

Airborne Allergic Contact Dermatitis From Tylosin in Pharmacy Compounders and Cross-Sensitization to Macrolide Antibiotics

Viba Malaiyandi, MD, Marie Claude Houle, MD, FRCPC, and Sandy Skotnicki-Grant, MD, FRCPC

Tylosin is a broad-spectrum macrolide antibiotic that is restricted to veterinary use. Allergic contact dermatitis (ACD) caused by tylosin has been reported in the literature from the farming industry and veterinary medicine. It is also reported as the most common antibiotic to cause ACD in the previously mentioned occupational settings. We present 2 cases of airborne ACD from tylosin among veterinary pharmaceutical compounding technicians. To our knowledge, only one other case of patch test–confirmed tylosin ACD has been reported in the manufacturing setting. Based on our results, cross-sensitization to other clinically relevant macrolides does not appear to be a concern. Our cases highlight the importance of patch testing among pharmaceutical compounders where the incidence of an airborne contact may be greater, given that the exposure is to the powdered form of potential allergens.

ALLERGIC CONTACT DERMATITIS (ACD) to antibiotics is a well-documented adverse effect whether in the context of treatment or occupational exposure.¹ In the occupational setting, health care workers, veterinary surgeons, and employees of pharmaceutical companies are particularly at increased risk for developing ACD, with an overall prevalence of 40%.² Among healthcare workers and employees of pharmaceutical companies penicillins, cephalosporins, and aminoglycosides are most commonly implicated in occupational ACD^{2,3}; however, among veterinary surgeons and farmers, it is tylosin,² a macrolide antibiotic restricted to veterinary use.

Macrolides are a class of broad-spectrum antibiotics used to treat cutaneous and respiratory tract infections. Clinically important macrolides include azithromycin, clarithromycin, erythromycin, and spiramycin. Azithromycin, clarithromycin, and erythromycin are commonly encountered in clinical practice, whereas spiramycin is used in Europe and Canada to treat more rare infections such as toxoplasmosis. Tylosin also belongs to this class of antibiotics, but its use is restricted to veterinary medicine. Its indications include the treatment of swine dysentery and respiratory infections in poultry, and it is often mixed in animals' feed or water.

Allergy-mediated adverse drug reactions to macrolide antibiotics in the therapeutic context are 0.4% to 3%.⁴ However, there have been reported cases to systemically and topically administered macrolides, and these include anaphylaxis, angioedema, Stevens-Johnson syndrome, urticaria, fixed drug reaction, and ACD.

Similarly, occupational ACD to macrolide antibiotics is also rare. In the pharmaceutical and manufacturing industries, cases of ACD to azithromycin^{5–7} and 1 case to tylosin⁸ have been reported. Tylosin ACD has been more commonly described in the farming industry^{9–13} and among veterinary surgeons.^{14,15} In the pharmaceutical and manufacturing settings, all the reported cases have been an airborne ACD; there is 1 reported case of airborne ACD to tylosin in an animal feed worker.¹¹

Airborne contact dermatitis, whether irritant or allergic, is not uncommon in the occupational setting. Potential irritants/allergens, whether vapors, gases, droplets, or solid particles, are present in the atmosphere and then settle on exposed skin. The clinical picture of airborne dermatitis is consistent with areas of unprotected skin being affected. The dermatitis is usually symmetric in distribution and involves the face, eyelids, scalp, top of the ears, V of the neck, outer arms, and legs.

We present 2 cases of airborne ACD from tylosin, briefly review the literature on ACD from clinically and occupationally important macrolide antibiotics, and discuss whether cross-sensitization is a concern.

CASE REPORTS

Case 1

A 50-year-old woman was referred to our clinic with a history of facial dermatitis for 1½ years. She was otherwise completely well and

From the Department of Occupational and Environmental Health, St Michael's Hospital, Toronto, Ontario, Canada.

Address reprint requests to Sandy Skotnicki-Grant, MD, FRCPC, Occupational Health Clinic, St Michael's Hospital, Shuter Wing, 4th Floor, 30 Bond St, Toronto, Ontario, Canada. E-mail: sandyskotnicki@baydermatologycentre.com.

