Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20181659

Case Report

A fixed dose combination of ofloxacin and ornidazole induced fixed drug eruptions

Ravi Shankar Manchukonda, Chandrakantha Thippeswamy*

Department of Pharmacology, Adichunchanagiri Institute of Medical Sciences, B G Nagara, Karnataka, India

Received: 01 March 2018
Accepted: 29 March 2018

***Correspondence to:**
Dr. Chandrakantha Thippeswamy,
Email: drchandru84476@gmail.com

ABSTRACT

Fixed drug eruptions (FDEs) may account for 16-21% of all cutaneous drug eruptions. Recent research suggests a cell-mediated process that initiates both the active and quiescent lesions. The major categories of causative agents of fixed drug eruption include antibiotics, antiepileptics, nonsteroidal anti-inflammatory agents, sildenafil, and phenothiazines, although numerous other agents and certain foods such as cashews and licorice have also been reported as causative agents. A 38 year old male presented to the dermatology OPD with hyperpigmented and erythematous macular eruptions on the neck, chest, right arm, left scapular region, left wrist and left knee. The eruptions were associated with burning sensation and itching. He informed having taken medications for gastroenteritis the night before. The medications were Ofloxacin and Ornidazole (FDC), Omeprazole and Domperidone (FDC) and Paracetamol. He gave a history of a similar event, a year ago, with the same antimicrobial combination (Ofloxacin and Ornidazole), although the macular eruptions were restricted to the neck, arm and knee with bleb formation and severe burning sensation. Since the macular eruptions reoccurred, although with extra regions being affected, a diagnosis of FDEs was made. The most probable cause for these FDEs seems to be FDC of Ofloxacin and Ornidazole, because the patient gives history of taking Omeprazole and Paracetamol before without any FDEs. According to Naranjo's Adverse Drug Reaction Probability Scale, the FDC of Ofloxacin and Ornidazole is a definite cause for the FDEs. (Score = 9).

Keywords: Adverse reactions, Drug induced cutaneous disorders, Fixed drug eruptions, Fixed dose combination, Naranjo's ADR probability scale, Ofloxacin and ornidazole

INTRODUCTION

Adverse reactions to medications are common and often manifest as a cutaneous eruption.

Drug-induced cutaneous disorders frequently display a characteristic clinical morphology such as morbilliform exanthem, urticaria, hypersensitivity syndrome, pseudolymphoma, photosensitivity, pigmentary changes, acute generalized exanthematous pustulosis, lichenoid dermatitis, vasculitis, Stevens-Johnson syndrome, or fixed drug eruption (FDE).

The term fixed drug eruption describes the development of one or more annular or oval erythematous patches as a result of systemic exposure to a drug; these reactions normally resolve with hyperpigmentation and may recur at the same site with re exposure to the drug. Repeated exposure to the offending drug may cause new lesions to develop in addition to "lighting up" the older hyperpigmented lesions.

Several variants of fixed drug eruption have been described, based on their clinical features and the distribution of the lesions. These include the following:[1]

- Pigmenting fixed drug eruption
- Generalized or multiple fixed drug eruption
- Linear fixed drug eruption
- Wandering fixed drug eruption
- Nonpigmenting fixed drug eruption
- Bullous fixed drug eruption
- Eczematous fixed drug eruption
- Urticarial fixed drug eruption
- Erythema dyschromicum perstans-like fixed drug eruption
- Vulvitis
- Oral
- Psoriasiform
- Cellulitis like eruption[2]

The prevalence of drug eruptions has been reported to range from 2-5% for inpatients and greater than 1% for outpatients.[3] Fixed drug eruptions may account for as much as 16-21% of all cutaneous drug eruptions. The actual frequency may be higher than current estimates, owing to the availability of a variety of over-the-counter medications and nutritional supplements that are known to elicit fixed drug eruptions.

