Advances in Pharmacology and Therapeutics Journal
Shahid Sadoughi University of Medical Sciences, Yazd, Iran

SHAHID SADOUGHI UNIVERSITY OF MEDICAL SCIENCES

Case Report

Mupirocin–Induced Allergic Contact Dermatitis: A Case Report and a Review of the Literature

Running Title: Mupirocin–Induced Allergic Contact Dermatitis

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ARTICLEINFO

Received: 11/19/2023
Accepted: 12/05/2023

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Abstract

Background: Mupirocin, an antibiotic, is frequently used to treat special traumatic infected skin lesions, such as impetigo, methicillin-resistant Staphylococcus aureus (MRSA), burn, scratch after operation, etc. Topical use of mupirocin can lead to some adverse drug reactions (ADR).

Objectives: To report a case of mupirocin-induced contact dermatitis and a review of the literature to identify the causative factors and clinical characteristics.

Methods: We report a case of contact dermatitis in a 39-year-old woman which happened 2 days after mupirocin ointment application on her hand. Also, a review of the literature was done according to PRISMA guidelines. PubMed, Scopus, Web of Science, and Google Scholar were searched. Time or language filters were not used and all related reports were included.

Results: In the mentioned case, mupirocin has a causative role in dermatitis. The review showed 10 cases of mupirocin-induced allergy. The clinical presentations included serum sickness, diffuse urticaria, fever, arthralgias, toxic epidermal necrolysis, pruritus, rash, breathlessness, palpitations, flushing, redness all over the body, low blood pressure, severe allergic contact dermatitis, pruritic papular eruption, extensive contact dermatitis, allergic contact hypersensitivities. All cases were improved after anti-allergic treatments except one who had been tracheostomy and was in serious condition.

Conclusions: this is the first review of mupirocin-induced allergy. Although these incidences are rare, clinicians should be aware to prevent severe reactions with serious consequences.

Keywords: Mupirocin; Contact Dermatitis; Adverse Drug Reaction; Allergy

Citation: Dara T, Zabihi M. Mupirocin–Induced Allergic Contact Dermatitis: A Case Report and a Review of the Literature. Adv Pharmacol Ther J. 2023;3(3): 123-134.

Case Report

A 39-year-old woman was referred to the Center of Registration and Investigation of Adverse Drug Reaction (ADR); with a burn-like extending left hand **(Figure 1)**. She said that she washed clothes with her hands and used washing machine powder, one week ago. After four days, she felt dryness, itching, and irritation in her hands. She said that she did not have any history of allergies or asthma and did not take any medicine. For treatment, she had seen a doctor, and the physician prescribed Clobetasol cream and Mupirocin ointment to apply topically twice a day. For some reason, she did not use clobetasol and only used mupirocin on her left hand. Two days after drug usage, her left hand started to swell and blister. All five fingers, thenar and hypothenar eminence, and areas around them were swelled up like balloons so that her weird rings became extremely tight on her fingers. Only the central part of the palm was not swollen. Her hand developed swelling, itching, pain, burning, and blistering. Due to continuing symptoms, she saw a dermatologist, who prescribed Dexamethasone ampoule, 2 intramuscularly daily for six days; Loratadine tablet once a night for pruritus; and acetaminophen tablet for pain relief. She was followed as an outpatient. Fortunately, at follow-up 10 days later, the affected hand was healed and there was no infection or changes in pigmentation. The patient was instructed to use moisturizing cream on the affected areas. The sequelae were observed until one month later and gradually disappeared. However, the patient was advised not to re-use that washing powder and mupirocin ointment; a month later, she was re-exposed to that detergent because of forgetfulness, but the allergic reaction did not occur. Given this incident, and that the sensitivity only occurred on the left hand that was rubbed with the ointment it can be possible that mupirocin has a causative role in the dermatitis.

This report emphasizes the need to consider the possibility of adverse drug reactions due to topical mupirocin, however, is not critical but potentially affects the quality of a patient's life.

