Atatürk Üniversitesi Vet. Bil. Derg.
2018; 13(1): 92-97

Case Report/Olgu Sunumu
DOI:10.17094/ataunivbd.297133

Atatürk Üniversitesi Veteriner Bilimleri Dergisi
http://dergipark.gov.tr/ataunivbd

Postmastectomy Life-threatening Hypersensitivity Reactions Induced by Rifamycin SV in Companion Animals: Evaluation of 7 Cases

Hatice Esra ÇOLAKOĞLU[1]✉, İbrahim Mert POLAT[2], Murat Onur YAZLIK[1], Ekrem Çağatay ÇOLAKOĞLU[3]

1. University of Ankara, Faculty of Veterinary Medicine, Department of Obstetrics and Gynecology, Ankara, TURKEY.
2. University of Kırıkkale, Faculty of Veterinary Medicine, Department of Obstetrics and Gynecology, Kırıkkale, TURKEY.
3. University of Ankara, Faculty of Veterinary Medicine, Department of Internal Medicine, Ankara, TURKEY.

Geliş Tarihi/Received	Kabul Tarihi/Accepted	Yayın Tarihi/Published
10.03.2017	08.11.2017	25.04.2018

Bu makaleye atıfta bulunmak için/To cite this article:
Çolakoğlu HE, Polat İM, Yazlık MO, Çolakoğlu EÇ: Postmastectomy Life-threatening Hypersensitivity Reactions Induced by Rifamycin SV in Companion Animals: Evaluation of 7 Cases. *Atatürk University J. Vet. Sci.*, 13 (1): 92-97, 2018. DOI: 10.17094/ataunivbd.297133

Abstract: Drug-induced hypersensitivity and adverse symptoms related to the high mortality remain as a major problem for veterinary practitioners. Although application of Rifamycin SV without intradermal susceptibility tests have been commonly used in wound management in veterinary medicine, there is no literature about this subject. In cases presented here, neoplastic masses on the mammary glands of queens (n=3) and bitches (n=4) were removed by mastectomy. Subcutaneous Rifamycin SV was performed intra- and post-operatively. After the multiple subcutaneous usage of Rifamycin SV, acute symptoms including hypersensitivity reactions such as facial and sublingual swelling, hypersalivation, respiratory distress, tachycardia, acute vomiting, erythema and itchiness around the face, seizures and ataxia developed. In conclusion, although Rifamycin SV provides better healing effects on incision line, veterinary practitioners should consider the serious side effects of subcutaneous Rifamycin SV usage after gynaecological surgeries in companion animals.

Keywords: Bitch, Gynaecological surgery, Hypersensitivity, Queen, Rifamycin SV.

Evcil Hayvanlarda Operasyon Sonrası Rifamisin Nedenli Hayati Hipersensitivite Reaksiyonları: 7 Olgunun Değerlendirilmesi

Öz: İlaç nedenli hipersensitivite ve yüksek mortalite ile ilişkili yan etkiler veteriner hekimler için halen büyük bir sorun teşkil etmektedir. Her ne kadar veteriner pratikte intradermal duyarlılık testi olmaksızın yara sağaltımında Rifamisin SV uygulaması yaygın şekilde kullanılsa da konuyla ilgili literatür veri bulunmamaktadır. Sunulan olgularda, kedi (n=3) ve köpeklerin (n=4) meme bezlerinde bulunan neoplastik kitleler mastektomi operasyonu ile uzaklaştırıldı. Rifamisin SV'nin subkutanöz uygulaması intra ve post operatif olarak yapıldı. Rifamisin SV'nin multipl subkutanöz kullanımı sonrasında yüz ve dil altında ödem, hipersalivasyon, solunum güçlüğü, taşikardi, akut kusma, yüzde eritem ve kaşıntı, nöbet ve ataksi gibi hipersensitivite reaksiyonlarını içeren akut semptomlar gelişti. Sonuç olarak her ne kadar Rifamisin SV, insizyon hattında daha iyi iyileştirici etki sağlasa da veteriner hekimler özellikle jinekolojik operasyonlar sonrası topikal Rifamisin SV kullanımının şiddetli yan etkilerine karşı dikkatli olmalıdırlar.