Most studies report fixed drug eruptions to be the second or third most common skin manifestation of adverse drug events.[4]

Fixed drug eruptions have no known racial predilection. A genetic susceptibility to developing a fixed drug eruption with an increased incidence of HLA-B22 is possible.[5,6]

One large study of 450 patients revealed a male-to-female ratio of 1:1.1 for fixed drug eruptions.[1] Fixed drug eruptions have been reported in patients as young as 1.5 years and as old as 87 years. The mean age at presentation is 30.4 years in males and 31.3 years in females.[1]

The prognosis is very good, and an uneventful recovery should be expected. No deaths due to fixed drug eruption have been reported. Residual hyperpigmentation is very common, but this is less likely with the no pigmenting variant.

Widespread lesions may initially mimic toxic epidermal necrolysis, but they have a benign clinical course.[7] Again, localized hyperpigmentation is a common complication, but pain, infection, and, rarely, hypopigmentation, also may occur.[1]

CASE REPORT

A 38 year old male presented himself to the dermatology OPD with hyperpigmented and erythematous macular eruptions on the neck, chest, right arm, left scapular region, left wrist and left knee (Figure 1A to Figure 1F). The eruptions were associated with burning sensation and itching. He said that he noticed these lesions from the morning of the same day.

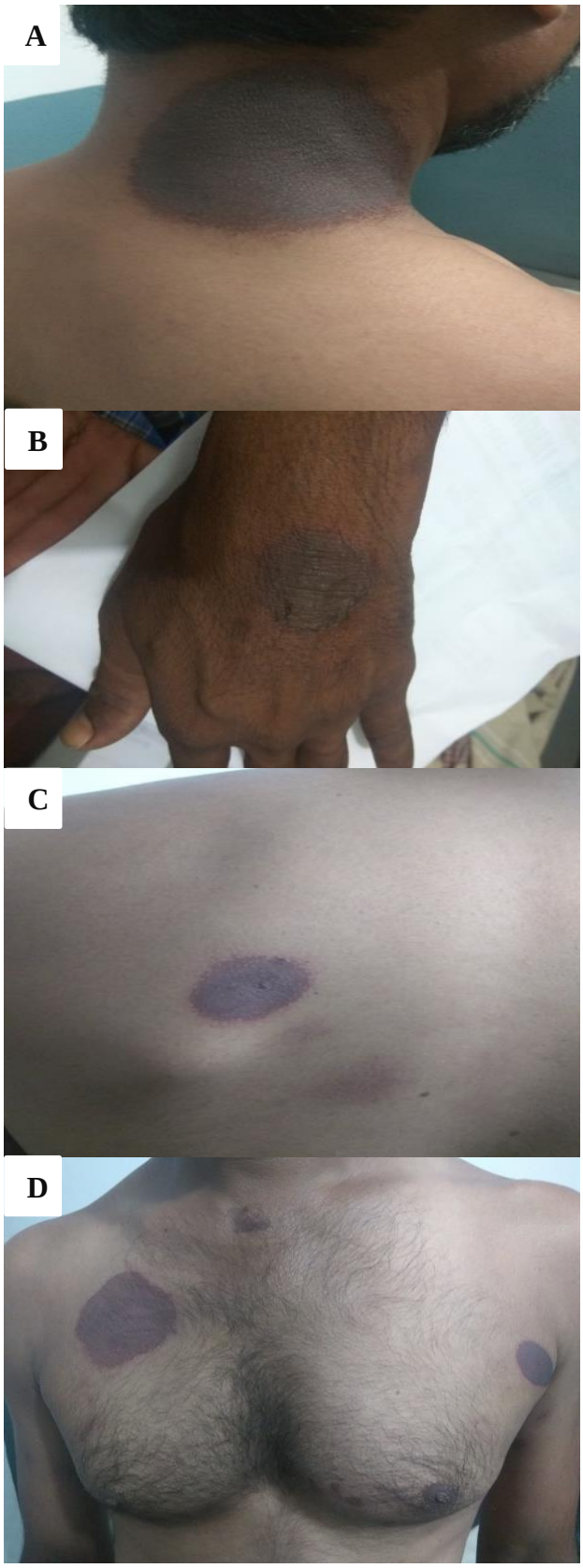

Figure 1

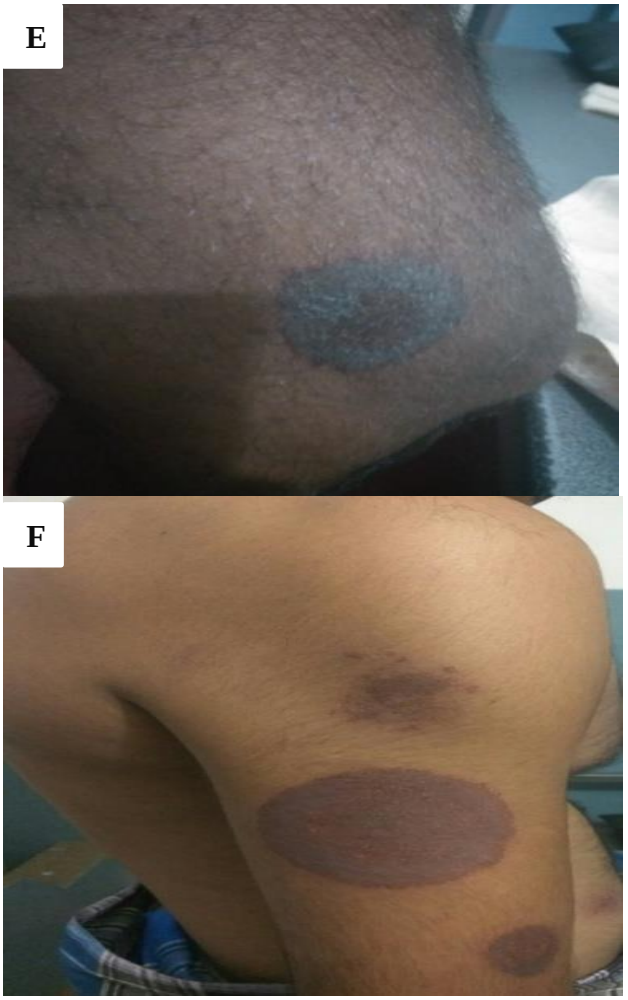

Figure 1 (A to F): Hyperpigmented and erythematous fixed drug eruptions after the present exposure with additional sites involvement.

On eliciting the medication history, he informed that he took medications for gastroenteritis the night before after consulting a general practitioner.

He showed the medications which turned out to be:

- Ofloxacin and Ornidazole (FDC) (antimicrobial)
- Omeprazole and Domperidone (to counter the gastritis)
- Paracetamol (for fever)

He gave a history of a similar event, a year ago, with the same antimicrobial combination (Ofloxacin and Ornidazole), although the macular eruptions were restricted to the neck, arm and knee with bleb formation and severe burning sensation. (Figure 2A and Figure 2B), Figure 3 and Figure 4.

The patient was prescribed the following medications by the consulting dermatologist:

Tablet Levocetirizine 5mg once daily. Fusidic acid cream for topical application at the site of the eruptions Tab Prednisolone 10mg once daily for five days.

