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A study of drugs causing fixed drug eruptions in a Tertiary Care Hospital

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Abstract
Adverse drug reactions (ADR) are among the most frequent problems encountered clinically and represent a common cause for hospitalization.Fixed drug eruptions are common cutaneous ADR.The aim of this study is to evaluate the drugs and the clinical pattern of drug induced Fixed Drug Eruptions (FDE), in a tertiary care hospital, in the southern region of Tamil Nadu. Sixty cases with established FDE were evaluated clinically. The drugs commonly reported were Cotrimoxazole (25%), Non Steroidal AntiinflammatoryDrugs (NSAID) (21.7%), Tetracyclines (11.7%), Ciprofloxacin (6.7%), Amoxycillin (5%) and Metronidazole (3.3%). Cotrimoxazole was the leading etiological agent in our population. The lesions were found to be distributed on the oro-genital mucosa, trunk and the acral regions.The clinical pattern and drugs causing FDE were almost similar to those observed in other countries except for some minor variations, which may be due to the differences in the individual's health care seeking behavior.

Key-Words: ADR, FDE, Cotrimoxazole, NSAID

Introduction
All drugs whether used topically or systemically are capable of producing noxious, unintended, undesired sequelae of symptoms in man(Seth S D 2009). An Adverse Drug Reaction has been defined as "any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug''(Tripathi K D 2008). All cutaneous eruptions are distinct disease entities and different drugs are associated with different types of reactions. The term Fixed Drug Eruptions describes the development of one or more annular or oval, erythematous patches as a result of systemic exposure to a drug, which usually resolves with a residual hyperpigmentation(David F et al 2010). They recur at the same site with each exposure to a particular medication, usually those taken intermittently. The characteristic early lesion is a sharply demarcated macule,round or oval in shape,occurring within minutes to hours after ingestion of the offending drug.

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The lesions may become edematous,thus forming a plaque,which may evolve to become a bulla and then a erosion and heals, with or without pigmentation (Klaus Wolff 2005).The morphological features would be the same in both mucosal and cutaneous leisons. Though numerous drugs were implicated as causatives for FDE, the causative drugs and the pattern of distribution varies with each country, because of the difference in the health seeking behaviour of the individuals in different countries.

Based on this objective, this study was carried out to present a series of cases of FDE attending the outpatient department of a tertiary care hospital,over a period of twelve months, to diagnose the suspected drug and to identify the pattern of distribution of FDE, due to different drugs, so that awareness could be created among the patients regarding the FDE inducing drugs.

Material and Methods
It was a clinical, observational study,conducted in the Institute of Pharmacology, Madurai Medical College, Madurai and in the Out-patient Department of Dermatology, Govt.Rajaji Hospital, Madurai, over a period of twelve months.(December 2010 - November 2011). Patients with drug induced fixed eruptions, of both gender, under all age group were included. Fixed

eruptions due to other causes.(cashew,liqorice) and other cutaneous eruptions caused by drugs(Steven Jonson syndrome,Toxic epidermal necrolysis) were excluded. Drugs causing FDE was taken as the Primary end point; nature of the lesion – bullous / non-bullous and pattern of distribution – skin / mucosa was taken as the secondary end point.

A detailed history regarding the drug intake, mode of drug administration, nature of illness for which the drug was taken, total number of doses taken, whether had been prescribed by a Registered Medical Practioner or taken over the counter, was evaluated.A thorough clinical examination was carried out. To establish the etiologic agent, attention was paid to the history of drug intake, temporal correlation with the drug intake, approximate incubation period, improvement of lesions on withdrawal of the drug and recurrence of the lesions on rechallenge. All the informations were carefully recorded in a specially designed proforma.The significance of the preferential site of involvement due to specific drugs was statistically evaluated by Fischer's exact test (Kulkarni S 2009). P value of < 0.05 was considered to be statistically significant. The statistical analysis was carried out only for drugs that caused lesions in more than ten patients.

Results and Discussion

Of the sixty cases seen, there were 32 males (53.3%) and 28 females (46.7%).The age of the patients ranged between 10 months and 70 years (mean=29.6).The distribution of cases in relation to age and gender are provided in Table-1. Females were predominant among the age group between 30 & 39years (mean=33.1); no such predominance was observed in males.The drugs were taken commonly for fever, upper respirtory tract infection, urinary tract infection or for tooth-ache.The incubation period varied between 2 hours to 20 days.Fifteen patients (25%) had taken the drug over the counter, without a proper prescription from a Registered Medical Practitioner.The causative drugs for FDE are shown in Table – 2.

