

[prev](#) [abstract](#) [next](#)

Immune Tolerance to Drugs. I. Long-Term Tolerability of Rokitamycin in Patients with Antibiotics Hypersensitivity

Introduction

Patients and Methods

Results

Discussion

Acknowledgments

References

List of Tables

Immune Tolerance to Drugs. I. Long-Term Tolerability of Rokitamycin in Patients with Antibiotics Hypersensitivity

Authors: E. Netti^a; M. C. Colanardi^a; R. Di Paola^a; G. Mangialardi^a; A. Ferrannini^a; A. Tursi^a

Affiliation: ^a Department of Internal Medicine, Immunology and Infectious Diseases, Section of Allergy and Clinical Immunology, University of Bari, Bari, Italy

DOI: 10.1081/IPH-120024504

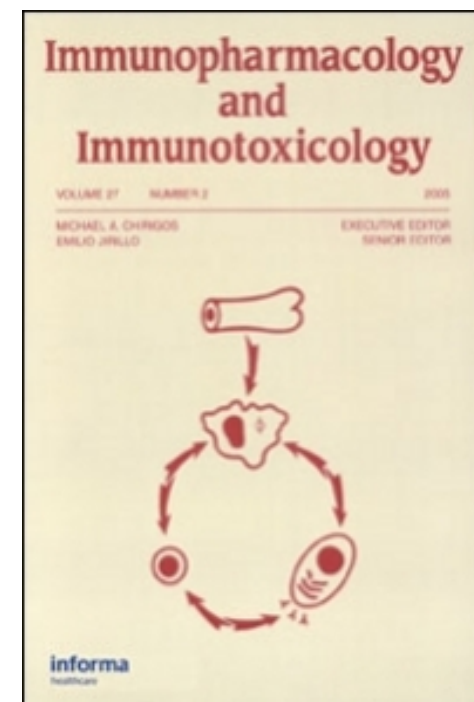
Publication Frequency: 4 issues per year

Published in:  Immunopharmacology and Immunotoxicology, Volume 25, Issue 3 October 2003 , pages 365 - 375

Abstract

Macrolides are considered one of the safest anti-infective groups in clinical use and are well-tolerated as alternative antibiotics in patients with a previous adverse reaction to other classes of antibiotics.

However there is scarce information in the literature about their long-term tolerability. The present study was performed to determine whether the results of a challenge test with rokitamycin could predict the response to ingestion of rokitamycin during illness. The study was carried out on 335 patients, who experienced adverse reactions to one or more antibiotics. All patients received peroral challenges with rokitamycin (granules or capsules). On the first day patients received a number of placebo doses equivalent to the rokitamycin doses. One week later, the test was administered by increasing doses of rokitamycin at 60 min intervals until the common daily therapeutic dose of 406.25 mg was reached



(31.25-93.75-125-156.25 mg). A questionnaire was distributed to all subjects. In particular, subjects were asked to clarify any reactive symptom they had developed after ingestion of the drug. It was found that only 3.1% (4/129) of subjects, who used this drug, reported adverse reactions: three experienced urticaria/angioedema and one patient experienced erythema multiforme during treatment. This study, points out a low percentage of adverse reactions to rokitamycin after a negative challenge test, thus, emphasizing both safety and good predictive value as a challenge test.

Keywords: Antibiotic hypersensitivity; Follow-up; Peroral challenge test; Rokitamycin

Abbreviations: FEV1, Forced expiratory volume in 1 second; MIC, Minimum inhibitory concentrations; LMA7, Leucomycin A 7; LMV, Leucomycin V; NSAIDs, Non steroidal anti-inflammatory drugs; ADR, Adverse drugs reactions

Introduction

Antibiotics are the most frequently prescribed drugs in medical practice and, therefore, are most often involved in adverse reactions.^[1]

The pathogenesis of these reactions is often unclear. However, there is convincing evidence of the involvement of an immunological mechanism, as reported following the use of β -lactams.^[2]

The most common approach in choosing the safest antibiotic agent for patients, who experienced a previous adverse reaction to antibiotics, is to perform a challenge test. This consists of the careful administration of the alternative agent.^{[3], [4]}