Background

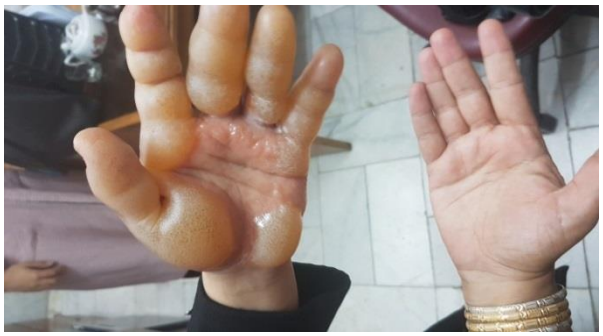
Mupirocin is a topical antimicrobial drug, which has good effects on staphylococcal and streptococcal infections. There are FDA-approved formulations including topical cream and ointment as well as a nasal ointment. The mechanism of mupirocin action is reversible binding to isoleucyl-transfer RNA synthetase to suppress the bacterial protein and RNA production in the sites of application. Mupirocin is used topically, but currently, it is not possible to use it systemically because it hydrolyzes quickly. Although, resistance to this drug is reported worldwide; it is still prescribed for the prevention and treatment of most cases of skin infection such as a variety of wounds, lesions, furuncle, and impetigo. Besides, the application of this ointment on wounds provides a sterile and moist covering that is beneficial for optimum healing (1-3). Mupirocin may be used in other situations. For example, in psoriasis, though it is not a standard treatment; it is used in the conditions of colonization of bacteria. In addition, recently it was found that epidermal isoleucyl-tRNA synthetase (IARS) has an essential role in

DOI: https://doi.org/10.18502/aptj.v3i3.14416

psoriasis inflammation, which could be inhibited by mupirocin (4).

Adverse Drug Reactions of mupirocin have been reported in some cases after topical administration. However, it is said that less than 3% of mupirocin users have experienced temporary skin symptoms such as burning and pain, and fortunately, systemic side effects are rare (1). This article describes a new case report **(Figure 1)** followed by a review to explore and summarize the literature to provide a useful standpoint for clinicians and pharmacists about mupirocin-induced adverse drug reactions.