PATTERN OF DISTRIBUTION:

Regarding the pattern of distribution of the lesion, the most frequently involved site was the oro-genital mucosa among males; trunk and extremities among females.Cotrimoxazole preferentially caused FDE in the mucosa (Fig.1) and NSAID in the skin (Fig.2). The localisation of leisons in relation to drugs is shown in table 3.

NATURE OF THE LESION:

Ten patients had more than 5 lesions and cotrimoxazole was the offending agent in eight. Thirteen patients had bullous FDE, cotrimoxazole being the offending agent, followed by Doxycycline. Size of the lesions ranged between 1 – 10 cm. Lesions were mainly of a classical type presenting with erythematous macules and occasional bulla formation. Most of the solitary lesions on the glans penis were exclusively bullous.

Adverse drug reactions are claimed to be the fourth leading cause of death,preceded by Cancer Lung , AIDS, accidents and automobile deaths(Bertram 2009).FDE was observed as a common ADR due to drugs (Sharma V K et al).A slight male preponderance was observed, (M:F = 1.4 : 1) as already been reported (Sharma V K et al 1996). Persons around 11 – 40 years are commonly affected(Mehta et al 1971).Most of the drugs were taken for fever, upper respiratory tract infections or urinary tract infections.Majority of patients had eruptions following a single dose and few patients after three doses. Some patients had taken more than one drug over the counter without proper prescription by a registered medical practitioner.

In concordance with the findings of others,(Mehta et al 1971)Cotrimoxazole was the most common drug causing FDE in our study.The prevalence varies with different studies (Mehta et al 1971, Parischa J S 1979) Tetracyclines were reported to be the commonest cause of FDE in one study(Parischa J S 1979) , and in another study, ciprofloxacin was more common (Dhar S et al 1996).

Regarding the pattern of distribution, cotrimoxazole induced FDE were mainly located on the oro-genital mucosa (Kanwar et al 1988),followed by trunk and extremities(Thankappan et al 1991).In two studies investigating the drug related specific pattern in FDE, tetracyclines was the only significant cause of FDE on male genitals, although cotrimoxazole was the most common offender for FDE(Thankappan et al 1991, Sharma V K et al 1996).In our study also tetracyclines had induced FDE on male genitalia. In concordance with the previous studies, NSAID induced FDE were located on the trunk and extremities (Sharma V K et al 1998).Among the NSAID's Brufen, Nimesulide and Paracetamol had caused FDE.In patients who had taken Paracetamol, it was not the sole agent and it was taken in combination with other NSAID's or antibiotics.These drugs had been taken by the patients themselves over the counter and some had been prescribed by registered medical practitioners also. Amoxycillin induced FDE were confined to the palms and soles. Other drugs like ciprofloxacin and metronidazole had induced FDE on the extremities.Repeated attacks of FDE, would always result in pigmentation (Esen Ozkaya et al 2000).

Almost all the patients with recurrent FDE had residual pigmentation.

The main goal of treatment would be to identify the causative agent and avoid it.Otherwise the treatment for FDE would be symptomatic.Systemic anti-histamines and topical corticosteroids would be sufficient.The clinician should consider discontinuing all but the essential drugs required for the patient care.The patients could be prescribed with the medications with the same pharmacological effects but with different chemical structures from those of drugs in question.(Susan Burgin 2009)Post-marketing voluntary reporting of these FDE's remains crucial to enhance the safe use of pharmaceutical agents.(Neil H 2003)

Conclusion

From this study it was observed, that Cotrimoxazole(25%) was the major etiological agent in causing FDE in the southern part of Tamilnadu, followed by NSAID's (21.7%),Tetracyclines (11.7%),Ciprofloxacin (6.7%), Amoxycillin (5%), Metronidazole(3.3%)and Cephalosporins (1.7%). Few patients (21.7%) had bullous FDE, of which Cotrimoxazole was the offending agent, followed by Doxycycline.In males oro-genital mucosa was commonly affected; whereas in females the lesions were distributed among the trunk and extremities.