Priority of challenges was determined by both the antimicrobial spectrum of non-tolerated drug(s) and possible side effects of

In fact, macrolides are considered to be one of the safest anti-infective groups in clinical use with rare severe adverse reactions [5], [6] and are well-tolerated as alternative antibiotics in patients with a previous adverse reaction to other classes of antibiotics. [3], [4]

Macrolides are an old and well established class of antimicrobial agents that account from 10% to 15% of worldwide oral antibiotic market.[7] They derived from fungi of the genus *Streptomyces* and they are characterized by their basic structure made up of a lactonic cycle with two osidic chains. They are classified according to the number of carbo atoms in the cycle: 14 membered macrolides such as erythromycin, roxithromycin, and clarithromycin and 15-membered macrolides such as azithromycin and 16-membered macrolides such as spiramycin and josamycin.

Macrolides are bacteriostatic, that specifically bind to the site where tRNA transferase acts, thus inhibiting the transfer of the aminoacid to the forming protein. Therefore, macrolides inhibit bacterial protein synthesis.

A wide spectrum of macrolides activity includes *Gram-positive Cocci*, *Haemophilus influenzae*, *Gram-negative Cocci*, *Mycoplasma*, and *Chlamidia*. Macrolides are also effective in opportunistic infections associated with AIDS. In addition, the use of macrolide antibiotics has recently been extended to the treatment of *Helicobacter pylori* infection, which is a common cause of gastritis and peptic ulcer.[8], [9]

term macrolide treatment was recently found to be effective in subjects with chronic lower respiratory tract inflammation. It was reported that these drugs regulated functions of neutrophils and lymphocytes, reduced mucous secretion and modulated cytokine release from bronchial epithelial cells in humans.^[10] Thus, immunoregulatory effects of this class of drugs seem apparent. In addition, selected macrolide antibiotics have steroid-sparing effects in patients with steroid-dependent asthma: they inhibit methylprednisolone clearance displaying anti-inflammatory effects.^[11]

Among this class of antibacterial agents, rokitamycin is a new semi-synthetic macrolide with a 16-member ring. It is one of the most useful and effective macrolides for the treatment of upper and lower respiratory infections due to intracellular microorganisms, because it offers marked lipophilia and excellent intracellular penetration.^[12] It should be mentioned that rokitamycin has a more potent antibacterial activity: the binding affinity of ribosomes to it was about seven times greater than the one to erythromycin and rokitamycin. Rokitamycin also has a wider spectrum than other macrolides.^[13]

Rokitamycin could be an alternative in subjects with adverse reactions to other classes of antibiotics. However, there is no data available about the long term tolerability of rokitamycin.

The present paper provides follow-up data on patients with a history of adverse reactions to antibiotics and who were subjected to peroral challenge testing with rokitamycin.

Patients and Methods

The study was carried out from September 1992 to January 1997 on 335 patients (204 females; 131 males; mean age 36.9 ± 17.45 ; age 14-87) who referred to the Allergy Clinic of the University of Bari for well-documented adverse reactions to one or more antibiotics, diagnosed either by an allergologist and/or a dermatologist (**Table 1**). Adverse manifestations included urticaria/angioedema in 377 cases, anaphylactic shock in eight, erythema multiforme in six, exanthematous eruptions in five, and asthma with or without rhinitis in five cases.

Table 1. Antibiotics reported as a cause of adverse reactions in 335 subjects

Note: U/A, urticaria/angioedema.

a: β -Lactams + Clavunilic acid or Sulbactam.

Drug class	U/A	Asthma	Anaphylactic shock	Erythema multiforme	Exanthematosus eruptions	Total (%)
β -Lactams						
Penicillins	140	4	6	6	3	159 (39.6)
Combinations ^a	47					47 (11.7)
Cephalosporins	74		1			75 (18.7)
Monobactams	2					2 (0.5)
Quinolones	22					22 (5.5)
Sulphamides, trimethoprim, analogues	53		1		2	56 (14)
Tetracyclines	13					13 (3.2)
Aminoglycosides	11					11 (2.7)
Lincosamides	5	1				6 (1.5)
Rifamicins	3					3 (0.8)
Fosfomycin	3					3 (0.8)
Teicoplanin	2					2 (0.5)
Thiamphenicol	2					2 (0.5)

Total	377	5	8	6	5	401 (100)
-------	-----	---	---	---	---	-----------

Challenge Test

Between 1992 and 1995, all patients received peroral challenges with rokitamycin (granules or capsules) (Rokital, Formenti, Milan, Italy).