Figure 1: picture of mupirocin-induced contact dermatitis



Methods

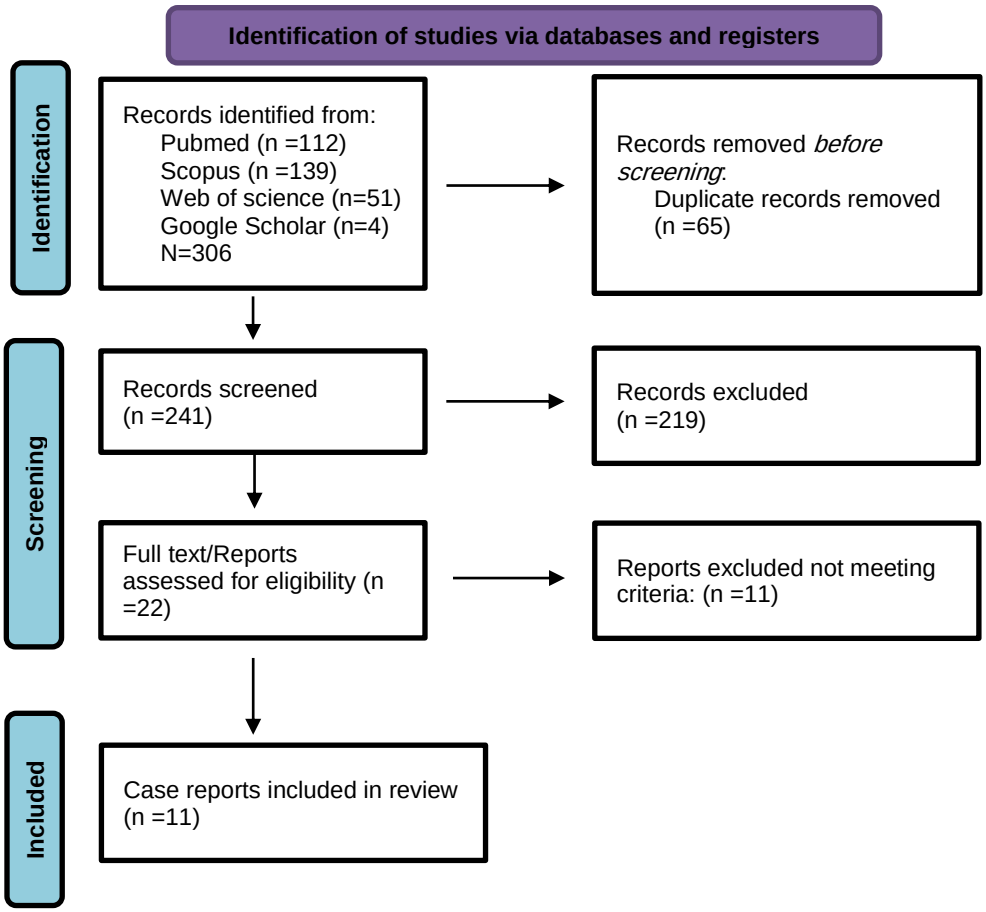
This is a case report which is following the CARE guidelines (5). Besides, a review of the literature was undertaken to identify articles published on this topic until January 6, 2023, following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (6). The following search strategy of keywords was used by two independent investigators: (("mupirocin"[MeSH] OR "mupirocin"[Title] OR "mupirosin"[Title] OR "mupirocine"[Title] OR "bactroban"[Title]) AND ("dermatitis"[MeSH] OR "dermatitis"[Tiab] OR "allergy"[Tiab] OR "allergy"[Tiab] OR "side effect"[Tiab] OR "side effects"[Tiab] OR "adverse effect"[Tiab] OR "toxicity"[Tiab] OR "allergic"[Tiab] OR "sickness"[Tiab] OR "adr"[Tiab] OR "toxic"[Tiab] OR "necrosis"[Tiab])) NOT ("rats"[Title] OR "mice"[Title] OR "rabbits"[Title] OR "mouse"[Title] OR "animals"[Title] OR "animal"[Title] OR "rat"[Title]). Studies not dealing with clinical reports, which had words rats, mice, rabbits, mouse, animals, animal, and rat in the title of the article were excluded.

Articles were mined from PubMed, Scopus, Web of Science, and Google Scholar. Time or language filters were not used and all related reports were included. The reference lists of the related articles were also checked out for eligibility. Complemental details of the search are stated in **Figure 2**. An overview of the included reports is shown in **Table 1**, where, the following items of cases were available: reference, age (yrs), sex, form of mupirocin/ duration of dermal exposure, indication, the onset of symptoms, clinical presentation, treatment, prognosis, and additional comments of the case.

Results

This review was performed following the PRISMA 2020 statement guidelines (6). Publications were screened and investigated as illustrated in the PRISMA flowchart **(Figure 2)**.

Figure 2: PRISMA flowchart



were removed because of duplication. 241 titles and abstracts were screened, and 22 of them were assessed for eligibility. 11 reports were excluded as they did not meet the criteria. All the rest articles (n=11) were included in the review. One case is repeated because it has shown sensitivity twice. Ten cases are human and the last one is a poodle dog which is included in **Table 1** because it is relevant to the topic. From 10 cases, there are 5 females (50%) and 5 males (50%). The median age of human cases was 42.5 years, ranging from 24 days to 80 years. In seven cases, patients used mupirocin ointment form, and in one case, cream, and in two cases, the formulation was not mentioned. Mupirocin was indicated for various wounds and dermatological conditions consisting of recurrent stasis dermatitis and ulceration, cellulitis, blisters on foot, after an operation, phimosis, dry burn, chemical-induced burn, a procedure used to remove basal cell carcinoma, benign fibrous histiocytoma, infection of the venous leg ulcers, and lip dermatitis. The reported clinical presentations after mupirocin usage are as follows: serum sickness, diffuse urticaria, fever and arthralgias, toxic epidermal necrolysis, pruritus, and rashes; which developed to breathlessness, palpitations, flushing, redness all over the body, low blood pressure, severe allergic contact dermatitis, pruritic erythematous papular eruption, extensive contact dermatitis, allergic contact hypersensitivities, and positive reactions to patch tested of 2 kinds of mupirocin ointments. In the dog case, canine pemphigus foliaceous was diagnosed. Treatments were mainly