The patients were seen through the Ontario Disability Support program, which is funded by the Workplace Safety and Insurance Board.

The authors have no conflicts to declare.

DOI: 10.1097/DER.0b013e318262cadb

© 2012 by the American Contact Dermatitis Society. All Rights Reserved.

had no history of atopic diatheses. She had been working in a veterinary pharmacy as a compounding technician. Her primary duty involved compounding powdered medications with a mortar and pestle to form a paste. Her symptoms, which started as mild itching on the eyelids and temples, began 1½ years after starting this position and progressed slowly overtime. She developed a classic textbook case of airborne contact dermatitis with lichenified and crusted dermatitis over the cheeks, eyelids, forehead, central chest, upper back, ears, and outer forearms (Fig. 1). The anterior portion of the neck and submandibular regions were spared. This was a result of her looking down while compounding the drugs, resulting in these areas being protected from the aerosolized particles. Based on the patient's occupational history and after reviewing the MSDS (material safety data sheets), tylosin tartrate and clindamycin were identified as likely potential allergens.

She was patch tested to the North American Standard and tylosin tartrate 5% in petroleum (pet) (St Michael's Hospital inpatient pharmacy, Toronto, Ontario, Canada), clindamycin HCl 0.1% and 0.5% in aqueous (aq), and clindamycin phosphate 1% in aq (Pharmacy.ca, Toronto, Ontario, Canada) as suggested in the literature.^{9–11} Given that the distribution of her dermatitis strongly suggested an airborne contact, she was also tested to penicillins (Pharmacy.ca), as this class of antibiotic is known to cause airborne contact dermatitis.⁴ In addition, to assess for cross-sensitivity, she was patch tested to all clinically important macrolide antibiotics: spiramycin 5% pet, azithromycin 5% pet, erythromycin 5% pet, and clarithromycin 10% pet (St Michael's Hospital inpatient pharmacy). The concentrations and vehicles of these were determined from the literature^{16,17}

She had a very strongly positive reaction to tylosin at both 48- and 120-hour readings and had a questionable reaction to 1% clindamycin HCl (Fig. 2). Her patch test results (case 1) are shown in Table 1.

She attempted to use protective measures but was not able to tolerate the skin irritation resulting from these. She began to ex-



Figure 1. Lichenified eczema on the cheeks, eyelids, ears, forehead, and central chest. Note that the anterior portion of the neck and submandibular regions are spared. Permission to publish photographs was obtained with signed informed consent.

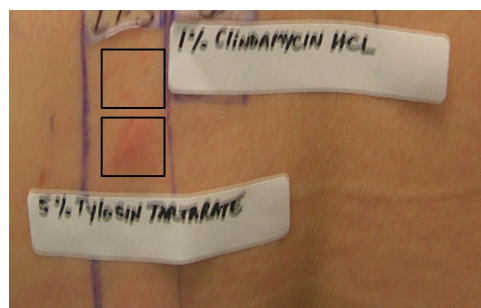


Figure 2. Patch test results at 120 hours are shown for our first patient (case 1).

perience facial pruritus even when coworkers were counting tylosin capsules at a distance of 5 ft. The sensitivity was so strong that she could identify, based on her symptoms, when her coworkers were handling tylosin. As a result of the severity of her sensitivity, she could no longer work in the facility; her symptoms completely resolved once the exposure to tylosin ceased.

Case 2

We subsequently identified another compounding technician from the same company, a 37-year-old woman, who was also referred for facial dermatitis. She did not have a personal or family history of atopy. The nature of her work and her exposure were identical to that in the first case described previously, only differing in the time of exposure to tylosin. Her symptoms began 6 months after starting the position, and similarly, the distribution of the dermatitis was consistent with an airborne contact, but in this case, it was less severe. Patch testing was conducted identically to that in our first patient. This patient (case 2) tested positive only to tylosin (Table 1). Fortunately, in this case, the dermatitis resolved once protective measures were taken.

