to this agent. To the best of our knowledge, this is the first report in the English literature of a severe immediate-type reaction during desensitization to rifampicin.

A 72-year-old man presented to the outpatient pulmonary clinic of "Sotiria" General Hospital, Athens, Greece, with fever, nonproductive cough, and weakness, lasting for 2 weeks. His medical history was significant for adult-onset diabetes mellitus and rheumatoid arthritis, treated with metformin and low-dose prednisone and intravenous infliximab, respectively. The patient was diagnosed with miliary TB and was started on anti-TB treatment with isoniazid (300 mg/day), rifampicin (600 mg/day), pyrazinamide (1500 mg/day), and ethambutol (1200 mg/day). Within 2 weeks after initiation of the above regimen, and 30 minutes after administration of the last dose of rifampicin, the patient developed fever and widespread urticaria; all drugs were subsequently discontinued and gradually reintroduced—after resolution of the cutaneous reaction—to identify the culprit drug. Urticaria, palmoplantar, and oropharyngeal pruritus were noted within 5 minutes after reintroduction of rifampicin and the drug was stopped; rifampicin was thereafter replaced with rifabutin. Ten days after initiation of rifabutin, the patient developed a maculopapular rash that affected the trunk and lower

extremities. A skin biopsy was compatible with drug-induced eruption and rifabutin was discontinued. Approximately 3 years after his initial diagnosis of TB, the patient developed recurrent TB and was again started on a multidrug anti-TB regimen comprising isoniazid, rifabutin, pyrazinamide, and ethambutol. Twelve days after initiation of treatment a maculopapular rash appeared on the patient's upper and lower extremities; rifabutin was again discontinued, followed by gradual resolution of the eruption, and the patient was referred to the Allergy Department of our hospital for further evaluation and management.

At the time of the patient's presentation to our department, skin prick test (SPT) and intradermal (ID) skin testing to rifampicin were performed, based on previous recommendations defining the highest nonirritant intradermal skin concentration of rifampicin (0.002 mg/mL).⁷ Histamine and saline were also used as positive and negative controls, respectively. SPT at a concentration of 2 mg/mL was negative, whereas a positive reaction (with a wheal of 15 × 17 mm and a flare of 42 × 44 mm) was shown on ID skin testing at a concentration of 0.002 mg/mL. After obtaining the patient's informed consent, oral desensitization to rifampicin was carried out in the intensive care unit. Premedication with antihistamines or steroids was not used (prednisone was discontinued for 3 days before the procedure) because these drugs may mask initial symptoms of anaphylaxis during desensitization, as previously emphasized,² and the patient was not taking β -blockers or angiotensin-converting enzyme inhibitors. Increasing dosages of rifampicin were administered every 30 minutes, at a starting dose of 0.0002 mg followed by gradual dose escalation (Table 1), as described in previously published desensitization protocols.⁶ Twenty minutes after administration of the 50 mg rifampicin dose, the patient started complaining of pruritus of the palms, soles, and groin followed by facial and trunk erythema, cough, generalized urticaria, hypotension, and sinus tachycardia followed by sinus bradycardia (without other ECG abnormalities). The desensitization procedure was discontinued, and the patient was treated with IV fluids, oxygen and nebulized salbutamol, intramuscular adrenaline, and intravenous methylprednisolone, dimetindene and ranitidine, with gradual recovery. Serum tryptase obtained at 1 hour after the onset of symptoms was 25 μ g/L. Repeat serum tryptase, measured 1 week later, was found to be within normal limits (4 μ g/L). Given the patient's anaphylactic reaction during rapid desensitization, anti-IgE treatment and desensitization to rifampicin using slow dose increment over several days were recommended but the patient refused.

Hypersensitivity reactions to anti-TB agents are relatively uncommon, encountered in approximately 4%-5% of the treated population, but may as well lead to withdrawal of the culprit drug and switching to an alternative agent.³ Rifampicin, in particular, is generally considered a well-tolerated drug with a low percentage of adverse events, especially when administered in usual therapeutic doses and outside the context of HIV infection.^{1,8} Delayed reactions, including a variety of cutaneous manifestations, are the commonest adverse reactions induced by rifampicin, whereas severe immediate reactions, such as anaphylaxis, are exceedingly rare.^{1,8}

TABLE I. Rifampicin desensitization protocol

Time (min)	Concentration (mg/mL)	Volume (mL)	Dose (mg)	Total dose (mg)
0	0.001	0.2	0.0002	0.0002
30	0.01	0.2	0.002	0.0022
60	0.01	2	0.02	0.0222
90	0.1	2	0.2	0.2222
120	10	0.2	2	2.2222
150	10	0.4	4	6.2222
180	10	0.8	8	14.2222
210	10	1.6	16	30.2222
240	100	0.3	30	66.2222
270	100	0.5	50	116.222
300	100	1	100	216.222
330	100	1.5	150	366.222
360	100	2.5	250	616.222