DOI: https://doi.org/10.18502/aptj.v3i3.14416

corticosteroids and antihistamines. In all patients, the prognosis was a resolution of symptoms, except for one case, in which mupirocin was used intranasally after a tracheostomy operation, albeit, the patient already had cancer and other problems.

Table 1: cases reported of mupirocin adverse drug reaction

	Reference	Age (yrs), sex	Form of mupirocin/ duration of dermal exposure	Indication	onset of symptoms	Clinical presentation	Treatment	prognosis	Additional comments
1	Daly B M. 1987 (21)	53, Male	Bactroban ointment/4 weeks	Recurrent stasis dermatitis and ulceration	After 4 weeks	Widespread vesicular dermatitis/positive patch testing to PEG 400, 3350	NR	NR	Positive sensitivity history to neomycin, soframycin, and wool alcohols
2	Eedy DJ. 1995 (9)	80, Male	Bactroban ointment/ NR	Superficial infection in the venous leg ulcers	After a few weeks	Allergic contact hypersensitivities	NR	NR	He had a history of positive patch testing for something
3	Zappi EG. 1997 (10)	68, Female	ointment/ NR	curettage and desiccation to remove basal cell carcinoma of the trunk	After 14 days	pruritic erythematous popular eruption	NR	NR	allergy to neomycin and bacitracin
4	Praz S-M. 2003 (11)	76, Female	Intranasally/after four times application	methicillin-resistant Staphylococcus aureus positive sputum culture after tracheostomy operation	2 days	Toxic epidermal necrolysis	No treatment	Dead after 5 days	She was allergic to penicillin and had asthma
5	Ö Erdeve 2011 (12)	24-day-old male infant	Ointment/NR	Penile abrasion (phimosis)	1 day	diffuse rash, urticaria	Cetirizine, methyl-prednisolone	lesions disappeared on the following day	His mother was allergic to penicillin
6	Asawa A. 2014 (13)	44, Female	NR	cellulitis of the right foot	2 weeks later	Serum sickness	antihistamines but was not beneficial.	symptoms resolved over a few months. asymptomatic for the next 4	

								years.	
7	Asawa A. 2014 (13)	44, Female (The previous case)	NR	blisters on her right foot	1 day	diffuse urticaria, fever, and arthralgias. The serum levels of C3 and C4 were normal, but C1Q binding and ESR were elevated. That was consistent with the diagnosis of serum sickness.	corticosteroid and ciclosporin.	Resolution	
8	Zhang AJ 2018 (14)	31, Female	Mupirocin and pimecrolimus	pruritic lip dermatitis	After 5 days of patch test	positive reactions to tested mupirocin ointments	NR	NR	
9	Assier H. 2019 (15)	37, Female	Cream/ NR	benign fibrous histiocytoma of the thigh	NR	extensive contact dermatitis	diflucortolon valerate cream	Resolution over 3 weeks	She had a history of contact allergies which had been confirmed by patch tests
10	Seo D-H. 2020 (16)	41, Male	ointment/daily	Acid-induced first-degree burn on the left elbow	After 2 days	Exfoliative skin lesion and bullae which rapidly spread to the whole left upper extremity. (severe allergic contact dermatitis)	normal saline irrigation and wet-gauze dressing	Epithelization and wound healing after 2 weeks	
11	Mishra A. 2021 (1)	39, Male	Dressing with ointment/ in the second use	Dry burn injury	After few seconds	Mild skin allergic reactions (pruritus, rashes), later he developed breathlessness, palpitations, flushing, redness, low blood	Hydrocortisone 100 mg and Avil stat (IV) and 0.5 cc diluted adrenaline SC	Resolution after 15-20 min	

