Drugs Causing Fixed Drug Eruption: A Clinical Study

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ABSTRACT

Objectives: To identify the causative drugs of fixed drug eruption, and to assess drug-related body site distribution of fixed drug eruption.

Methods: This study was conducted at Prince Rashid Hospital and Queen Alia Hospital during the period between January 2008 and June 2009. A total of 64 patients who attended the dermatology clinic with fixed drug eruption were asked about the offending drug.

Results: Trimethoprim-sulphamethoxazole was the causative agent in 43 cases (70.3%), followed by Furosemide in 5 cases (7.8%), and Tetracyclines in 4 cases (6.3%). Other causative drugs included Diclofenac sodium 3 (4.7%), Ciprofloxacin 3 (4.7%), Ibuprofen 2 (3.1%), Metronidazole 2 (3.1%), Norfloxacin 1 (1.6%), and aspirin 1 (1.6%). The glans penis of the male genitalia was the most commonly involved site (58.0%), followed by the extremities (39.0%), the trunk (20.3%), and the lips (6.3%). The female genitalia (clitoris) was involved only in two patients (3.1%). Only one patient (1.6%) developed a generalized bullous drug reaction.

Conclusions: Our study highlighted the common occurrence of FDEs, and the range of causative drugs. They were most commonly encountered with trimethoprim-sulphamethoxazole, but quinolones were increasingly seen as causative agents for FDEs. Our study also showed that FDE usually presented as solitary lesion, and in terms of body site distribution the genitalia (mainly the glans penis) was the most frequently involved site.

Key words: Fixed drug eruption.

JRMS September 2011, 18(3): 16-20

Introduction

Adverse drug reactions are very common. They range in severity and type. In the general population drug-related problems occur in about 5%, and in hospitalized patients this figure rises to 20 %.[1] The most commonly involved organ by drug reactions is the skin.[1] The cutaneous adverse drug reactions range in severity from transient maculopapular rash to fatal toxic epidermal necrolysis. The most common types of cutaneous drug reactions are the maculopapular rash (35%), fixed drug eruption (30%) and urticaria (14%).[2]

Fixed drug eruption (FDE) is a type of allergic reaction to drugs. It characteristically recurs in the same sites each time a particular drug is taken. FDE is usually solitary in the initial attack, but with each subsequent exposure, the number of involved sites may increase and pre-existing ones may increase in size. The lesions usually develop within 30 minutes to 8 hours of taking a drug. The lesions are often painful, clearly demarcated oval or round erythematous plaques, becoming violaceous 1-2

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Manuscript received September 2009; 27. Accepted January 28, 2010

Table I. Drugs causing fixed drug eruption.

Offending drug	Gender		Total	%
	Male	Female		
Trimethoprim-sulphamethoxazole	39	4	43	70.3
Furosemide	1	4	5	7.8
Tetracycline	1	3	4	6.3
Diclofenac sodium	0	3	3	4.7
Ciprofloxacin	3	0	3	4.7
Ibuprofen	0	2	2	3.1
Metronidazole	1	1	2	3.1
Norfloxacin	0	1	1	1.6
Aspirin	1	0	1	1.6
Total	46	18	64	103.2

Table II. Drug-related body site distribution of fixed drug eruption.

Offending Drug	Genitalia		Lips	Trunk	Extremities	Generalized
	Glans penis	Clitoris				
Trimethoprim-sulphamethoxazole	36	2	1	5	10	1
Furosemide	0	0	0	4	2	0
Tetracyclines	0	0	0	1	4	0
Diclofenac Sodium	0	0	0	1	3	0
Ciprofloxacin	1	0	2	1	2	0
Ibuprofen	0	0	1	0	1	0
Metronidazole	0	0	0	1	1	0
Norfloxacin	0	0	0	0	1	0
Aspirin	0	0	0	0	1	0
Total	37	2	4	13	25	1
(Percentage)	(58.0%)	(3.1%)	(6.3%)	(20.3%)	(39.0%)	(1.6%)

Table III. Distribution of lesions according to number of sites involved per case

Number of body sites involved	Number of cases
1	47
2	12
3	2
4	0
Generalized	1
Total	62

days later. As healing occurs, after about 1 week, crusting and scaling are followed by a persistent dusky brown color. This may fade but often persists between attacks. The limbs are more commonly involved by FDE than the trunk. The hands, feet and male genitalia (glans penis) are the favorite sites of FDE. General symptoms accompanying a FDE are usually mild or absent.[3]