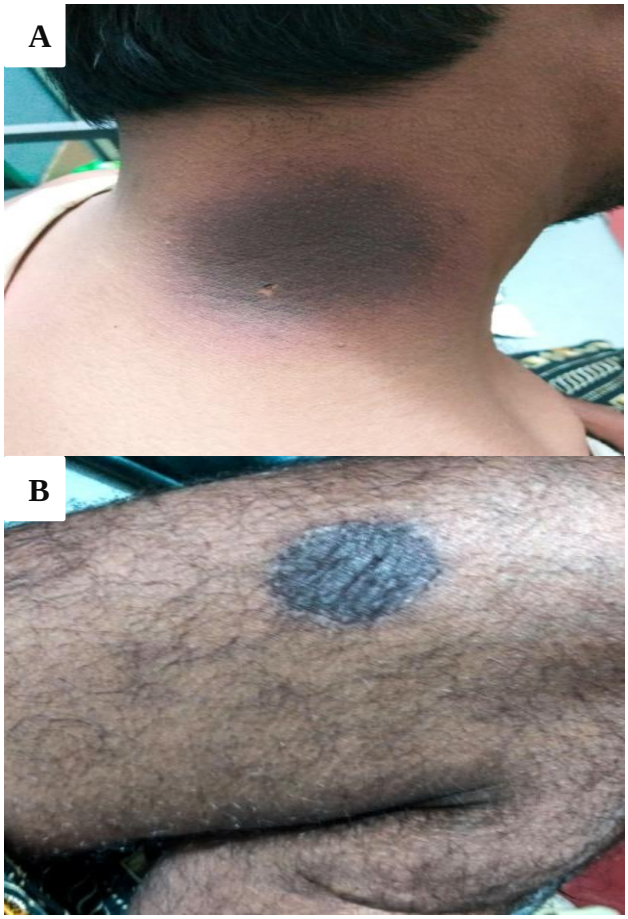

Figure 2 (A and B): Drug eruptions due to previous exposure (one year back)- Hyperpigmented eruption.

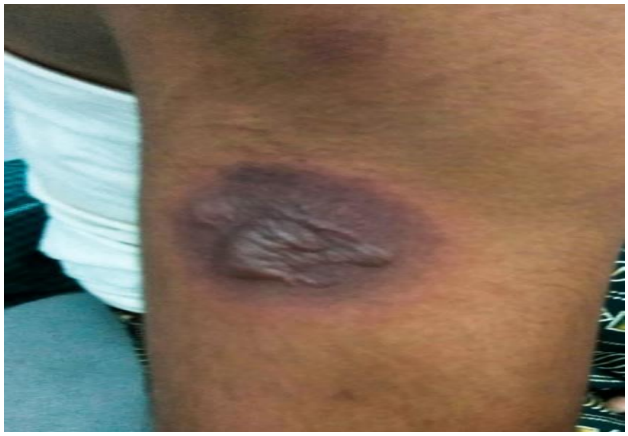

Figure 3: Drug eruptions due to previous exposure (one year back)- Bleb formation.

Since the macular eruptions reoccurred, although with extra regions being affected, a diagnosis of Fixed Drug Eruptions (FDEs) was made.

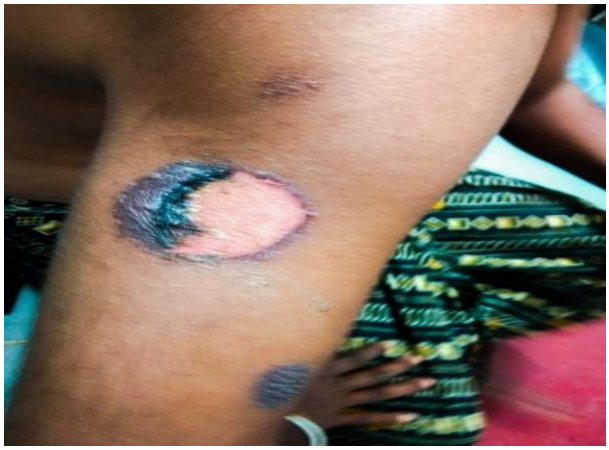

Figure 4: Drug eruptions due to previous exposure (one year back)- Peeling of skin.

The most probable cause for these fixed drug eruptions (FDEs) seems to be fixed dose combination (FDC) of Ofloxacin and Ornidazole, because the patient gives history of taking Omeprazole and Paracetamol before without any event of FDEs.

According to Naranjo's Adverse Drug Reaction Probability Scale, the FDC of Ofloxacin and Ornidazole is a definite cause for the Fixed Drug Eruption. (Score = 9).

DISCUSSION

Drug eruptions are among the most common cutaneous disorders encountered by the dermatologist. Some drug eruptions, although trivial, may cause cosmetic embarrassment and fixed drug eruption (FDE) is one of them. The diagnostic hallmark is its recurrence at previously affected sites.