None presented significant cutaneous or respiratory tract symptoms at the time of testing, and pulmonary function test showed stable FEV1s that were >80% of predicted values in all cases. Antihistamines and other drugs had been discontinued seven or more days before challenges (4 weeks in the case of astemizole). Each test was performed over 2 days under single-blinded conditions.

On the first day patients received a number of placebo doses equivalent to the rokitamycin doses. One week later, the test was administered by increasing doses of rokitamycin at 60 min intervals until the common daily therapeutic dose of 406.25 mg was reached (31.25-93.75-125-156.25 mg); in each case, a higher dose was administered only when previous dose showed no response. In the peroral challenge test with granules, the placebo administered was saccharose diluted in water; in the peroral challenge test with capsules the placebo administered was talc in an inert capsule as vehicle.

Arterial blood pressure and FEV1 were monitored both during the observation period and at the end of the test. A positive reaction was defined as an appearance of urticaria/angioedema, cutaneous rash of any morphology, a $\geq 20\%$ decrease of FEV1, occurrence of nasal or ocular symptoms and hypotension (systolic blood pressure <90 mmHg). Informed written consent was

obtained from all subjects and resuscitation equipment was available at all times during the tests. All patients remained in the day hospital under medical supervision for 6 hours after each challenge and were then asked to come back or call the hospital between 24 and 48 hours thereafter, as to exclude delayed reactions.

Questionnaire

At the time of challenge tests a questionnaire was distributed to all tested subjects. It included questions about the ingestion of rokitamycin, the number of doses taken and concomitant therapies. In particular, subjects were asked to clarify any reactive symptoms that they had developed after ingestion of the drug, their type, intensity, time-relation with the drug ingestion and eventual concomitant therapy (**Table 2**).

Table 2. Questionnaire given to all patients who underwent tolerance testing

1. Have you taken rokitamycin after testing?	Yes	No
If no, why?		
If yes, which illnesses have you treated with rokitamycin?		
2. How many times have you intaken the drugs?		
3. Have you used any concomitant medications?	Yes	No
4. Have you had itching, redness, swelling or other cutaneous symptoms following ingestion of rokitamycin?	Yes	No
5. Have you experienced difficulty in breathing following ingestion of rokitamycin?	Yes	No
6. Have you experienced rhynorrea following ingestion of rokitamycin?	Yes	No
7. Have you experienced hypotension or loss of consciousness following ingestion of rokitamycin?	Yes	No
<i>If you have experienced at least one sign/symptom at points 4, 5, 6, 7</i>		
How many time after intaking rokitamycin?		
Has/have they/it appeared on the first day of treatment?	Yes	No
Have you had taken rokitamycin other times without any reactions?	Yes	No

Have you been examined by a physician?	Yes	No
Have you treated the reaction with antihistamine, corticosteroid, or epinephrine?	Yes	No
Have you taken other drugs, in addition to rokitamycin, when you experienced the reactions?	Yes	No

All patients were re-examined from 1995. At re-examination, they were carefully and personally interviewed by using the designed questionnaire previously distributed in order to assess information about intake of rokitamycin.

Results

All patients submitted to the tolerance test did not experience any reaction against placebo and against rokitamycin.

Answers to the questionnaire were obtained from 283 subjects, who had tolerated rokitamycin at the time of the challenge test (189 females and 94 males).

Out of those who responded, 154 (54.4%) did not use rokitamycin: in 94 cases ingestion of the drug was not necessary, while 60 subjects avoided using the drug because they were worried about possible adverse reactions.

We found that only 3.1% (4/129) of subjects, who used this drug, reported adverse reactions always diagnosed by a specialist. All four patients produced well-documented data from medical reports. The remaining 125 patients, who did not experience adverse reactions to rokitamycin, took the drug 0.5-42 months after the test. All patients had taken rokitamycin in capsules.