Anahtar Kelimeler: Hipersensitivite, Jinekolojik operasyon, Kedi, Köpek, Rifamisin SV.

✉Hatice Esra ÇOLAKOĞLU
University of Ankara, Faculty of Veterinary Medicine, Department of Obstetrics and Gynecology, Ankara, TURKEY.
e-mail: canatan@ankara.edu.tr
Preliminary version of this report with two cases was presented at the 17th FECAVA Eurocongress, 7-10 September 2011, Istanbul/TURKEY

INTRODUCTION

Local antimicrobial agents with saline irrigation to prevent wound infection in humans have been used widely after the major or minor surgical procedures (1). Although saline irrigation has an ability to remove the debris and foreign material on surgical wounds, it could not provide the sufficient elimination of bacterial contamination. Therefore, local antibiotics have been instilled directly into the wounds or used in the irrigation solutions in human medicine (2). In humans, many local antibiotics have been reported to prevent the surgical wound infections (1-3). Beneficial effects of Rifamycin SV in variable doses have also been reported in humans (4-6). Subcutaneous usage of Rifamycin SV without intradermal sensitization tests has been applied widely in wound management (5-7). Despite the common use of Rifamycin SV, few reports of Rifamycin SV-induced hypersensitivity reactions have been reported in medical literatures (3,8). There is no information about the subcutaneous application of Rifamycin SV in veterinary literature. The purpose of the cases presented here is (1) to demonstrate the usage of Rifamycin SV as an antimicrobial agent throughout the incision line for veterinary practitioners and (2) Rifamycin SV-induced hypersensivity reactions after mastectomy.

CASE REPORT

Four domestic queens and three mixed breed bitches with the history of perforated neoplastic masses on mammary glands were referred to Veterinary Teaching Hospital. Historical information and physical examination findings of all cases are listed in Table 1. Samples for complete blood count were collected from cephalic vein into the tubes with EDTA. Routine preoperative blood analysis in all cases revealed any abnormalities (Table 2). However, the radiographic examinations in all cases revealed no metastasis in the thorax and abdomen. After the preoperative examinations and diagnostic applications, a bilateral or unilateral mastectomy operation with or without ovariohysterectomy was performed under the general anaesthesia in all cases. Atropine sulphate (0.02 mg/kg sc) was administered for premedication. General anaesthesia was induced with propofol (4 mg/kg, IV) and maintained with Isoflurane delivered in 100% oxygen. Two curved incisions in the skin and subcutaneous tissue were performed from the first to the fifth mammary glands and then the mammary chain was removed from the abdominal wall. Rifamycin SV (250 mg/3 ml ampoule) was used (one ampoule) in all cases for prophylaxis before the closure of subcutaneous tissue throughout the incision line (5,6). All cases were postoperatively initiated the following medications: routine fluid therapy (5 % dextrose and 0.9 % sodium chloride solution for two days), amoxicillin-clavulanic acid (25 mg/kg, PO, q12h, for seven days), carprofen (4 mg/kg, IV, once) and famotidine (0.5 mg/kg, IV, once). Wound care (including wound flushing with saline) and periodic bandage changes were performed every other day. The application of subcutaneous Rifamycin SV (250 mg/3 ml ampoule) throughout the incision line was performed in each postoperative control. No reactions were initially observed in this process. After the multiple applications, acute symptoms including hypersensitivity reactions such as facial and sublingual swelling (Figure 1), hypersalivation, respiratory distress, tachycardia, acute vomiting, erythema and itchiness around the face (Figure 2), seizures and ataxia developed. All cases were immediately treated with epinephrine (0.01-0.02 mg/kg, IV, single dose), dexamethasone (1 mg/kg, IV, single dose), mepyramine maleate (1 mg/kg, IM, single dose) and routine fluid therapy (0.9% sodium chloride solution, shock dose 90 ml/kg for dogs and 45-60 ml/kg for cats with monitorization of heart and respiratory rate). Supplemental oxygen was also provided. Clinical signs and recovery times of the acute symptoms following treatment were listed in Table 3. Complete blood counts and peripheral blood smears were also obtained in some cases when the acute symptoms were stabilized (Table 4). However, severe eosinophilia was identified on smears indicating the immune reaction to Rifamycin SV. No recurrence in systemic reactions during the following 4 weeks after therapy. Sutures were removed on days 10-14 postoperatively without any complications with wound healing in all cases.