Although the exact mechanism is unknown, recent research suggests a cell-mediated process that initiates both the active and quiescent lesions. The process may involve an antibody-dependent, cell-mediated cytotoxic response.[8] $CD8^+$ effector/memory T cells play an important role in reactivation of lesions with re-exposure to the offending drug.[9,10]

The offending drug is thought to function as a hapten that preferentially binds to basal keratinocytes, leading to an inflammatory response.[11] Through liberation of cytokines such as tumor necrosis factor-alpha, keratinocytes may locally up-regulate expression of the intercellular adhesion molecule-1 (ICAM1).[12] The up-regulated ICAM1 has been shown to help T cells (CD4 and CD8) migrate to the site of an insult.[13,14]

The newly arriving and residential CD8 cells likely perpetuate tissue damage by their production of the inflammatory cytokines interferon-gamma and tumor necrosis factor-alpha. CD8 cells isolated from active lesions have also been shown to express alpha E beta 7, a ligand for E-cadherin, which may further contribute to the lymphocyte's ability to localize to the epidermis. Other cell surface molecules, such as CLA/alpha4beta1/CD4a, that bind E-selectin/vascular cellular adhesion molecule-2/ICAM1 help to further attract CD8 cells to the area.[8]

Changes in cell surface markers allow vascular endothelium to select CD4 cells for migration into active lesions. These regulatory CD4 cells likely produce interleukin 10, which has been shown to help suppress immune function, resulting in a resting lesion.[8] As the inflammatory response dissipates, interleukin 15 expression from keratinocytes is thought to help ensure the survival of CD8 cells, helping them fulfill their effector memory phenotypes. Thus, when reexposure to the drug occurs, a more rapid response develops in the exact location of any prior lesions.[8]

The initial eruption is often solitary and frequently located on the lip or genitalia. Rarely, the eruption may be intraoral. Other common locations of the initial lesion are the hip, lower back/sacrum, or proximal extremity. With the initial fixed drug eruption attack, a delay of up to 2 weeks may occur from the initial exposure to the drug to the development of the skin lesion.[15] Skin lesions develop over a period of hours but require days to become necrotic. Lesions may persist from days to weeks and then fade slowly to residual oval hyperpigmented patches.

Subsequent reexposure to the medication results in a reactivation of the site, with inflammation occurring within 30 minutes to 16 hours.[16] The reactivation of old lesions also may be associated with the development of new lesions at other sites.

The major categories of causative agents of fixed drug eruption include antibiotics, antiepileptics, nonsteroidal anti-inflammatory agents, sildenafil, and phenothiazines, although numerous other agents and certain foods such as cashews and licorice have also been reported as causative agents. Ingestion of the causative agent may occur via any route, including oral, rectal, or intravenous.[17,18]

In this clinical scenario, the patient gives history of taking the following medications before the eruptions started.

1. Ofloxacin and Ornidazole. Ofloxacin is a first generation fluoroquinolone which is indicated for the treatment of bacillary dysentery. Ornidazole is a nitroimidazole which is indicated for the pharmacotherapy of amoebic dysentery. The fixed dose combination of these two antimicrobials has been used frequently for the treatment of diarrheas and dysenteries of unknown cause. It is not possible to find out which amongst these is responsible for the skin eruptions.
2. Omeprazole is a proton pump inhibitor indicated for the pharmacotherapy of acid-peptic disorders. Here it had been prescribed to counter the gastric irritation which could possibly occur due to the antimicrobial

combination. Domperidone is a prokinetic agent which has been used in combination with a proton pump inhibitor.

3. Paracetamol is a non-steroidal anti-inflammatory agent prescribed to reduce the fever in this patient.

Lesions of fixed drug eruption resolve spontaneously with avoidance of the inciting drug. Additional medications should be used to relieve symptoms associated with the condition. Generally, an oral antihistamine (eg, hydroxyzine) and a topical corticosteroid may be sufficient. The use of corticosteroids may interfere with later diagnostic provocation testing. Hyperpigmentation may take many months to resolve. Incontinent pigment in the dermis responds poorly to topical bleaching agents such as hydroquinones.

CONCLUSION

The cutaneous disorder in this clinical scenario was diagnosed as "Ofloxacin and Ornidazole induce fixed drug eruptions". The diagnosis was based on the temporal association between the drug intake and the development of the skin eruptions and also a previous history of cutaneous eruptions on exposure to the same fixed dose combination of Ofloxacin and Ornidazole. The causality association between the implicated medications and the adverse drug reaction was found to be definite based on the Naranjo's adverse drug reaction probability scale. The patients have to be educated to exercise caution and not get exposed to drugs which have caused allergic reactions in them previously. The prescribing physicians should also elicit a previous drug history and any associated events before prescribing medications to their patients.