Patient 1

A 27-year-old woman with a history of seasonal rhinoconjunctivitis was prescribed rokitamycin for acute sinusitis. She had

undergone a challenge test with rokitamycin, because she experienced two episodes of adverse drug reactions following β -lactams administration.

She underwent oral chemotherapy 24 months after testing. Within 30 min after intake of the first single dose on the first day of treatment, generalized urticaria appeared. The lesions resolved within a few hours following antihistamine administration.

Patient 2

A 41-year-old woman suffering from asthma. This patient underwent a challenge test with rokitamycin, because she experienced one episode of adverse drug reactions following β -lactams administration.

She was prescribed rokitamycin for pharyngitis 28 months after the challenge test. About 20 min after oral intake of the first dose on the first day of treatment, the patient developed lip oedema, pruritic and urticarial lesions on the trunk, and extremities. After treatment with antihistamines and corticosteroids, symptoms subsided within a few hours.

Patient 3

A 37-year-old woman with a history of seasonal rhinoconjunctivitis. This patient underwent a challenge test with rokitamycin, because she experienced an episode of adverse drug reactions following β lactams administration. She took rokitamycin once after the test and tolerated the drug. Fifteen months after the oral challenge her dentist prescribed for the second time rokitamycin orally as a treatment for oral abscess.

About 20 min after taking the first dose of rokitamycin on the first day of treatment, she experienced facial pruritus, facial swelling and a sensation of tightening in her throat. She immediately began taking antihistamines and corticosteroids and swelling and other symptoms resolved within a few hours.

Patient 4

A 38-year-old man, without a personal history of atopy. This patient submitted a challenge test with rokitamycin, because he experienced one episode of adverse drug reaction with cotrimoxazole.

Twenty-eight months after the challenge test, for the first time his general practitioner prescribed rokitamycin orally as treatment for a respiratory infection.

Seven days later, he developed symmetrical erythematous lesions. The rash was located on palms and soles, dorsum of the hands and extensor surfaces of extremities. Pruritus was absent, but patient felt burning sensation in affected areas. The lesions evolved into classic target lesions, with bright red borders and central petechia. He stopped the rokitamycin immediately and was examined by a dermatologist, who diagnosed “erythema multiforme minor.” Patient began taking cortisone and was cured in 2 weeks, however post inflammatory hyperpigmentation remained. At the time of the adverse reaction, the patient 4 did not have Herpes simplex infection.

All patients denied any concomitant medication use together with rokitamycin.

Discussion

Rokitamycin is marketed in Italy and Japan (Ricamycin), where it is indicated in the treatment of:

- Pharyngitis, tonsillitis, chest infections (bronchitis, pneumonitis).
- Otitis and sinusitis.
- Odontostomatological infections.
- Skin and soft tissue infection.

Rokitamycin has good activity against Gram positive organisms, such as *Streptococci* and *Staphilococci* and Gram negative bacteria such as *H. influenzae*, *B. pertussis*, *N. gonorrhoeae*, and against *Ureaplasma*, *Chlamydia* and *M. Pneumoniae*.[\[14\]](#)

In addition it is effective against *Helicobacter pilory* and *Borrelia burgdoferi*.[\[8\]](#), [\[9\]](#), [\[15\]](#)

Rokitamycin for adults is supplied in capsules and powder form (400 mg). To fight most infections, the dose for adults is 400 mg each day for 8 days and it should be taken on an empty stomach. Unlike other macrolides that tend to be absorbed only when gastric juice is acidic, rokitamycin is adsorbed even when gastric juice is hypoacidic or anacidic.[\[16\]](#) Thus, it is considered to be a suitable antibiotic for the treatment of infectious respiratory disease in the elderly whose gastric juice is often hypoacidic.