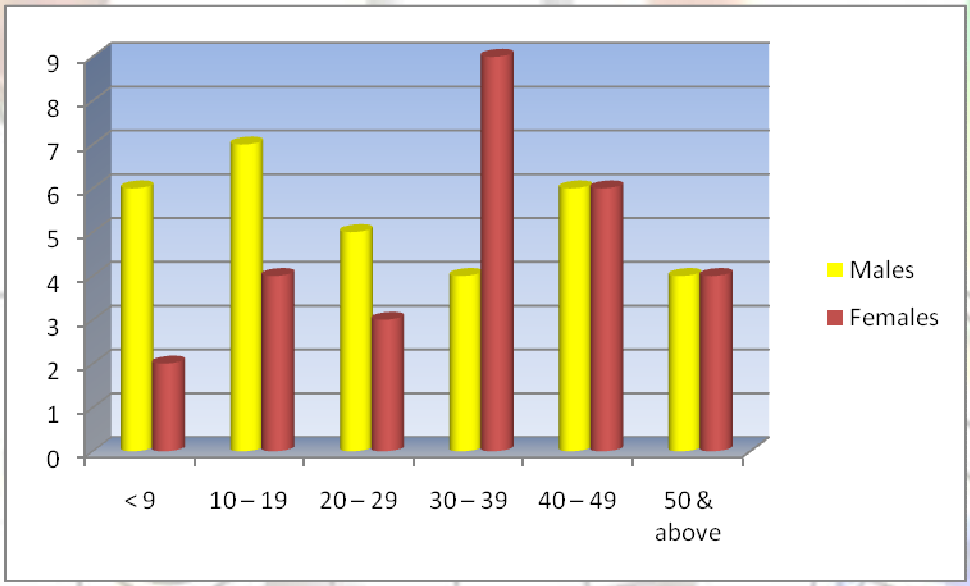
The treatment of FDE was only symptomatic,which includes administration of systemic anti-histaminics and topical corticosteroids.The patients could be advised to carry a card containing the details of the drug to which they develop FDE or to wear a bracelet(eg: medicAlert) detailing the nature of the reaction and the drugs causing them to avoid unnecessary causality in the future.The essential drug list varies,depending upon the priority health care needs of each country;similarly it is apparent that each country has to establish its own list of the most frequent FDE inducers, as drugs used in various countries differ from each other.These drug lists can be published by the Government, to create awareness among the patients; so that the patients may seek the help of a registered medical practitioner to get rid of their infections, instead of taking the drug over the counter.

References

1. Bertram G.Kakung, Susan B.Masters, Anthony J.Trevor.B.Basic and clinical pharmacology, 11th edition, 2009: p-73.
2. David F – Butler, Jordan R.Ilse.Fixed drug eruptions, E-medicine Dermatology-2010.
3. Dhar S, Sharma VK. Fixed drug eruptions due to ciprofloxacin.Br J Dermatol 1996; 13: 156 - 158.
4. Esen Ozkaya – Bayazit, Halil Bayazit, Guzin Ozarmagan.Drug related clinical pattern in fixed drug eruptions; European J of Dermatol.2000; 10:288-91.
5. Kanwar AJ, Bharija SC, Singh M, and Belhaj MS.Ninety eight fixed drug eruptions with provocation tests. Dermatologica 1988; 177:274-9.
6. K.D.Tripathi.Essentials of Medical Pharmacology, 6th edition. JP Brothers Medical Publisher's: 2008.p- 78.
7. Klaus wolff, Richard Allen Johnson, Dick Suurmond.Colour atlas and synopsis of Clinical Dermatology: 5th edition.McGraw Hill: 2005.p-556.
8. Kulkarni S K.Handbook of experimental Pharmacology,3rd edition.vallabah prakashan.2009.p- 182-183.
9. Mehta TK, Marquis L, Shelty JN.A Study of seventy cases of drug eruptions.Indian journal of Dermatology, Venereology and Leprology.1971; 37:1-5.
10. Neil H shear,Sandra R.Knowler,Lori Shapiro.Fitzpatrick's dermatology in general medicine,7th edition.the McGraw – Hill companies;2003.p-359-362.
11. Parischa JS.Drugs causing fixed drug eruptions.Br J Dermatol. 1979; 100; 183-185.
12. Sehgal VN, Gangwani OP.Fixed drug eruptions – current concepts. Int.J.Dermatol 1987; 26:67-74.
13. Seth.S.D, Vimlesh Seth. Textbook of Pharmacology, 3rd edition. Reed Elsevier India Private Limited; Elsevier: 2009.P-I.48.
14. Sharma VK, Dhar S, Gill AN.Drug related involvement of specific sites in fixed eruptions: a statistical evaluation.J Dermatol 1996; 23:530-4.
15. Sharma V.K., G.sethuraman, B.Kumar.Cutaneous Adverse drug reaction patterns to Antimicrobial drugs in North-India.J.Assoc Physicians India 1998; 46:1012-15.
16. Susan Burgin, Stephen E.Wolverton, Jeffry P.Callen.Dermatological signs of internal disease, 4th edition. Elsevier Inc.2009.p- 409.
17. Thankappan TP, Zachariah J.Drug specific clinical pattern in fixed drug eruptions. Int.J.Dermatol.1991; 30:867-70.