ACKNOWLEDGEMENTS

Authors are grateful to the Department of Deramatology, Sri Adichunchanagiri Institute of Medical Sciences, Balagangadharanthaswamy Nagara.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Mahboob A, Haroon TS. Drugs causing fixed eruptions: a study of 450 cases. Int J Dermatol. 1998 Nov;37(11):833-8.
2. Fathallah N, Ben Salem C, Slim R, Boussofara L, Ghariani N, Bouraoui K. Acetaminophen-induced cellulitis-like fixed drug eruption. Indian J Dermatol. 2011 Mar;56(2):206-8.
3. Krahenbuhl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krahenbuhl S. Drug-related problems in hospitals: a review of the recent literature. Drug Saf. 2007;30(5):379-407.
4. Lee AY. Fixed drug eruptions. Incidence, recognition, and avoidance. Am J Clin Dermatol. 2000 Sep-Oct;1(5):277-85.
5. Pellicano R, Ciavarella G, Lomuto M, Di Giorgio G. Genetic susceptibility to fixed drug eruption: evidence for a link with HLA-B22. J Am Acad Dermatol. 1994 Jan;30(1):52-4.
6. Pellicano R, Lomuto M, Ciavarella G, Di Giorgio G, Gasparini P. Fixed drug eruptions with feprazone are linked to HLA-B22. J Am Acad Dermatol. 1997 May;36(5 Pt 1):782-4.
7. Baird BJ, De Villez RL. Widespread bullous fixed drug eruption mimicking toxic epidermal necrolysis. Int J Dermatol. 1988 Apr;27(3):170-4.
8. Teraki Y, Shiohara T. IFN-gamma-producing effector CD8+ T cells and IL-10-producing regulatory CD4+ T cells in fixed drug eruption. J Allergy Clin Immunol. 2003 Sep;112(3):609-15.
9. Mizukawa Y, Shiohara T. Fixed drug eruption: a prototypic disorder mediated by effector memory T cells. Curr Allergy Asthma Rep. 2009 Jan;9(1):71-7.
10. Shiohara T. Fixed drug eruption: pathogenesis and diagnostic tests. Curr Opin Allergy Clin Immunol. 2009 Aug;9(4):316-21.
11. Weedon D. The lichenoid reaction pattern ('interface dermatitis'). Skin Pathology. 2nd Ed. London, England: Churchill Livingstone; 2002:42-43.
12. Smoller BR, Luster AD, Krane JF, Krueger J, Gray MH, McNutt NS, et al. Fixed drug eruptions: evidence for a cytokine-mediated process. Journal of cutaneous pathology. 1991 Feb 1;18(1):13-9.
13. Hindsen M, Christensen OB, Gruic V, Lofberg H. Fixed drug eruption: an immunohistochemical investigation of the acute and healing phase. Br J Dermatol. 1987 Mar;116(3):351-60.
14. Shiohara T, Nickoloff BJ, Sagawa Y, Gomi T, Nagashima M. Fixed drug eruption. Expression of epidermal keratinocyte intercellular adhesion molecule-1 (ICAM-1). Arch Dermatol. 1989 Oct;125(10):1371-6.
15. Bolognia JL, Jorizzo JL, Rapini RP. Fixed drug eruptions. Dermatology. London, England: Mosby; 2003:344-345.
16. Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI. Fixed drug eruptions. Fitzpatrick's Dermatology in General Medicine. 6th Ed. New York, NY: McGraw-Hill; 2003:1333.
17. Sehgal VN, Srivastava G. Fixed drug eruption (FDE): changing scenario of incriminating drugs. Int J Dermatol. 2006 Aug;45(8):897-908.
18. Choi SY, Suh JH, Park KY, Li K, Kim BJ, Seo SJ, et al. Fixed Drug Eruption Caused by Sildenafil Citrate. Ann Dermatol. 2017 Apr;29(2):247-8.

Cite this article as: Manchukonda RS, Thippeswamy C. A fixed dose combination of ofloxacin and ornidazole induced fixed drug eruptions. Int J Basic Clin Pharmacol 2018;7:1043-7.