DOI: https://doi.org/10.18502/aptj.v3i3.14416

						pressure (90/60 mm Hg), and high pulse rate (110/min)			
12	Ferreira T. 2019 (17)	1, a Poodle dog	aqueous spray (0.2%)/ In the first use	superficial bacterial folliculitis	After application	canine pemphigus foliaceous	Tacrolimus for ocular lesions, prednisolone, and azathioprine as systemic treatment	Resolution after 10 days	

Discussion

To the best of our knowledge, this is the first review of case reports of mupirocin-induced adverse drug reactions. Here, the cases summarized in **Table 1** are described.

1) Daly B M. in 1987, reported the first mupirocin (Bactroban) ointment allergy. The case is a 53-year-old man who applied Bactroban ointment under a semi-occlusive bandage. After four weeks, a widespread vesicular dermatitis occurred. The causality of this reaction was evaluated by patch testing, which indicated patient sensitivity to Bactroban ointment and its excipients (polyethylene glycol). The author has suggested that PEG played a role in sensitization (7). Although allergic reactions to PEG are usually dramatic (8), in this case, because the patch test is +++ in the Bactroban ointment, sensitivity to mupirocin cannot be ignored.

2) Eedy DJ in 1995, reported the mupirocin allergy in an 80-year-old man who used mupirocin (Bactroban) ointment on his leg ulcers. By performing a patch test, it was found that the patient was allergic to calcium mupirocin without excipient and showed a ++ reaction, while he did not react to the base of the ointment. In this report, it is stated that the systemic absorption of this drug through damaged skin, as well as the specific metabolite of mupirocin (monic acid), which can be detected in the urine, can be the cause of hypersensitivity (9).

3) Another similar case was reported by Eugene G. Zappi in 1997. A pruritic erythematous popular eruption occurred in a 68-year-old woman after 14 days of topical usage of mupirocin ointment on her surgical sites. She had suffered from basal cell carcinoma of the trunk, which was removed by electrodesiccation and curettage. The woman was previously allergic to neomycin and bacitracin. The patch test proved that she is allergic to mupirocin and not to the placebo vehicle (10).

4) The first report of mupirocin-induced toxic epidermal necrolysis (TEN) was published by Sophie-Maria Praz in 2003. The case was a 76-year-old woman, who suffered from oropharyngeal carcinoma. Eighteen days after the tracheostomy procedure, treatment with chlorhexidine bath and mupirocin ointment intranasally started; because of MRSA-positive sputum culture. After two days, a skin eruption around the nose appeared and developed rapidly to bullae and progressed to the lower parts of the face and neck. Drug treatments were discontinued but large bullae spread to 20% of the body area as

well as fever; TEN was clinically diagnosed due to positive Nikolasky sign. Because of a bad oncologic prognosis, she did not get life support and after five days she died of sepsis. It is noteworthy that, this patient was already suffering from asthma and was atopic and allergic to penicillin. Also, because of the nasogastric intubation, the nasal mucosa had been injured. These factors can cause the exacerbation of hypersensitivity to topical mupirocin and its progression to TEN (11).

5) Erdeve in 2011 reported a 24-day-old male infant referred to the hospital because of urticaria and diffuse rash. He suffered from phimosis. To treat the penile abrasion, mupirocin ointment was applied to his glance. One day later, maculopapular, and migratory rash with maculoerythematous lesions developed. Blood tests including partial thromboplastin, prothrombin time, CBC, and C-reactive protein were normal which ruled out the possibility of hematological diseases or infection. But moderate eosinophilia (8%) was indicated. His mother had an atopy history and was allergic to penicillin. The physical examination, laboratory tests, and family history led to the diagnosis of urticaria. This infant was treated with oral cetirizine drop and methyl-prednisolone (IM) and the lesions faded during one day. There are few reports of urticaria in children younger than six months. Although, the most common etiology of urticaria in children is infection, insect bites, food, and drug allergies, in infants under 6 months, infection, and food rather than drugs are the most causative factors. In this case, probably due to the history of familial atopy, and penile abrasion, the hypersensitivity to topical mupirocin increased and led to urticaria, which should be taken into consideration when prescribing (12).