Non-pigmented fixed drug eruptions have been reported with pseudoephedrine.[4]

The histopathology of FDE is characterized by hydropic degeneration of the basal cell layer with secondary pigmentary incontinence. Civatte bodies (representing apoptotic keratinocytes) are frequently seen in the epidermis. Bullae and confluent epidermal necrosis are not infrequently seen in severe reactions. Histopathological differential diagnosis of FDE includes erythema multiforme and toxic epidermal necrolysis.[5]

Methods

This study was conducted out at Prince Rashid Hospital and Queen Alia Hospital during the period between January 2008 and June 2009. All patients who attended the dermatology clinic with characteristic clinical findings of FDE were included in the study. Patients with suspected FDE were evaluated by two dermatologists. The patients were thoroughly inquired about their drug history. The clinical history and physical examination included the following points: Types of drugs taken in the last 24 hours, previous history of similar attacks induced by the same offending drug, previous history of similar attacks induced by a drug other than the

current offending drug, the involved sites, and any family history of fixed drug eruptions. Skin biopsy was done in suspicious cases. Statistical analysis using Chi-square test to investigate the difference between males and females regarding the drug side effect (FDE) was done.

Results

Sixty- four patients, with a mean age of 46 years (range between 12 and 80 years). The most affected age group was between 20 to 29 years of age. There were 46 males and 18 females with male: female ratio of 2.6:1.

The results were as outlined in Tables I, II, III.

Trimethoprim-sulphamethoxazole was the leading causative agent in 43 cases (70.3%), followed by furosemide 5 (7.8%), tetracyclines 4 (6.3%), diclofenac sodium 3 (4.7%), and ciprofloxacin 3 (4.7%). Other drugs involved were: ibuprofen 2 (3.1%), metronidazole 2(3.1%), norfloxacin 1 (1.6%), and aspirin 1 (1.6%). There was a significant difference between males and females regarding the FDE (P value < 0.05).

The genitalia were the most commonly involved site in 39 cases (61.1%); (37 males (glans penis) and 2 females (clitoris)). FDE at the genitalia was induced mainly by trimethoprim-sulphamethoxazole. Other common sites of involvement include: Extremities (39.0%), followed by trunk (20.3%), and lips (6.3%). One patient (1.6%) developed a generalized bullous reaction in the third attack of FDE secondary to trimethoprim-sulphamethoxazole ingestion; the initial two attacks were limited to the patient's glans penis and extremities.

Overall, a total number of 82 body sites were involved in 64 cases affected by FDE. In the majority of cases, only one or two sites were involved (73.4% and 21.9% respectively); usually involving the genitalia and/or the extremities. In contrast, three regions of the body were involved in 2 cases (3.1%), and no cases involved four body regions. A summary is outlined in Table III.

Cross-sensitivity was noticed in two patients. The first patient developed his first attack of FDE on the glans penis after trimethoprim-sulphamethoxazole ingestion. Two months later, he developed FDE on the glans penis and the extremities secondary to ciprofloxacin intake. The second patient developed severe FDE on her extremities after only one dose of ciprofloxacin which was prescribed for a presumed urinary tract infection (UTI). Ciprofloxacin was discontinued and replaced by intravenous second generation cephalosporin. One month later, she developed another attack of UTI, for which she received norfloxacin. Immediately, she developed flare up of her FDE at the same sites of the previous attack. New sites were also involved. None of our patients gave family history of FDE.

Discussion

Fixed drug eruption (FDE) is a distinctive variant of drug-induced dermatoses, with characteristic recurrence at the same site of the skin or mucous membranes. FDE was first described by Brocq in 1884, who reported FDE in a patient on antipyrine therapy.[6] Since then, scores of drugs have been reported from different parts of the world to cause FDE. The traditional etiologic agents associated with FDE are sulfonamides, phenazones, and tetracyclines. The incidence of FDE worldwide varies from time to time and place to place; depending upon relative prevalence of the various drugs that are being used by a particular population.