Table1: Distribution of cases in relation to age and gender

Age in years	Males	Females	Total
< 9	6	2	8
10 – 19	7	4	11
20 – 29	5	3	8
30 – 39	4	9	13
40 – 49	6	6	12
50 & above	4	4	8
Total	32	28	60

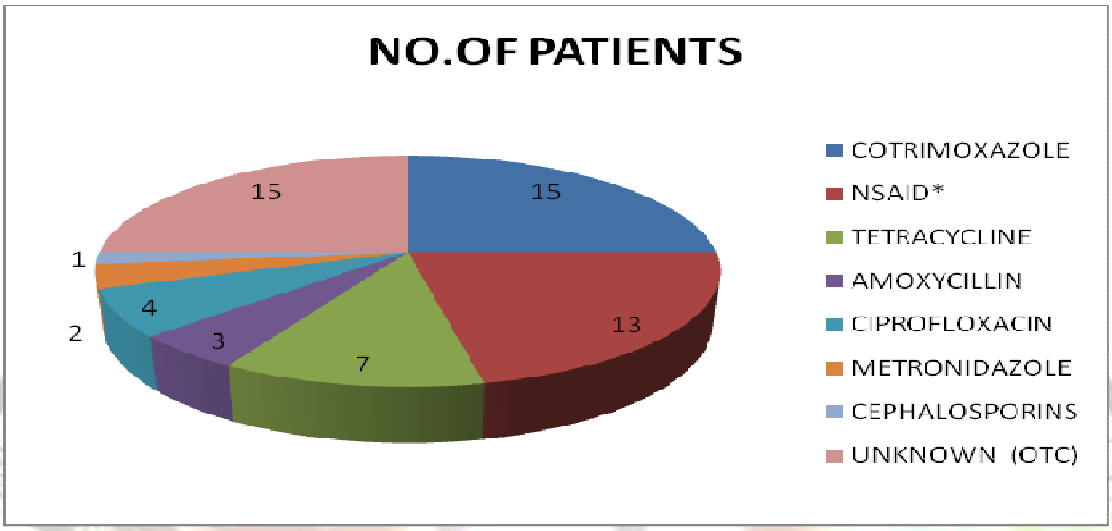


Graph 1: Distribution of cases in relation to age and gender

Table 2: Drugs causing fixed drug eruptions

Drugs	No. of Patients	Percentage
COTRIMOXAZOLE	15	25
NSAID*	13	21.7
TETRACYCLINE	7	11.7
AMOXYCILLIN	3	5
CIPROFLOXACIN	4	6.7
METRONIDAZOLE	2	3.3
CEPHALOSPORINS	1	1.7
UNKNOWN (OTC)	15	25

OTC – Drugs taken over the counter, *NSAID – Brufen, Nimesulide, Paracetamol.

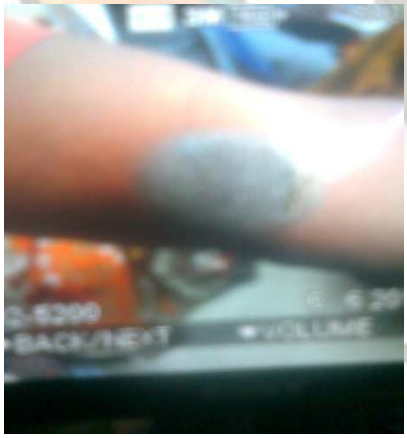


Graph 2: Drugs causing fixed drug eruptions

Table 3: Localisation of leison

DRUG	MUCOSA	FACE	TRUNK & EXTREMITIES	ACRAL LEISONS	TOTAL NO. OF CASES
COTRIMOXAZOLE	12*	1	2	-	15
NSAID	4	-	9*	-	13
TETRACYCLINES	4	-	3	-	7
AMOXYCILLIN	-	-	-	3	3
CIPROFLOXACIN	1	1	2	-	4
METRONIDAZOLE	1	-	1	-	2
CEPHALOSPORINS	-	-	1	-	1
UNKNOWN	4	1	7	3	15
TOTAL	26	3	25	6	60

*statistically significant ($p<0.01$)



(Fig. 1)

(Fig. 2)