RESULTS

There was no cross-reactivity to clinically important macrolide antibiotics in either of our patients (Table 1). Patch tests with

TABLE 1. Patch Test Result

Allergen	Concentration	Case 1		Case 2	
		48 h	120 h	48 h	120 h
Tylosin tartrate powder	5% pet	2+	2+	–	+
Clindamycin HCl	1% aq	–	+/-	–	–
Clindamycin HCl	0.5% aq	–	–	–	–
Clindamycin phosphate	0.1% aq	–	–	–	–
Penicillin G	10,000 U/g pet	–	–	–	–
Penicillin VK	10,000 U/g pet	–	–	–	–
Spiramycin	5% pet	–	–	–	–
Azithromycin	5% pet	–	–	–	–
Erythromycin	5% pet	–	–	–	–
Clarithromycin	10% pet	–	–	–	–
North American Standard		–	–	–	–

tylosin tartrate in 5% pet in 5 healthy controls, with no occupational exposure to tylosin, were negative at both 48 and 120 hours.

DISCUSSION

Allergic contact dermatitis from tylosin has been reported in the literature among farmers, animal feed workers,^{9–13} and veterinary surgeons.^{2,14,15} A case series of 5 workers, from the same manufacturing company with facial dermatitis, strongly suggestive of an airborne exposure, has also been reported.⁸ However, patch testing confirming an allergy to tylosin was performed only on 1 of the workers in this series. We confirmed tylosin ACD in both of our cases, and the occupational history and clinical presentations were clearly consistent with an airborne exposure. To our knowledge, the case mentioned previously⁸ is the only other patch test–confirmed report of tylosin airborne ACD in the manufacturing setting.

Further confirming that the etiology was due to an allergy, we observed a relationship between the length of exposure and degree of sensitivity. In our first patient, the exposure time to tylosin was 1½ years before an occupational allergy was suspected to be the cause of her symptoms and precautionary measures were initiated. In our second patient, the time between initial exposure and the onset of symptoms was 6 months, and precautions were implemented sooner. Our first patient was highly sensitized to tylosin, with symptoms occurring at a distance of 5 ft from the drug. She could not work in the same environment because of the severity of her sensitivity, whereas our second patient was able to continue to work with appropriate protective measures. These findings on history correlated nicely with our patch test results (Table 1) in that our first patient (case 1) showed a strongly positive reaction even at

48 hours, and our second patient (case 2) showed a weakly positive reaction only at 120 hours. These cases highlight the importance of recognizing the distribution of an airborne dermatitis, the possibility of an allergic etiology, and the importance of patch testing.

Although allergic reactions to systemically administered macrolide antibiotics are rare, cases have been reported.⁴ Similarly, the literature suggests that ACD to topical macrolide antibiotics is also rare. Bernstein and Roenigk¹⁸ reviewed 27,655 surgical cases in which erythromycin 2% pet ointment was used postoperatively for wound care. They reported a sensitization rate of 0.022% (6/27 [655 cases]; patch testing methods and results were not reported). Although few in number, case reports of patch test–confirmed sensitization to erythromycin ointment used for the treatment of acne,¹⁹ venous leg ulcers,²⁰ rosacea,²¹ and erythrasma²² have been described. One case of ACD to azithromycin eye drops, used for wound care after ocular surgery, has also been reported,¹⁷ and reports of fixed drug eruption following systemic administration of clarithromycin have been described.^{23–25} To our knowledge, there are no reports of allergic reactions to spiramycin when used therapeutically.

In the clinical setting, evaluation for cross-sensitization within the macrolide class of antibiotics by patch testing has not been consistently performed. In the few cases where it has been done,^{23,24} cross-sensitization does not appear to be a concern. In cases of ACD to tylosin from occupational exposure, cross-sensitivity to spiramycin has been suggested,^{12,14} but this has not been described in all cases.^{10,11,13}

Given the level of the sensitivity to tylosin in our first patient and the potential for further airborne exposure to various drugs in pharmaceutical compounding, we tested for cross-sensitization to