The most characteristic feature of FDE is reactivation of the inflammatory process in the previously involved site(s) with each subsequent exposure.[7] The classic morphology of FDE lesion is dusky red painful patch (es) that leaves long-lasting or permanent deep postinflammatory hyperpigmentation. Other, non classic, lesions of FDE are occasionally seen including: erythema multiforme, Steven Johnson syndrome, cheilitis, psoriasis, lichen planus-like, hand eczema, melasma, discoid lupus erythematosus, pemphigus vulgaris or hypermelanosis of the vulva and peri-anal area.[7]

The underlying pathophysiology of FDE remained unclear for years. However, cell-mediated, rather than humoral immunity is believed to be involved. Recent studies suggest that the CD8 intra-epidermal T-cells (memory T-cells) residing in the FDE lesion persist in a state of activation (express an early activation marker CD69) even in the resting lesions,[8] in contrasts to their counterparts in the dermis and peripheral blood. On re-exposure to the same antigen (offending drug), those intra-epidermal T-cells acquire a potent cytotoxic activity via the production of large amounts of interferon-gamma with kinetics much faster than their dermal counterparts at mRNA and protein levels. Such early interferon-gamma production was only observed in the intra-epidermal T-cells resident in the FDE

lesions, but not those in the peri-lesional skin. Subsequently, leading to localized epidermal injury.[8]

The diagnosis of FDE is primarily based on the patient's history and clinical picture. In some cases an oral challenge may be done but this is avoided by most physicians, including ourselves, because oral provocation carries a risk of generalized serious drug reactions.[1,6] Patch testing has been utilized as an alternative to oral testing, but only positive tests are helpful.[1]

In our study, trimethoprim-sulphamethoxazole was the major causative agent of FDE, which is consistent with the results of other similar studies.[6,7,9] According to the sites involved by FDE, the glans penis was the most commonly involved site (58.0%). This is in contrast to other studies,[6,7] which found the lips to be the most common site for FDE. In the study by Mahboob and Haroon,[7] the genitalia constituted only 20% of all cases. In our study, genital FDE (in males and females) was mainly induced by trimethoprim-sulphamethoxazole, which is consistent with the study by Thankappan and Zachariah.[9] The next common sites of FDE involvement revealed by our study were: the extremities (39.0%), the trunk (20.3%), the lips (6.3%), and the female genitalia (3.1%). Only one patient (1.6%) developed a generalized bullous reaction.

Ciprofloxacin is a considerable offender in our study, causing 3 cases (4.7% of total). This percentage is not seen in previous similar studies.[6,7] In 1996, Dhar and Sharma reported 7 cases of ciprofloxacin-induced FDE, and they suggested that ciprofloxacin could become one of the common drugs causing FDE.[10] Norfloxacin-induced FDE has been reported less frequently,[11] and may have cross-sensitivity with ciprofloxacin, as seen in one of our cases.[12]

Other drugs implicated in causing FDEs have included lamotrigine,[13] codeine,[14] and terbinafine,[15] as well as many non-steroidal anti-inflammatory drugs and many antibiotics (such as penicillins, erythromycin, clindamycin and metronidazole).[7]

FDE has been reported in male patients after history of sexual contact with their spouses, who were found to be receiving the same medication to which the male partners were hypersensitive. It is hypothesized that sexual transfer of the drug antigen occurs through the vaginal fluid on the sensitized area of the male genitalia.[16]

Fluconazole (a triazole antifungal) is a newly reported causative agent of fixed drug eruption.[17] Additional report from India showed a case of FDE due to cross reaction between two azoles, this was in 27 years old female patient due to fluconazole ingestion , similar eruption and at the same sites was triggered by tinidazole ingestion before 4 years.[18]

Finasteride (a competitive inhibitor of a 5 α-reductase enzyme), has been reported recently as a causative agent of solitary penile FDE.[19]

Familial occurrence of FDE has also been reported. Pellicano *et al*[20] suggested a genetic predisposition to FDE and linkage to major histocompatibility class I (HLA-1). In 2001, Ozkaya *et al*[21] published a study that gave new evidence for a link between HLA-1 and trimethoprim-sulphamethoxazole-induced FDE. No familial cases of FDE were present in our study.

The management of fixed drug eruption depends on the severity of the reaction. Of paramount importance is the withdrawal of the offending drug, and its avoidance in the future along with similar drugs in the same drug family, or those with reported cross-sensitivity. For mild cases, withdrawal of the offending drug, with application of mild to moderate topical corticosteroids, and systemic antihistamines are usually sufficient. In severe reactions, the management is similar to other cases of severe allergic reactions, including: intensive supportive, maintaining fluid and electrolyte balance, infection control, systemic corticosteroids, and systemic antihistamines.[3]

Conclusion

Our study highlighted the common occurrence of FDEs, and the range of causative drugs. They were most commonly encountered with trimethoprim-sulphamethoxazole, but quinolones were increasingly seen as causative agents for FDEs. Our study also showed that FDE usually presented as solitary lesion, and in terms of body site distribution the genitalia (mainly the glans penis) was the most frequently involved site.

