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Fixed drug eruptions : A systemic review of published case reports in Indian Scenari

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Abstract:

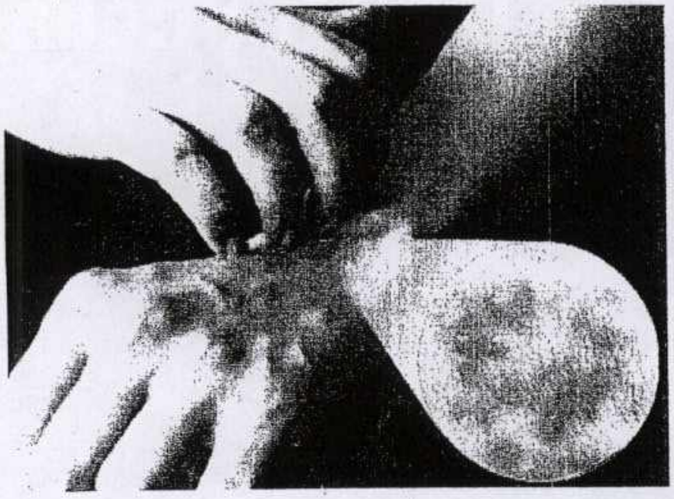
Context: The number of drugs causing Fixed Drug Eruption (FDE) keeps on increasing as new drugs get discovered. The distribution of the condition also varies according to the type of drugs used in the particular area.

Aims: The authors analysed 43 case reports of FDEs reported from India in the past twenty five years with the objective of adding rarer and new cases to the existing list of drugs causing FDE in India.

Methods and Material: Using PUBMED, google as well as manual search, the authors searched for articles from 1982 to June 2007 in the Indian setting. Criteria such as age of patient, sex, drug causing FDE with trade name, indication for use, dose, route of administration and duration of therapy, type and severity of FDE, time of onset of symptoms, dechallange if done, time for recovery, rechallange if carried out, time of onset on rechallange, past history and skin biopsy if taken were also noted. The level of evidence for each drug was assigned as 'certain', 'probable', 'possible', 'unlikely' according to the WHO classification.

Results: A total number of 43 cases were evaluated. Most of the reactions were caused by antibiotics (n=21), 8 being caused by ciprofloxacin. Of the 46 drugs causing reactions, the evidence was certain in 38 cases, probable in 5 cases and possible in 3 cases.

Key-words:
fixed drug eruption, systematic review



Introduction:

Fixed Drug Eruptions (FDEs) can be defined as sudden onset of round and/ or oval, oedematous, dusky red macules/ plaques on the skin and or mucous membranes, accompanied by burning and/ or itching. Vesicles, bullae and denuded skin, which is the extensive form of fixed drug eruptions, may also be present. The most important feature of this condition is the recurrence of the lesion on precisely the same site when the drug is reused.[1] Usually one drug is involved, although independent lesions from more than one drug have been described.[2] FDE is more common on limbs than trunk; the hands, feet and genitalia are favourite sites. Pigmented macules of tongue have also be reported as' fixed drug eruptions.[3] A number of drugs have been incriminated in causing FDE ever since it was first defined by Brocq in 1894.[4] The list keeps increasing as new drugs get discovered. The drugs causing the FDEs also vary in different geographic areas, depending on the diseases prevalent and the available medicines.[1]

We analysed 43 case reports of FDEs reported from India in the past twenty five years with the objective of adding rarer and new cases to the existing list of drugs causing FDE in India. We also analysed the level of evidence for each case to determine the quality of reporting.

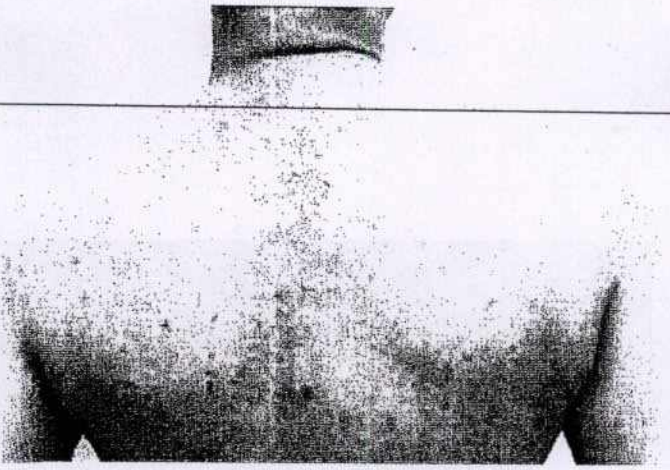
Methods:

An extensive search was carried out by the two authors independently. It included an internet search as well as a manual search through Indian Medical journals. Using PUBMED and a popular search engine 'google', the authors searched the internet for articles from 1982 to June 2007 using search words 'fixed drug eruption', 'case reports', 'FDE'. Articles from Indian journals as well as non-Indian journals but reported from an Indian setting were included. A manual search through

indication for use, dose, route of administration and duration of therapy were recorded. Type and severity of FDE, time of onset of symptoms, dechallange if done, time for recovery, rechallange if carried out, time of onset on rechallange, past history and skin biopsy if taken were also noted. Exclusion criteria included non-English language articles, insufficient data, and pediatric age group. Reviews and case reports were excluded due to lack of information on individual cases. The level of evidence for each drug was assigned as 'certain', 'probable', 'possible', 'unlikely' according to the WHO classification.[5] We did not use 'unclassifiable' since articles with insufficient information were excluded from the study. The data recording as well as the level of evidence assignment was done independently by the two authors, and the results were compared and differences settled through discussion.

Results:

Between 1982 and June 2007, a total of 48 articles were retrieved from the internet as well as manual search by the two authors. Of these, 11 were excluded, 4 since they contained cases from pediatric age group and 7 since they contained case series that did not provide any information on individual cases. All the 37 articles included were in English language. A total number of 43 cases were evaluated from these included articles (since 1 study reported 7 cases). The mean age of the included patients was 38±13.50 years. 31 patients were males and 11 were females. The sex of 1 patient was not specified. 1 patient reacted to 3 drugs and another to 2 drugs on different occasions; hence the total number of incidents where the patients reacted was 46. The trade names of most causative drugs were not specified. On 42 occasions, drugs were administered orally and twice by injection. The route of administration on 2 occasions was not specified. In nine cases, lesions were located on the genitalia. The lesions varied from macules and patches to blebs and bullae with erosions. The time of onset of symptoms varied from few minutes to 4 days. Twelve cases did not



time of onset of reactions was specified only in 18 cases and varied from half an hour to 2 days. 12 cases came with a past history of fixed drug eruption. The drugs causing the reactions as well as the level of evidence in each case is presented in Table 1. Antibiotics caused most of the reactions. (n=21). This was followed by NSAIDs (n=6), anti-fungals (n=5), anti-leprosy drugs (n=4), anti-histamines (n=3), anti-helminthics (n=2), and anti-hypertensives (n=2). There was 1 case each reported about anti-tubercular drug (thiacetazone), immunomodulator (azathioprine) and multivitamin multimineral preparation. Of the 46 occasions in which the drugs caused reactions, the evidence was certain in 38 cases (thirty-one cases confirmed by therapeutic rechallange and seven cases confirmed by repeated administration of the drug on a different occasion), probable in 5 cases and possible in 3 cases. Most cases (n=8) were caused by ciprofloxacin.

Discussion:

An adverse reaction is a reaction which is noxious and unintended and which occurs at dosages normally used in man for prophylaxis, diagnosis or therapy of disease or modification of physiological function.[6] Fixed drug eruption is a common type of adverse drug reaction encountered in skin clinics.[7] The characteristic feature of this condition is that the lesion appears at the same site each time the person takes the drug.[8] Though it may appear trivial in most cases, it can cause cosmetic embarrassment.[9] Drugs causing FDEs include phenolphthalein, sulfonamides, phenylbutazone, barbiturates, dapsone, chlordiazepoxide, indomethacin, quinine, salicylates and tetracyclines.[10] More and more drugs are being added to the list, as newer drugs are being discovered.[1]