Rokitamycin is rapidly adsorbed and reaches C max in 30-60 min. The concentration of antibacterial action is near to minimum inhibitory concentrations (MICs). Rokitamycin is rapidly metabolised into leucomycin A7 (LMA 7), leucomycin V (LMV), 10"-OH-rokitamycin, and 14-OH-rokitamycin. LMV and LMA 7 are considered to be the major metabolites of rokitamycin in humans, their

formation is mediated via human liver esterase and they were reported to possess some antibacterial activity.[17] Unlike other macrolides, limited drug-rokitamycin interaction studies reported that rokitamycin did not significantly alter the pharmacokinetics of theophylline.[18]

In vivo plasma protein binding rate of rokitamycin is about 70%,[19] however its rat hepatic tissue concentration is 10-fold greater than that in plasma,[20] as rokitamycin is a lipophilic drug. The hepatic metabolism of rokitamycin is reduced in patients with hepatic impairment so that dose adjustments necessary have to be made.

The half-life elimination of rokitamycin is about 2 hours in humans and renal elimination is about 1-2% while most of it undergoes a hepatic elimination. The side effect of rokitamycin mostly affects the digestive system. They include diarrhea, nausea, and pain in the abdomen. In very few patients have been reported alterations of hepatic functionality index.

Our follow up revealed long-term tolerance to rokitamycin in 96.9% of the patients, who had used this drug after the challenge test. Almost all reactions (3/4) consisted of urticarial eruptions. In the remaining case, the patient experienced erythema multiforme. The mechanism of the adverse reactions is not determined even if hypersensitivity to macrolides is extremely rare (0.4-0.3% of treatments).[21], [22]

Unfortunately, there are still no data available on hypersensitivity related to rokitamycin and only a few cases of urticaria related to the ingestion of this drug are reported in literature though the pathogenesis remains unknown.[23]

Most hypersensitivity reactions related to macrolides regard erythromycin and spiramycin. Macrolides elicit a full range of reactions from urticaria, angioedema and anaphylaxis to contact eczema, macula-papulous eruption, vasculitis and fixed drug eruptions. However, there are also some cases of occupational asthma due to exposition to spiramycin. Mechanism of reactions in some cases with erythromycin was shown as IgE-dependent,[24] but often it remains unknown. Generally patients reported adverse reactions to a single macrolide. There is only one report about cross-reaction between different macrolides chemically closely related.[25]

In this study, some lines of evidence seem to evoke an immune pathogenesis:

1. Even if uncertain, in the pathogenesis of erythema multiforme certain histopathologic features suggest an immune mechanism; in particular, reactions may be type III and type IV;[26], [27] however, since the patient claimed not to have the Herpes simplex infection, which is one of the most frequent causes of erythema multiforme, it is difficult, on the bases of the patient's history, to determine whether the rokitamycin or the infection treated with rokitamycin was responsible for the disease.
2. Urticaria and angioedema observed in this study could be IgE-mediated. The 1st and 2nd patient were sensitized during the challenge test, while the 3rd patient could have been sensitized during the test or before therapeutic administration of rokitamycin.
3. All subjects, who experienced urticaria and angioedema, were atopic and, because atopy represents a genetic predisposition to develop specific IgE and allergic diseases, these adverse reactions to rokitamycin might be IgE-mediated. Previous studies[28], [29] reported that atopy represents a risk factor for antibacterial drug intolerance and, in particular, for reactivity against alternative NSAIDs (non steroideal anti-inflammatory drugs).[30], [31] Further discussion on this observation is not possible due to the small sample size (4 subjects) of the study. We can suppose, furthermore, that a history of personal atopy could predispose patients to certain clinical manifestations of intolerance. In fact, all atopic subjects experienced urticaria and/or angioedema related to the ingestion of rokitamycin.
4. Reactions to a few classes of drugs are more commonly caused by immune mechanisms. In contrast, cases of adverse reactions to multiple classes of drugs are more likely to reflect a non immunological mechanism. Patients, who experienced adverse drugs reactions (ADR) to rokitamycin, were unable to tolerate only one antibiotic or one class of antibiotics before challenge. This implies that reactions to rokitamycin could be immune-mediated, probably because of a weak suppression of the immune response to haptens.
5. IgE-mediated reactions are more common among patients allergic to β -lactams.[32] All patients examined in this study, who experienced urticaria or angioedema after rokitamycin intake, had a history of ADR to one β -lactam agent.