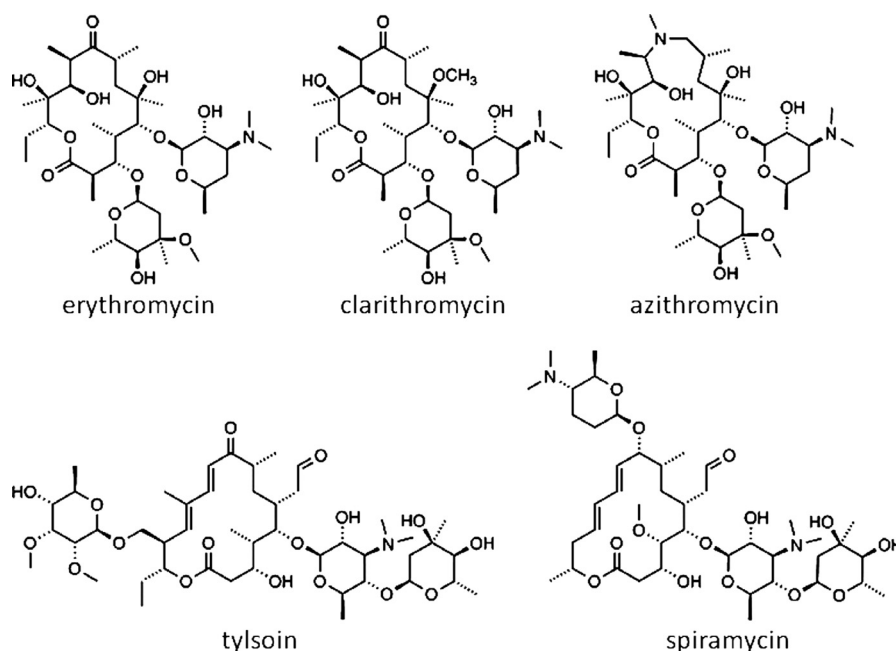


Figure 3. Chemical structures of 14-, 15-, and 16-member-lactone-ring macrolide antibiotics are shown. Image modified from McCoy et al²⁷ and permission obtained from John Wiley and Sons for reproduction.

clinically important macrolide antibiotics in both of our patients. However, patch testing to azithromycin, clarithromycin, erythromycin, and spiramycin did not show cross-reactivity in our tylosin-sensitized patients (Table 1).

Tylosin is a macrolide antibiotic and is produced by fermentation of *Streptomyces* strains. Similar to other macrolide antibiotics, it is characterized by a lactone ring and 2 glycosidic side chains.²⁶ Macrolide antibiotics are further classified based on the size of the lactone ring. Erythromycin and clarithromycin have 14-member rings, whereas azithromycin has a 15-member ring. Tylosin and spiramycin both have 16-member lactone rings and are structurally most similar (Fig. 3).²⁷ It is plausible that tylosin and spiramycin may show cross-reactivity, but the data from the initial studies suggesting cross-sensitivity show that the majority of patients were exposed to both tylosin and spiramycin,¹² and the possibility of contamination while handling both drugs could not be excluded.¹⁴ Subsequent studies did not find cross-reactivity between tylosin and spiramycin.^{10,11,13} Our results were consistent with these studies and did not show cross-reactivity between tylosin and spiramycin or other clinically relevant macrolides.

In summary, we confirmed 2 cases of patch test–positive airborne contact dermatitis from tylosin in the manufacturing industry among pharmaceutical compounders. In both of these cases, patch test results strongly support an airborne ACD caused by tylosin, and symptoms resolved once the exposure ceased or protective measures were implemented. Based on our results, there is no concern for cross-sensitization with clinically important macrolide antibiotics. Our cases highlight the importance of recognizing the pattern of airborne exposure and patch testing in the manufacturing industry, where there may be a greater incidence of airborne contact dermatitis.