Desensitization to rifampicin may be safely performed in both adults and pediatric patients using rapid or slow desensitization protocols, as those described in previous case reports.²⁻⁶ With the exception of a single case of unsuccessful intravenous desensitization to rifampicin,⁹ presumably because the reaction was not IgE-mediated, a successful outcome was noted in the remaining of the reported cases.²⁻⁶ Although adverse events (fever, facial flushing, and chest discomfort) during rapid oral desensitization to rifampicin were noted in 2 of these patients,^{3,4} these reactions were mild and transient, were promptly and effectively controlled, and did not prevent the successful completion of the desensitization procedure. Fenniche et al¹⁰ also reported a case of anaphylaxis during desensitization to rifampicin, with a favorable outcome after administration of corticosteroids and antihistamines. In contrast, a recent Japanese study, which investigated the clinical usefulness of desensitization therapy for allergic reactions to anti-TB drugs, showed failure of desensitization to isoniazid and rifampicin in 7 of 30 cases (23%) and 3 of 16 cases (19%), respectively, among a total of 46 patients who underwent the desensitization procedure.¹¹ Notably, the adverse events leading to failure of desensitization included drug fever and eruption—but not immediate-type reactions as the anaphylactic reaction observed in the present case—whereas it was concluded that successful desensitization may be associated with a longer interval between desensitization therapy and withdrawal of the culprit drug.¹¹

Our reported case of a severe anaphylactic reaction during rapid oral desensitization to rifampicin highlights that clinicians should maintain a high degree of vigilance for the possibility of life-threatening complications, such as anaphylaxis, during the procedure of desensitization. Furthermore, positive skin testing to rifampicin may strongly suggest the presence of IgE-mediated hypersensitivity.

^aAllergy Department, "Sotiria" General Hospital, Athens, Greece

^b3rd Department of Medicine, University of Athens, School of Medicine, "Sotiria" General Hospital, Athens, Greece

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts.

Received for publication July 2, 2015; revised August 24, 2015; accepted for publication September 10, 2015.

Available online October 24, 2015.

Corresponding author: Dimitra Grapsa, MD, PhD, 3rd Department of Medicine, University of Athens, School of Medicine, "Sotiria" General Hospital, Mesogion 152, 115 27 Athens, Greece. E-mail: dimgrap@yahoo.gr.

2213-2198

© 2015 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2015.09.009>

REFERENCES

- Sanchez-Borges M, Thong B, Blanca M, Ensina LF, Gonzalez-Diaz S, Greenberger PA, et al. Hypersensitivity reactions to non beta-lactam antimicrobial agents, a statement of the WAO special committee on drug allergy. *World Allergy Organ J* 2013;6:18.
- Hildebrand KJ, Atkinson A, Kitai I. Rifampin hypersensitivity in a 2-year-old child with successful rapid oral desensitization. *Pediatr Infect Dis J* 2004;33:787.
- Holland CL, Malasky C, Ogunkoya A, Bielory L. Rapid oral desensitization to isoniazid and rifampin. *Chest* 1990;98:1518-9.
- Kim JH, Kim HB, Kim BS, Hong SJ. Rapid oral desensitization to isoniazid, rifampin, and ethambutol. *Allergy* 2003;58:540-1.
- Buerger S, Scherer K, Hausermann P, Bircher AJ. Immediate hypersensitivity to rifampicin in 3 patients: diagnostic procedures and induction of clinical tolerance. *Int Arch Allergy Immunol* 2006;140:20-6.
- Logsdon S, Ramirez-Avila L, Castells M, Dioun A. Successful rifampin desensitization in a pediatric patient with latent tuberculosis. *Pediatr Allergy Immunol* 2014;25:404-5.
- Broz P, Harr T, Hecking C, Grize L, Scherer K, Jaeger KA, et al. Nonirritant intradermal skin test concentrations of ciprofloxacin, clarithromycin, and rifampicin. *Allergy* 2012;67:647-52.
- Harland RW, Lindblom SS, Munnell MO. Anaphylaxis from rifampin. *Allergy* 1992;92:581-2.
- Dutau H, Saadjan M, Bonneau V, Charpin D. Unsuccessful rapid intravenous desensitization to rifampicin. *Allergy* 2000;55:778-9.
- Fenniche S, Maalej S, Hassene H, Belhabib D, Medgiche ML. Manifestations of rifampicin-induced hypersensitivity. *Presse Med* 2003;32:1167-9.
- Kobashi Y, Abe T, Shigeto E, Yano S, Kuraoka T, Oka M. Desensitization therapy for allergic reactions to antituberculous drugs. *Inter Med* 2010;49:2297-301.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.