Table 1. Historical information and pyhsical examination findings in cases.
Tablo 1. Olguların anamnez bilgileri ve fiziksel muayene bulguları.

	Breed	Age	Intact/ Neutered	Localization of Mammary Tumors	Physical Appearance of Mammary Tumors	Physical Examinations and History	**Surgery**
Case 1	Persian Cat	9	Neutered	Bilaterally localised masses on both mammary chain	Ulceration-related bleeding of the masses	Anorexia, abdominal pain and ınability to exercise, body temperature: 39.8°c, HR: 190 bpm	Bilateral mastectomy
Case 2	Pitbull Terrier Bitch	7.5	Neutered	Bilaterally localised masses on both mammary chain	Ulcerative masses	Anorexia, vomiting, local pain, lethargy, mucosal pallor, body temperature: 40.1°C, HR: 172 bpm	Bilateral mastectomy
Case 3	Short Hair Cat	11	Intact	Unilaterally localised masses on left mammary chain	Warm, firm and ulcerative masses	Anorexia, mucosal pallor, dehydration, weight loss, body temperature: 37.8°C, HR: 201 bpm	Unilateral mastectomy and ovariohysterectomy
Case 4	Anatolian Shepherd Bitch	10	Intact	Bilaterally localised masses on both mammary chain	Firm, skin-covered masses	Anorexia, local pain, inability to exercise body temperature: 39.9°C, HR: 120 bpm	Bilateral mastectomy and ovariohysterectomy
Case 5	Angora Cat	9.5	Intact	Bilaterally localised masses on both mammary chain	Attached to underlying tissues, ulcerative masses	Anorexia, hypothermia, vomiting, icterus, abdominal pain, body temperature: 37.4°C, HR: 110 bpm	Bilateral mastectomy and ovariohysterectomy
Case 6	Short Hair Cat	12	Intact	Unilaterally localised mass on right mammary chain	Firm and skin-covered mass, moveable	Local pain, body temperature: 38°C, HR: 210 bpm	Unilateral mastectomy and ovariohysterectomy
Case 7	Mix Breed Bitch	13	Neutered	Unilaterally localised mass on left mammary chain	Firm and ulcerative mass	Local pain, body temperature: 38.1°C, HR: 95 bpm	Unilateral mastectomy and ovariohysterectomy

Table 2. Preoperative blood analysis of cases.
Tablo 2. Olguların operasyon öncesi kan analizleri.