6) A case of serum sickness after mupirocin application was reported by Asawa A, in 2014. A 44-year-old woman, who four years ago had applied mupirocin on the cellulitis of her foot. After 14 days she had observed diffuse erythematous, blanched lesions, itching, inflammation in knees, and arthralgias. The symptoms slowly subsided and remained asymptomatic. Four years after this incident, she again used mupirocin on her leg blisters. After a day, a returned diffuse urticaria, hives, fever, arthralgias, and elevated C1Q binding and ESR were observed but the level of C3 and C4 tests were normal. These findings can prove secondary serum sickness caused by mupirocin (13).

7) In 2018, Amy J. Zhang published a case report about a 31-year-old woman who suffered from pruritic lip dermatitis for two years. She used pimecrolimus cream and mupirocin ointment. both lips showed edema and erythema. The brief description is that a patch test was done, and after 5 days, a weak positive reaction (+) to the mupirocin ointment was indicated. Since the only excipient of this ointment was polyethylene glycol and she did not react to it, it was proved that mupirocin was the cause of contact allergy in this case. A patch test was also performed for pimecrolimus cream and its excipients, and finally, as in the case of mupirocin, sensitivity to the active ingredient of pimecrolimus was confirmed; which is a rare case report; and it shows the importance of performing a patch test on the active ingredient (14).

DOI: https://doi.org/10.18502/aptj.v3i3.14416

8) Sever and prolonged contact allergy induced by mupirocin manifested in a polysensitized patient. Haudrey Assier in 2019 reported a female patient (37 years) received mupirocin cream on her thigh for a benign fibrous histiocytoma. But unintentionally, the lesions developed gradually. Following treatment was started. Neither roxithromycin tablets, nor multiple topical creams including clobetasol, ciclopirox, desonide, and econazole could prevent the spread of rashes to the whole thigh and the nummular lesions on the trunk. Finally, the symptoms were resolved by diflucortolon cream for 3 weeks. It is necessary to mention that she had a history of adverse skin reactions to several substances which was confirmed by patch tests. For this incident, patch tests were done again, which proved that mupirocin causes sensitivity in this person. It seemed that the severity and prolongation of this case is related to polysensitization to different types of allergens, which causes a person's reaction to an allergen to be stronger, more extensive, longer-lasting, and more widespread than the exposure site (15).

9) Du-Heon Seo in 2020 reported a severe allergic reaction to mupirocin after usage on an acid-induced burn wound. The case was a 41-year-old man who had no history of allergies. Mupirocin ointment was applied to his first-degree burn. Two days later, itching and spreading of lesions around the initial damaged area were experienced. On the third day, after the application of mupirocin, the condition of the ulcers worsened and widened. severe allergic contact dermatitis was diagnosed. To stop this condition, this ointment was discontinued and anti-allergic treatments were started. Although at first the worsening and spreading of the wounds were mistakenly attributed to a chemical burn, it was later determined to be a side effect of mupirocin. This rare complication should be noticed by physicians (16)

10) A severe systemic allergic reaction was reported by Adesh Mishra in 2021. A 39-year-old man was referred to the hospital after a dry burn. He had drug-controlled hypertension, without any other medical history. The patient received intravenous antibiotics and topical mupirocin ointment. On his follow-up visits, the application of mupirocin was repeated. pruritus and rashes were observed immediately and developed into hypotension, palpitations, flushing, breathlessness, and skin redness. The complete blood count and the level of IgE were in normal ranges. As mentioned, at first, local allergic reactions happened, which developed into severe systemic allergic reactions. Although, this severe incidence of mupirocin is rare, but should be considered (1).