However, if we consider the features of rokitamycin, we can assume that adverse reactions reported in this study are not immune-mediated, because rokitamycin is rapidly metabolised and its metabolites have a short half life and therefore are possibly not recognized by the immune system and not capable of stimulating the formation of antibodies.

This study, which points out a low percentage of adverse reactions to rokitamycin after a negative challenge test, reveals the safety and a good long-term tolerability of this drug when it is taken by patients in multiple doses, during illness and without close physician's supervision. In addition, since only 3.1% of those, who well-tolerated rokitamycin in challenge test, experienced adverse reactions when multiple doses were taken, we could highlight that the challenge test, which is designed for routine use in clinical settings, proved to be rapid, safe and reasonably reliable as well as having a high predictive value. However, further investigations are required to determine pathophysiological mechanisms causing adverse reactions to rokitamycin and appropriate diagnostic tests. This drug is most likely an incomplete antigen and would need to combine with autologous host proteins to become immunogenic. Until now, there were no cases in literature of specific IgE detected to rokitamycin, because the antigenic determinants are not known.

Acknowledgments

The authors thank Dr. G. Strippoli, Mrs Luigina Di Terlizzi, and Dana Damon, Svmservice S.p.A, for their expert cooperation. The study was partly funded by a grant from the “Regione Puglia.”

References

- 45040001. Lode, H. and Stahlmann, R. (1990) Evaluation of safety and tolerance in clinical trials with antimicrobials agent. *Eur. J. Clin. Microbiol. Infect. Dis.* 9 , pp. 530-533. [[crossref](#)] [[pubmed](#)]
- 45040002. Shepherd, G. M. (1991) Allergy to β -lactams antibiotics. *Immunol. Allergy Clin. North Am.* 11 , p. 611.
- 45040003. Asero, R. (1998) Detection of patients with multiple drug allergy syndrome by elective tolerance test. *Ann. Allergy Asthma Immunol.* 80 , pp. 185-189. [[pubmed](#)]
- 45040004. Nettis, E., Colanardi, M. C., Paola, R. Di, Ferrannini, A. and Tursi, A. (2001) **Tolerance test in patients with multiple drug allergy syndrome.** *Immunopharmacol. Immunotoxicol.* 23 , pp. 617-626. [informaworld]
- 45040005. Naldi, L., Conforti, A., Venegoni, M., Troncon, M. G., Caputi, A., Ghiotto, E., Cocci, A., Moretti, U., Velo, G. and Leone, R. (1999) Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *Br. J. Clin. Pharmacol.* 48 , pp. 839-846. [[crossref](#)] [[pubmed](#)]
- 45040006. Van der Linden, P. D., van der Lei, J., Vlug, A. E. and Stricker, B. H. (1998) Skin reactions to antibacterial agents in general practice. *J. Clin. Epidemiol.* 51 , pp. 703-708. [[pubmed](#)] [[crossref](#)]
- 45040007. Periti, P., Mazzei, T., Mini, E. and Novelli, A. (1993) Adverse effects of macrolide antibacterials. *Drug Saf.* 9 , pp. 346-364. [[pubmed](#)]
- 45040008. Walsh, J. H. and Peterson, W. L. (1995) The treatment of *Helicobacter pylori* infection in the management of peptic ulcer disease. *N. Engl. J. Med.* 333 , pp. 984-991. [[pubmed](#)] [[crossref](#)]
- 45040009. Peterson, J. G. and McColl, K. E.L. (1997) Eradication of *Helicobacter pylori*: an objective assessment of current therapies. *Br. J. Clin. Pharmacol.* 43 , pp. 223-243. [[pubmed](#)]
- 45040010. Jaffe, A. and Bush, A. (2001) Anti-inflammatory effects of macrolides in lung disease. *Pediatr. Pulmonol.* 31 , pp. 464-273. [[pubmed](#)] [[crossref](#)]
- 45040011. Spahn, J. D., Fost, D. A., Covar, R., Martin, R. J., Brown, E. E., Szeffler, S. J. and Leung, D. Y. (2001) Clarithromycin potentiates glucocorticoid responsiveness in patients with asthma: results of a pilot study. *Ann. Allergy Asthma Immunol.* 87 , pp. 501-505. [[pubmed](#)]
- 45040012. Yu, K. W., Briones, F., Chin, N. X. and Neu, H. C. (1991) Antibacterial activity of rokitamycin compared with that of other macrolides. *Diagn. Microbiol. Infect. Dis.* 14 , pp. 331-335. [[pubmed](#)] [[crossref](#)]
- 45040013. Bryskier, A. and Labro, M. T. (1994) Macrolides. New therapeutic prospects. *Presse Med.* 23 , pp. 1762-1766. [[pubmed](#)]
- 45040014. Morohoshi, T., Tanini, T. and Nishino, T. (1984) Bacteriological evaluation of a new macrolide antibiotic TMS-19-19-Q (3-O-propionyl-leucomycin A5). *Chemotherapy* 32 , pp. 12-25.