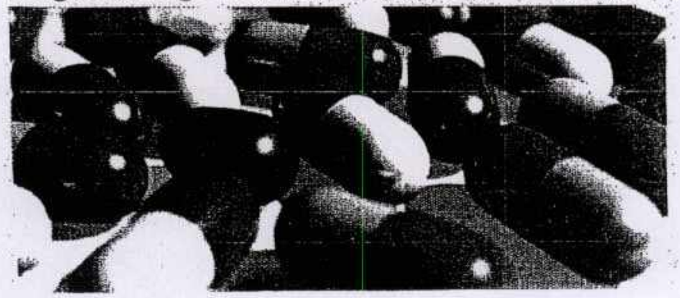


Table 1

Name of drug	Indication for use	Sites involved	Total no. of FDE reactions	Certain	Probable	Possible
Ciprofloxacin	Enteric fever, UTI (2 cases), gonococcal urethritis, RTI (2 cases) Recurrent furunculosis, PUO	Hand, trunk, arms, legs, lips	8	6	2	-
Rifampicin	Leprosy	Upper extremities (find out other sites)	4	3	1	-
Fluconazole	Candidiasis (2 cases), tinea cruris and corporis, pruritic eruption of glans	Palm, dorsum of hand, hard palate, glans and corona	4	4	-	-
Metronidazole	Amoebiasis, 1 case not specified	Male genitalia (2 cases), lower lip	3	3	-	-
Cetirizine	Urticaria (2 cases), T.corporis	Chest, trunk, forearm	3	3	-	-
Ampicillin	UTI, RTI	Chest, back	2	2	-	-
Demeclocycline	Post-op, 1 not specified	Male genitalia, upper extremity	2	2	-	-
Tinidazole	Diarrhoea, Amoebiasis	Glans, penis, lower lip (1case not specified)	2	1	1	-
Cotrimoxazole	Not specified	Buttock, thighs, forearms	2	2	-	-
Levamizole	Helminthiasis	Trunk, limbs	1	1	-	-
Mebendazole	Pruritis ani	Trunk, limbs	1	1	-	-
Amphotericin B	Chromoblas--tomycosis	Not specified	1	1	-	-
Azathioprine	Bullous pemphigoid	Feet	1	1	-	-
Analgin	Rheumatoid arthritis	check	1	1	-	-
Nimesulide	Not specified	Lips-check	1	-	1	-
NSAID	fever	Genital mucosa, hands, feet	1	-	1	-
Etoricoxib	Bursitis of knee	Forearm	1	1	-	-
Paracetamol	Fever	Leg	1	1	-	-
Aspirin	Not specified	Male genitalia, lips	1	1	-	-
Carvedilol	Hypertension	Not specified	1	1	-	-
Dihydralazine sulphate	Hypertension	Face	1	1	-	-
Multivitamin multimineral preparation	General debility	Upper arm	1	-	1	-
Trimethoprim	Not specified	Limbs, abdomen, glans penis	1	-	-	1
Thiacetazone	Tuberculosis	All over the body	1	1	-	-
Erythromycin	Chancroid	Glans penis	1	1	-	-

The incidence of FDE also varies according to the geographical area the drug is used. Genetic variation may also be responsible for causing FDE.[1] None of the earlier studies analysed reports of FDE only from India. We analysed the incidence of FDEs in India and also rated the level of evidence for each case to check out the reliability of the case reports.

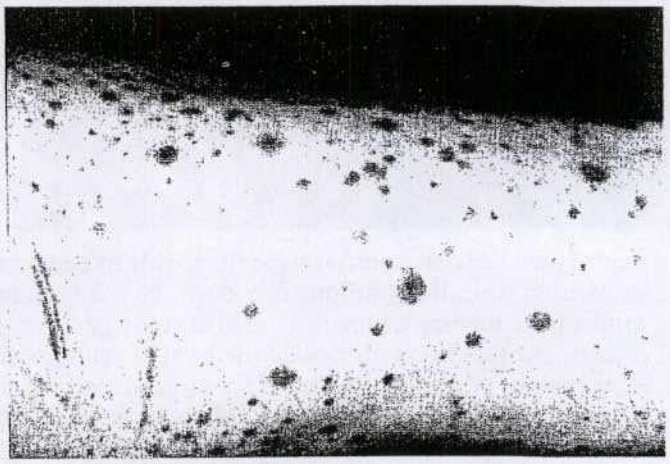
In our study, the mean age of patients included was 38±13.50 years. Most of the patients were males. This result is similar to those seen in other studies.[11] Trade names of drugs were not specified in most cases. Authors reporting cases should be encouraged to mention the trade names of the drugs since, sometimes the FDEs are not caused by the drugs themselves but by the additives such as colouring agents and flavouring agents.[12] For the same reason, re-challange should be done by the pure form or another brand of the same drug rather than the same brand. [13]

In our study, antibiotics caused maximum reactions. (n=21) This reflects the indiscriminate use of antibiotics in our country. [14] Majority of the drugs were administered orally. This can be attributed to the fact that most cases were outpatients.

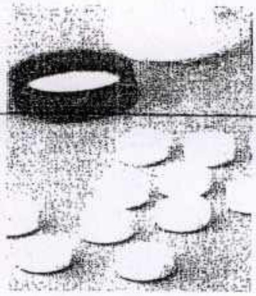
The level of evidence in most cases was certain as demonstrated by rechallange. This emphasises that usually good quality case reports were published in the literature.

In some cases, time for recovery and time of onset on rechallange was not specified. This warrants better reporting of cases. Also, skin biopsy, if taken, will help to get a confirmation of the case. Most FDEs were mild and subsided spontaneously or with antihistamines and/or steroids.

Many may argue that case reports may not provide reliable evidence for clinical decision making. Evidence provided by randomized controlled trials is usually considered most reliable.[15] Yet others say that they provide incomplete data and paint the wrong picture about the disease in question.[16] However, case reports do help to caution doctors and stimulate further research.[15] In addition, many important adverse drug reactions were initially discovered in case reports. We also need to emphasise that the authors are mainly concerned in bringing out the rarer cases of FDE in the Indian population rather than dwelling on the already known cases. The picture would have been more complete if case reviews and prospective and retrospective studies were also included, but we were unable to do so since details on individual cases were not provided



Conclusions



Indiscriminate use of antibiotics should be reduced. Though the quality of cases reported was good, better reporting of details of the cases is warranted in most cases.

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