	WBC (10^9/l)	LYM (10^9/l)	MONO (10^9/l)	NEUT (10^9/l)	EOS (10^9/l)	RBC (10^{12}/l)	HGB (g/dl)	HCT %	PLT (10^9/l)	UREA (mg/dl)	CRE (mg/dl)	ALP (IU/L)	ALT (IU/L)	AST (IU/L)	GLU (mg/dl)	ALB (g/dl)
Case 1	5.3	2.6	0.4	2.0	0.3	9.20	15.4	39.4	180	56.9	1.71	24.7	272.5	56.7	80	3.2
Case 2	7.4	1	0.2	5.9	0.3	5.43	13.3	38.5	424	65.1	1.4	36.6	81.2	24.2	107.9	3.4
Case 3	44.4	1.9	2.3	38.3	1.9	4.28	7.2	22.4	546	48	0.9	20	45.5	46.7	100.7	3.1
Case 4	14.1	1.8	0.6	10.6	1.1	6.69	17.3	42.6	332	45.3	0.82	149.1	63	20.3	81.9	3.3
Case 5	4.8	0.9	0.3	3.1	0.5	5	8.1	24	270	118	2.3	210	140	45	90	3.1
Case 6	10.5	1	0.3	8.7	0.5	8.50	13.7	33.7	218	77.7	1.63	25.2	40.7	36.9	191.7	2.7
Case 7	7.9	0.8	0.3	6.6	0.2	6.55	14.8	36	435	34.3	0.75	193.9	29.5	39.3	85	2.8
References-Cat	5.5-19.5	1.5-7	0-0.9	2.5-12.5	0-0.8	5-10	8-15	30-45	300-800	15-64.2	0.8-2	<200	<80	<80	75-160	2.1-3.4
References-Dog	5-14.1	0.4-52.9	0.1-1.4	2.9-12	0-1.3	5-7.9	12-18	37-55	211-621	15-59.9	1-2	<200	<100	<90	60-120	2.5-3.5

WBC: White blood cell, LYM: Lymphocyte, MONO: Monocyte, NEUT: Neutrophil, EOS: Eosinophil, RBC: Red blood cell, HGB: Hemoglobin, HCT: Hematocrit, PLT: Platelet, CRE: Creatinin, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GLU: Glucose, ALB: Albumin.

Table 3. Clinical signs associated with hypersensitivity reactions in cases.
Tablo 3. Olgulardaki hipersensitivite reaksiyonlarına ilişkin klinik bulgular.

	Reaction Times	Hypersensitivite Reactions-Clinical Sings	Recovery Times of the Acute Symptoms Following Treatment
Case 1	Within 5 min. following the 3rd subcutaneous tissue irrigation	Facial swelling, hypersalivation, respiratory distress, tachycardia, acute vomiting, seizures, ataxia, hyperthermia	Within 5 hours
Case 2	Within 10 min. following the 4th subcutaneous tissue irrigation	Facial swelling, erythema, hypersalivation, tachycardia	Within 5 hours
Case 3	Within 10 min. following the 3rd subcutaneous tissue irrigation	Facial swelling, pale gums, hypersalivation, tachycardia	Within 5 hours
Case 4	Within 10 min. following the 3rd subcutaneous tissue irrigation	Facial swelling, hypersalivation, hyperthermia	Within 5 hours
Case 5	Within 10 min. following the 4th subcutaneous tissue irrigation	Hypersalivation, tachycardia, seizures, hyperthermia, acute vomiting, involuntary urination and defecation, hyperemia and pruritus around the face	All sypmtoms excluding pruritus healed within 2 days. Pruritus healed within 3 days
Case 6	Within 10 min. following the 2nd subcutaneous tissue irrigation	Erythema around the face, hypersalivation, tachycardia	Within 3 hours
Case 7	Within 5 min. following the 3rd subcutaneous tissue irrigation	Hypersalivation, tachycardia, erythema	Within 3 hours

Table 4. Complete blood count profiles in cases following the recovery of the symptoms.
Tablo 4. Semptomların iyileşmesini takiben olguların tam kan profilleri.