REFERENCES

- Gehrig KA, Warshaw EM. Allergic contact dermatitis to topical antibiotics: epidemiology, responsible allergens and management. *J Am Acad Dermatol* 2008;58:1–21.
- Rudzki E, Rebendel P. Contact sensitivity to antibiotics. *Contact Dermatitis* 1984;11:41–42.
- Gielen K, Goossens A. Occupational allergic contact dermatitis from drugs in healthcare workers. *Contact Dermatitis* 2001;45:273–279.
- Demoly P, Benahmed S, Valembois M. Allergy to macrolide antibiotics. Review of the literature. *Presse Med* 2000;29:321–326.
- Milkovic-Kraus S, Macan J, Kanceljak-Macan B. Occupational allergic contact dermatitis from azithromycin in pharmaceutical workers: a case series. *Contact Dermatitis* 2007;56:99–102.
- Lopez-Lerma I, Romaguera C, Vilaplana J. Occupational airborne contact dermatitis from azithromycin. *Clin Exp Dermatol* 2009;34:e358–e359.
- Mimesh S, Pratt M. Occupational allergic airborne contact dermatitis from azithromycin. *Contact Dermatitis* 2004;51:148–158.
- Verbov J. Tylosin dermatitis. *Contact Dermatitis* 1983;9:325–326.
- Tuomi M, Rasanen L. Contact allergy to tylosin and cobalt in a pig farmer. *Contact Dermatitis* 1995;33:285.
- Danese P, Zanca A, Bertazzoni M. Occupational contact dermatitis from tylosin. *Contact Dermatitis* 1994;30:122–123.
- Barbera E, de la Cuadra J. Occupational airborne allergic contact dermatitis from tylosin. *Contact Dermatitis* 1989;20:308–309.
- Veien N, Hattel T, Justesen O, et al. Occupational contact dermatitis due to spiramycin and/or tylosin among farmers. *Contact Dermatitis* 1980;6:410–413.
- Caraffini S, Assalve D, Stingeni L, et al. Tylosin, an airborne contact allergen in veterinarians. *Contact Dermatitis* 1994;31:327–328.
- Hjorth N, Weismann K. Occupational dermatitis among veterinary surgeons caused by spiramycin, tylosin and penethamate. *Acta Dermatovenerol* 1973;53:229–232.
- Hjorth N, Roed-Petersen J. Allergic contact dermatitis in veterinary surgeons. *Contact Dermatitis* 1980;6:27–29.
- de Groot AC. *Patch Testing: Test Concentrations and Vehicles for 3700 Chemicals*. Amsterdam: Elsevier; 1994.
- Flavia Monteagudo Paz A, Slavador JFS, Martinez NL, et al. Allergic contact dermatitis caused by erythromycin in an eye drop. *Contact Dermatitis* 2011;64:289–302.
- Bernstein SC, Roenigk RK. Surgical pearl: erythromycin ointment for topical antibiotic wound care. *J Am Acad Dermatol* 1995;32:659–660.
- Martins C, Freitas JD, Goncalo M, et al. Allergic contact dermatitis from erythromycin. *Contact Dermatitis* 1995;33:360.
- Lombardi P, Campolmo P, Spallanzani P, et al. Delayed hypersensitivity to erythromycin. *Contact Dermatitis* 1982;8:416.
- Valsecchi R, Pansera B, Reseghetti A. Contact allergy to erythromycin. *Contact Dermatitis* 1996;34:428.
- Redondo VF, Casas L, Taboada M, et al. Systemic contact dermatitis from erythromycin. *Contact Dermatitis* 1994;30:43–44.
- Martinez Alonso JC, Callejo Melgosa A, Fuentes Gonzalo MJ, et al. Fixed drug eruption on the tongue due to clarithromycin. *Contact Dermatitis* 2005;53:121–122.
- Rosina P, Chieragato C, Schena D. Fixed drug eruption from clarithromycin. *Contact Dermatitis* 1998;38:105.
- Hamamoto Y, Ohmura A, Kinoshita E, et al. Fixed drug eruption due to clarithromycin. *Contact Dermatitis* 2001;26:48–49.
- Haltz R, Seno E, Stonesifer J, et al. Biosynthesis of the macrolide antibiotic tylosin. *J Antibiot* 1983;36(2):131–141.
- McCoy LS, Xie Y, Tor Y. Antibiotics that target protein synthesis. *WIREs RNA* 2011;2:209–232.