

IgE-mediated reactions to rifaximin and rifamycin SV and cross-reactivity among rifamycins

L. Antonicelli*, C. Micucci, M. B. Bilò, M. Manfredi, M. Valentini, P. Campi

Key words: adverse drug reaction; cross-reactivity; IgE, rifamycin SV; rifamycins; rifaximin.

Rifamycin SV, rifampicin, rifabutin, rifapentine and rifaximin are semi-synthetic antibiotics, owing to the class of rifamycins.

To date, several kinds of immune-mediated reactions to rifamycins have been described, including fever, rash, the flu-like syndrome, acute renal failure, haemolytic anaemia, thrombocytopenia and anaphylactic

events (1). Serum-specific IgE has been described towards rifamycin SV and rifampicin (2) only.

Due to its very poor absorption in the gastrointestinal tract (<0.4% of the drug is absorbed after oral administration), rifaximin is widely used for the local treatment of intestinal infections.

To the best of our knowledge, IgE-mediated reactions to rifaximin have never been demonstrated.

A 64-year-old man was referred to our allergy unit some weeks after a severe anaphylactic reaction (cough, dyspnoea, convulsions, transient loss of consciousness) which occurred a few minutes

following the topical medication of a surgical wound using rifamycin SV solution (Rifocin®, Sanofi-Aventis, Milan, Italy). His history revealed an episode of generalized urticaria after removing stitches following a saphenectomy 4 years previously; but no information was available regarding the drug used for disinfection. Three months before the life-threatening episode, he suffered from severe abdominal pain, dyspnoea and urticaria, requiring emergency admission, about 10 min after taking one tablet of rifaximin (Normix®, Alfa Wassermann, Bologna, Italy), prescribed for his diverticulitis.

The aim of the study was to verify if the patient presented IgE-dependent reactions to rifamycin SV and rifaximin and if any cross-reaction between these molecules occurred. The patient gave informed consent for *in vitro* studies.

The patient refused the skin tests with the suspected drugs.

Serum-specific IgE against rifamycin SV, rifampicin, rifabutin, rifapentin and rifaximin was assayed by radioimmunoassay using epoxy-activated sepharose 6B as solid phase following the Baldo's method (3). The patient's serum was studied twice: in March 2007 (1 month after the anaphylactic reaction) and in February 2008 (1 year after the anaphylactic reaction induced by rifamycin SV).

An inhibition of IgE binding to rifampicin-sepharose complex was performed by preincubation of the patient's serum with rifaximin.

At the first assay, we detected serum IgE to rifamycin SV and rifampicin, but not to rifaximin; total IgE was 415 kU/l (Table 1). However, the presence of specific IgE to rifaximin was shown, because preincubation of serum with rifaximin almost completely inhibited (90%) the binding of IgE to the rifampicin-sepharose complex (Fig. 1). The two most probable explanations for this result are either that rifaximin is not able to bind to sepharose or, more probably, that it can bind to this solid phase, but only at the same level of the unique IgE-epitope: in

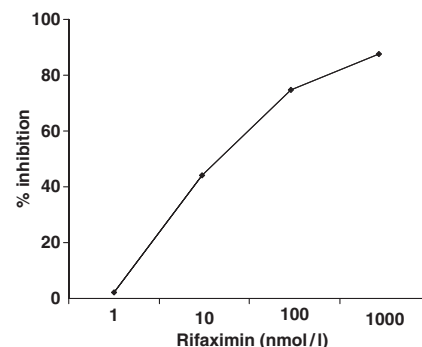


Figure 1. Percentage inhibition of IgE binding rifampicin-sepharose complex by rifaximin.

Table 1. Results of serum-specific IgE to rifamycins and total IgE assay

Drug	Percentage of bound radioactivity*			
	March 2007	Control serum	February 2008	Control serum
Rifamycin SV	13.38	0.81	7.40	0.66
Rifampicin	23.99	0.85	5.77	0.93
Rifaximin	0.90	0.42	N.D.	N.D.
Rifabutin	N.D.	N.D.	12.36	0.60
Rifapentin	N.D.	N.D.	6.32	0.83
Total IgE (kU/l)†	415		102	

*Positive values are those above two to three times the control serum (4).

†Normal values < 100 kU/l.

this case, the binding of IgE to the molecule would be hindered. We previously demonstrated similar behaviour from the molecule of cinoxacin towards the other quinolones (4). One year later, serum-specific IgE to rifampicin, rifabutin and rifapentin was still present; total IgE was 102 kU/l.

Our findings confirm previous reports showing IgE-mediated reactions to rifamycin SV (5); moreover, we demonstrated serum-specific IgE to rifaximin, by means of the inhibition test, and cross-reactivity among rifamycins.

The time course of the reactions could suggest that the scarce quantity of rifaximin absorbed, not only provoked the first, relatively mild systemic reaction, but could have induced a booster effect on the IgE synthesis to rifamycins (probably present since the first reaction, 4 years earlier), which enhanced the subsequent, very severe, reaction to rifamycin SV.

Indeed, the worsening onset of the allergic disease, due to the short time interval between two subsequent contacts with the same allergen has already been documented (6).

In conclusion, the presence of IgE-mediated cross-reactivity among rifamycins is a recommendation for the avoidance of rifaximin as well, despite its poor absorption.

The authors wish to thank Paul Bowerbank for his help in reviewing the English of the manuscript.

*SOD Allergologia
Ospedali Riuniti Ancona Via Conca – Torrette
Ancona 60126
Italy
Tel.: 39 071 596 5693
Fax: 39 071 596 3253
E-mail: l.antoniceilli@ao-umbertoprino.marche.it

Accepted for publication 28 December 2008
Allergy 2009
© 2009 John Wiley & Sons A/S
DOI: 10.1111/j.1398-9995.2009.02034.x

References

1. Martinez E, Collazos J, Mayo J. Hypersensitivity reactions to rifampin. Pathogenetic mechanisms, clinical manifestations, management strategies, and review of the anaphylactic-like reactions. *Medicine (Baltimore)* 1999;**78**:361–369.

2. Campi P, Manfredi M, Severino MG. IgE-mediated allergy to pyrazolones, quinolones and other non-beta-lactam antibiotics. In: Pichler WJ, editor. *Drug hypersensitivity*. Basel: Karger, 2007:216–232.
3. Baldo BA, Harle DG. Drug allergenic determinants. *Monogr Allergy* 1990;**28**: 11–51.
4. Manfredi M, Severino MG, Testi S, Macchia D, Ermini G, Pichler WJ et al. Detection of specific IgE to quinolones. *J Allergy Clin Immunol* 2004;**113**:155–160.
5. Ebo DG, Verheecke G, Bridts CH, Mertens CH, Stevens WJ. Perioperative anaphylaxis from locally applied rifamycin SV and latex. *Br J Anaesth* 2006;**96**:738–741.
6. Pucci S, Antoniceilli L, Bilò MB, Garritani MS, Bonifazi F. Shortness of interval between two stings as a risk factor for developing hymenoptera venom allergy. *Allergy* 1994;**49**:894–896.