	WBC (10^9/l)	LYM (10^9/l)	MONO (10^9/l)	NEUT (10^9/l)	EOS (10^9/l)	RBC (10^{12}/l)	HGB (g/dl)	HCT %	MCV (fl)	MCH (pg)	MCHC (g/dl)	**RDW (%)**	**PLT (10^9/l)**
Case 1	7.00	1.1	0.8	3.9	1.2	7.56	12.0	35.47	47	15.9	33.8	18.7	644
Case 2	11.7	4.3	0.4	5.1	1.9	4.92	12.5	37.2	61.3	21.4	31.2	13.81	553
Case 3	-	-	-	-	-	-	-	-	-	-	-	-	-
Case 4	-	-	-	-	-	-	-	-	-	-	-	-	-
Case 5	7.4	1.2	0.5	3.4	2.3	7.2	8.5	23.8	42.2	14.4	33.5	15.2	564
Case 6	-	-	-	-	-	-	-	-	-	-	-	-	-
Case 7	10.5	1.1	0.6	5.1	3.7	7.2	13.4	40.1	66.3	20.1	35.6	15.4	505
References-Cat[9,21]	5.5-19.5	1.5-7	0-0.9	2.5-12.5	0-0.8	5-10	8-15	30-45	39-55	13-17	30-36	14-18.5	300-800
References-Dog[9,21]	5-14.1	0.4-52.9	0.1-1.4	2.9-12	0-1.3	5-7.9	12-18	37-55	66-77	21-26.2	32-36.3	12-17.5	211-621

WBC: White blood cell, LYM: Lymphocyte, MONO: Monocyte, NEUT: Neutrophil, EOS: Eosinophil, RBC: Red blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, PLT: Platelet.

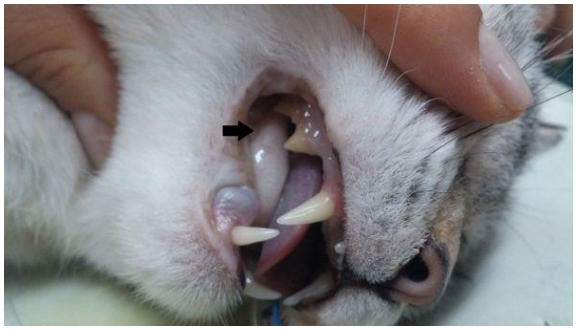

Figure 1. Facial and sublingual swelling in the cat (arrow).
Şekil 1. Bir kedide yüz ve dil altında oluşan ödem (ok).

Figure 2. Severe facial swelling and erythema in the dog (arrow).
Şekil 2. Bir köpekte yüzde şiddetli ödem ve eritem (ok).

DISCUSSION and CONCLUSION

Diagnosis and management of immune reactions remain challenging in veterinary practice. Obtaining a detailed history and to recognize the immune hypersensitivity reactions are crucial for evaluation of the cases. Drug-induced hypersensitivity reactions are common in veterinary medicine, but their relative prevalence is still unknown (9,10). Few reports of Rifamycin SV-induced hypersensitivity reactions have been described in human literature (3,8). Although topical or subcutaneous Rifamycin SV has been commonly used in wound management without intradermal susceptibility tests in veterinary medicine, no report is available to usage of Rifamycin SV in wound management after gynaecological surgeries. The purpose of the cases presented here is to demonstrate the usage of Rifamycin SV as an antimicrobial agent throughout the incision line for veterinary practitioners and Rifamycin SV-induced hypersensivity reactions after mastectomy.

Rifamycin has been used as an agent for open and closed wounds in humans. It has a large bactericidal spectrum on gram-positive and gram-negative microorganisms. The local action of Rifamycin SV has been furthered with the slow resorption rate depending on vascularization, contact surface, volume and frequency of administration (3). It has been reported that local usage of Rifamycin SV is well tolerated and does not induce the bacterial resistance (3,5). In addition, the healing rate in the usage of Rifamycin SV has been considered significantly higher compared to other forms of local antisepsis (5). The cases presented here closely reflects a usage of Rifamycin SV as an agent in humans. Subcutaneous application of Rifamycin SV was successfully used throughout the incision line for wound care in the cases presented here. To the best of authors' knowledge, the cases presented here were the first reports of Rifamycin SV usage on incision line in veterinary medicine. However, Rifamycin SV-induced hypersensivity reactions after mastectomy were also consistent with the reports previously described in human medical literatures (3,5,8).