- 45040015. Cinco, M., Padovan, D., Stinco, G. and Trevisan, G. (1995) In vitro activity of rokitamycin, a new macrolide, against *Borrelia burgdoferi*. *Antimicrob. Agents Chemoter.* 39 , pp. 1185-1186.
- 45040016. Morishita, M., Suzuki, T., Sakai, A., Endo, S., Watanabe, M., Nagata, A. and Ishioka, T. (1984) Studies on absorption, metabolism and excretion of TMS-19-Q in humans. *J. Chemother.* 32 , pp. 99-115.
- 45040017. Goto, S., Tsuji, A., Ogawa, M., Yokoyama, S., Sagai, H., Toriya, M., Morohoshi, T. and Hayano, K. (1984) Bacteriological evaluations of the metabolites of TMS-19-Q, a new macrolide antibiotic. *J. Chemother.* 32 , pp. 37-45.
- 45040018. Cazzola, M., Matera, M. G., Paterno, E., Scaglione, F., Santangelo, G. and Rossi, F. (1991) Impact of rokitamycin, a new 16-membered macrolide, on serum theophylline. *J. Chemother.* 3 , pp. 240-244. [[pubmed](#)]
- 45040019. Morishita, M., Suzuki, T. and Hayano, K. (1987) The in vivo pharmacokinetics of rokitamycin: a new macrolide antibiotic. *Chemother. Field* 3 , pp. 381-390.
- 45040020. Morishita, M., Ohno, M., Serizawa, K., Fujiwara, T. and Sakakibara, H. (1984) Isolation and identification of metabolites of TMS-19-Q. *J. Chemother.* 32 , pp. 85-92.
- 45040021. Slater, J. E. (1991) Hypersensitivity to macrolide antibiotics. *Ann. Allergy* 66 , pp. 193-195. [[pubmed](#)]
- 45040022. Demoly, P., Benahmed, S., Valembois, H., Sahla, H., Messaad, D., Goodard, P. H., Michel, F. B. and Bousquet, J. (2000) L'allergie aux macrolides. Revue de la littérature. *Press. Med.* 29 , pp. 321-326. [[pubmed](#)]
- 45040023. Kawauchi, K., Sato, Y., Kimura, S., Yonesaka, S., Yokoyama, M., Onishi, A., Asuka, T., Okamoto, T., Takebe, Y. and Tsushima, T. (1998) Clinical results of a rokitamycin dry syrup in pediatric infections. *J.P.N. J. Antibiot.* 41 , pp. 673-685.
- 45040024. Gallardo, M. A. and Thomas, I. (1999) Hypersensitivity reaction to erythromycin. *Cutis* 64 , pp. 374-376.
- 45040025. Kruppa, A., Scharffetter-Kochanek, K., Krieg, T. and Hunzelmann, N. (1998) Immediate reaction to roxithromycin and prick test cross-sensitization to erythromycin and clarithromycin. *Dermatology* 196 , pp. 335-336. [[pubmed](#)] [[csa](#)] [[crossref](#)]
- 45040026. Tonnesen, M. G., Harrist, T. J., Wintroub, B. V., Mihm Jr., M. C. and Soter, N. A. (1983) Erythema multiforme: microvascular damage and infiltration of lymphocytes and basophils. *J. Invest. Dermatol.* 80 , pp. 282-286. [[csa](#)] [[pubmed](#)]
- 45040027. Correia, O., Delgado, L., Ramos, J. P., Resende, C. and Torrinha, J. A. (1993) Cutaneous T-cell recruitment in toxic epidermal necrolysis: further evidence of CD8+ lymphocyte involvement. *Arch. Dermatol.* 129 , pp. 466-468. [[pubmed](#)]
- 45040028. Smith, J. W., Johnson, J. E. and Cuff, L. E. (1966) Studies on the epidemiology of adverse drug reactions. An evaluation of penicillin allergy. *N. Eng. J. Med.* 274 , pp. 998-1002. [[pubmed](#)]