References

1. **Braun-Falco O, Plewig G, Wolff HH, *et al.*** Reactions to medications. In: Braun-Falco O et al, editors. *Dermatology*. 2nd edition. Berlin: Springer 2000. p 403-430.
2. **Sharma VK, Sethuraman G, Kumar B.** Cutaneous adverse drug reactions: clinical pattern and causative

agents--a 6 year series from Chandigarh, India. *J Postgrad Med* 2001; 47(2), 95-99.
3. **Griffiths WA, Judge MR, Leigh IM**. Drug reactions. In: Champion RH, Burton JL, Burns DA, Breathnach SM. Rook/Wilkinson/Ebling Textbook of dermatology, 6th edition, Blackwell Science Ltd, *United Kingdom*, 1998; p 3349-3517.
4. **Vidal C, Prieto A, perez-Carral C, *et al.*** Nonpigmented fixed drug due to pseudoephidrine. *Ann Allergy Asthma Immunol* 1998; 80: 309-310.
5. **Horn T.** Cutaneous Toxicities of Drugs. In: Elder D et al, editors. Lever's Histopathology of the Skin. 8th edition. Philadelphia: Lippincott-Raven Publishers 1997. p. 289.
6. **Gupta R.** Drug causing fixed drug eruption:- confirmed by provocation tests. *Indian J Dermatol Venereol Leprol* 2003; 69: 120-121.
7. **Mahboob A, Haroon TS.** Drugs causing fixed drug eruption: a study of 450 cases. *Int J Dermatol* 1998; 37: 833-838.
8. **Yoshiko M, Yoshimi Y, Yuichi Toshimi *et al.*** Direct evidence for interferon-Gamma production by effector-memory-type intraepidermal T-cells residing at an effector site of immunopathology in fixed drug eruption. *Am J Pathol* 2002; 161:1337-1347
9. **Thankappan TP, Zachariah J.** Drug-specific clinical pattern in fixed drug eruption. *Int J Dermatol* 1991; 30: 867-870.
10. **Dhar S, Sharma VK.** Fixed drug eruption due to Ciprofloxacin. *Br J Dermatol* 1996; 134: 156-158.
11. **Fernandez-Rivas M.** Fixed drug eruption (FDE) caused by norfloxacin. *Allergy* 1997;52:477-478.
12. **Alonso MD, Martin JA, Quirce S, *et al.*** Fixed eruption caused by ciprofloxacin with cross-sensitivity to norfloxacin. *Allergy* 1993; 48: 296-297.
13. **Hsiao C, Lee J, Wong T, Sheu H.** Extensive fixed drug eruption due to lamotrigine. *Br J Dermatol* 2001; 144: 1289.
14. **Gonzalo MA, Revenga F.** Fixed drug eruption due to Codeine. *Br J Dermatol* 1996; 135: 661-662.
15. **Munn SE, Russell R.** Terbinafine and fixed drug eruption. *Br J Dermatol* 1995; 133: 815-816.
16. **Zawar V, Kirloskar M, Chuh A.** Fixed drug eruption - a sexually inducible reaction? *Int J STD AIDS* 2004; 15:560-563.
17. **Mahendra A, Gupta S, Gupta S, *et al.*** Oral fixed drug eruption due to fluconazole. *Indian J Dermatol Venereol Leprol* 2006; 72(5): 391.
18. **Bansal A, Kumari R, Ramam M.** Fixed drug eruption due to cross reaction between two azoles used for different indications. *Indian J Dermatol Venereol Leprol* 2008; 74(1): 81.
19. **Oyama N, Kaneko F.** Solitary fixed drug eruption caused by finasteride. *J Am Acad Dermatol* 2009; 60(1): 168- 169.
20. **Pellicano R, Ciavarella G, Lomuto M, *et al.*** Genetic susceptibility to fixed drug eruption: evidence for a link with HLA-B22. *J Am Acad Dermatol* 1994; 30: 52-54.
21. **Ozkaya-Bayazit, Akar U.** Fixed drug eruption induced by Trimethoprim-sulphamethoxazole: evidence for a link to HLA-A30 B13 Cw6 haplotype. *J Am Acad Dermatol* 2001; 45: 712-717.