Life threatening side effects of Rifamycin SV in various doses may be associated with gastrointestinal (nausea, vomiting, abdominal pain), neurological (seizures, ataxia, restlessness) and dermatological (facial swelling) symptoms. The potential adverse symptoms such as acute hemolytic anaemia, eosinophilia, bleeding tendency, renal failure, staining of body fluids, hyperthermia, hyperemia, conjunctivitis, and arthralgia have been reported in the usage of Rifamycin SV (3). In the cases presented here, similar hypersensitivity reactions such as swelling, hypersalivation, respiratory distress, tachycardia, acute vomiting, erythema, seizures and ataxia occurred after the applications of multiple doses of Rifamycin SV. All symptoms occurred within minutes following the application of second or fourth dose. Thus, we suggested the

reactions as type I hypersensitivities in the cases presented here (11). Voie *et al*. (12) and Hildebrand *et al.* (13) have also reported the signs of hypersensitivities following the antigen exposure. The signs in these cases were also consistent with the report previously described by Hildebrand et al (13).

In conclusion, although Rifamycin SV significantly provides better healing effects on incision line, veterinary practitioners should consider the serious side effects of subcutaneous usage of Rifamycin SV after gynaecological surgeries in companion animals.

REFERENCES

1. Falagas ME., Vergidis PI., 2005. Irrigation with antibiotic-containing solutions for the prevention and treatment of infections. Clin Microbio Infect, 11, 862-867.
2. Maurice-Williams RS., Pollock J., 1999. Topical antibiotics in neurosurgery: a re-evaluation of the Malis technique. Br J Neurosurg, 13, 312-315.
3. Cardot E., Tillie-Leblond I., Jeannin P., Facon A., Breuil K., Patte F., Tonnel AB., 1995. Anaphylactic reaction to local administration of Rifamycin SV. J Allergy Clin Immunol, 95, 1-7.
4. Saydam IM., Yilmaz S., Seven E., 2005. The influence of topically applied Nitrofurazone and Rifamycin on full-thickness wound healing. Cumhuriyet Medical J, 27, 113-120.
5. Kosus A., Kosus N., Guler A., Capar M., 2010. Rifamycin SV application to subcutaneous tissue for prevention of post-cesarean surgical site infection. Eur J Gen Med, 7, 269-276.
6. Aygun F., Kuzgun A., Ulucan S., Keser A., Akpek M., Kaya MG., 2014. The protective effect of topical rifamycin treatment against sternal wound infection in diabetic patients undergoing on-pump coronary artery bypass graft surgery. Cardiovasc J Afr, 25, 96-99.
7. Benfer J., Struck H., 1976. The effect of Rifamycin SV on the wound-healing process. Arzneimittelforschung, 26, 1361-1364.
8. Ebo DG., Verheecke G., Bridts CH., Mertens CH., Stevens WJ., 2006. Perioperative anaphylaxis from locally applied Rifamycin SV and latex. Br J Anaesth, 9, 738-741.
9. Dyer F., Diesel G., Cooles S., Trait A., 2009. Suspected adverse reactions, 2009. Vet Rec, 67, 118-121.
10. Shmuel DL., Cortes Y., 2013. Anaphylaxis in dogs and cats. J Vet Emerg Crit Care, 23, 377-394.
11. Mirsaeidi M., Schraufnagel D., 2014. Rifampin induced angioedema: a rare but serious side effect. Braz J Infect Dis, 18, 102-103.
12. Voie KL., Campbell KL., Lavergne SN., 2012. Drug hypersensitivity reactions targeting the skin in dogs and cats. J Vet Intern Med, 26, 863-874.
13. Hildebrand KJ., Atkinson A., Kitai I., 2014. Rifampin hypersensitivity in a 2-year-old child with successful rapid oral desensitization. Pediatr Infect Dis J, 33, 787.