11) The last case related to mupirocin side effects is a poodle dog. Although it is not included in the category of human cases, it is explained because of a close relationship with the subject and the associated histopathological examinations. The dog was referred to a clinic because of abdominal pruritus and licking its legs. For treatment, an aqueous spray of mupirocin 2% was used topically; which exacerbated the signs and induced urticaria, pustular lesions, and diffuse epidermal collars as well as nasal erythema, blepharitis, and fever. To determine the cause; bacterial culture from the skin secretions was

done but did not reveal any growth. While, biopsy and the cytological tests showed neutrophil accumulation and loss of coherence between epidermal cells (acantholysis), well-matched to canine pemphigus foliaceous. Although, in humans, drug-related pemphigus is a well-known complication; there has been no report about the dog so far (17).

Many articles express the effectiveness of mupirocin on various infections, especially on MRSA. Fortunately, in most of the clinical trials related to mupirocin, the safety of this antibiotic has been stated and no specific side effect or toxicity reported. In some articles, a brief mention has been made of the adverse reactions of this topical drug, which are mostly burning, itching, and pain in the exposure area (1, 18, 19).

Mupirocin in the body fluids hydrolyses monic acid and 9-hydroxynonanoic which have no antibacterial activity. For this reason, this drug has not been approved as a systemic antibiotic and is only used in the form of ointment, cream, and aerosol for topical application (3). Cross-reactivity is another problem related to the use of drugs. When a person is allergic to a chemical compound; he/she may show cross-sensitivity to other members of that drug class due to the similarity of the molecular structure. Because of the unique molecular structure of mupirocin and its dissimilarity with other chemical classes of antibiotics, cross-sensitivity is unlikely (3, 20).

Type 1 hypersensitivity reactions, which are also called immediate or IgG-mediated reactions, can occur as a result of the topical use of some antibiotics. These reactions occur immediately after exposure. The patient's symptoms can range from contact urticaria to fatal anaphylaxis. In almost all reports about topical antibiotics, there has been skin barrier disruption. So, it is suggested that the entry of these topical drugs into systemic circulation was a requirement for the development of these reactions (20). As mentioned above, since mupirocin is usually used on damaged skin or mucous membranes such as a variety of wounds including scratches, burns, cuts, stitches, etc.; at first, a slight burning and pain are felt in the exposed area. In addition, due to the skin barrier disruption, the possibility of systemic absorption of the drug increases. This systemic absorption and subsequent metabolization of mupirocin to monic acid can be the causative agents of hypersensitivity (9).

of the nine patients described above, five cases had personal or family history of allergy. In the other four cases, there is no mention of a history of allergy, but it does not mean that their histories are negative. Although the types of allergic reactions can happen in people with or without a history of sensitization, patients with a history of previous allergies should be more careful. Nowadays, the use of mupirocin is widespread, and consequently, bacterial strains with high-level resistance to mupirocin have spread and Low-level resistance can be developed. In many cases, this antibiotic is not used rationally, and many wounds and scratches can even be healed with the ointment base (petrolatum) or a non-antibiotic topical product (3, 20). These suggestions should be considered by physicians and patients to prevent the development of antibiotic resistance and to reduce the rate of drug side effects.

DOI: https://doi.org/10.18502/aptj.v3i3.14416

Conclusion

Fortunately, the prevalence of side effects of topical mupirocin is low; despite its widespread use. However, healthcare professionals must be aware of these side effects that can sometimes influence the quality of a patient's life and even be life-threatening. People with impaired skin barrier and a history of allergies are in the high-risk group. Application of mupirocin as well as other antibiotics should be limited to those that are necessary; in other cases, it can be replaced with non-antibiotic formulations or dressings. Further research is needed to study the prevalence of adverse drug reactions of mupirocin.

Acknowledgments: We thank the patient for the permission to publish the case and photo of her hand.

Conflict of interest: There is no conflict of interest.

Funding: There is no financial support

Ethical considerations: Written consent was obtained from the patient and her identity was kept confidential

Authors' contribution: All authors contributed to the reporting and writing of the article

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