- 45040029. Riario-Sforza, G., Zara, C. and Incorvaia, C. (1996) Atopy as a risk factor in drug allergy: a prospective study [abstract]. *Allergy* 51 , p. 74.
- 45040030. Pastorello, E. A., Zara, C., Riario-Sforza, G., Pravettoni, V. and Incorvaia, C. (1998) Atopy and intolerance of antimicrobial drugs increase the risk of reactions to acetaminophen and nimesulide in patients allergic to nonsteroidal anti-inflammatory. *Allergy* 53 , pp. 880-884. [[pubmed](#)]
- 45040031. Quiralte, J., Blanco, C., Castillo, R., Delgado, J. and Carrillo, T. (1996) Intolerance to nonsteroidal antiinflammatory drugs: results of controlled drug challenges in 98 patients. *J. Allergy Clin. Immunol.* 98 , pp. 678-685. [[crossref](#)] [[pubmed](#)]
- 45040032. Sullivan, T. J., Ong, R. C. and Gilliam, L. K. (1989) Studies of the multiple drug allergy syndrome. [abstract]. *J. Allergy Clin. Immunol.* 83 , p. 270. [[crossref](#)]

List of Tables

Table 1. Antibiotics reported as a cause of adverse reactions in 335 subjects

Note: U/A, urticaria/angioedema.

a: &b.beta;-Lactams + Clavunilic acid or Sulbactam.

Drug class	U/A	Asthma	Anaphylactic shock	Erythema multiforme	Exanthematosus eruptions	Total (%)
&b.beta;-Lactams						
Penicillins	140	4	6	6	3	159 (39.6)
Combinations ^a	47					47 (11.7)
Cephalosporins	74		1			75 (18.7)
Monobactams	2					2 (0.5)
Quinolones	22					22 (5.5)
Sulphamides, trimethoprim, analogues	53		1		2	56 (14)
Tetracyclines	13					13 (3.2)
Aminoglycosides	11					11 (2.7)
Lincosamides	5	1				6 (1.5)
Rifamicins	3					3 (0.8)
Fosfomycin	3					3 (0.8)

Teicoplanin	2					2 (0.5)
Thiamphenicol	2					2 (0.5)
Total	377	5	8	6	5	401 (100)

Table 2. Questionnaire given to all patients who underwent tolerance testing

1. Have you taken rokitamycin after testing?	Yes	No
If no, why?		
If yes, which illnesses have you treated with rokitamycin?		
2. How many times have you intaken the drugs?		
3. Have you used any concomitant medications?	Yes	No
4. Have you had itching, redness, swelling or other cutaneous symptoms following ingestion of rokitamycin?	Yes	No
5. Have you experienced difficulty in breathing following ingestion of rokitamycin?	Yes	No
6. Have you experienced rhynorrhea following ingestion of rokitamycin?	Yes	No
7. Have you experienced hypotension or loss of consciousness following ingestion of rokitamycin?	Yes	No
<i>If you have experienced at least one sign/symptom at points 4, 5, 6, 7</i>		
How many time after intaking rokitamycin?		
Has/have they/it appeared on the first day of treatment?	Yes	No
Have you had taken rokitamycin other times without any reactions?	Yes	No
Have you been examined by a physician?	Yes	No
Have you treated the reaction with antihistamine, corticosteroid, or epinephrine?	Yes	No
Have you taken other drugs, in addition to rokitamycin, when you experienced the reactions?	Yes	No

[Privacy Policy](#) | [Terms & Conditions](#) | [Accessibility](#) | [RSS](#)

FAQs in: [English](#) . [Français](#) . [Español](#) .

© 2009 Informa plc