

Pharmacology and therapeutics

Fixed drug eruption in Bangladeshi population: confirmed by provocative test

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Abstract

Background Fixed drug eruption is designated as a typical allergic reaction occurring due to exposure to a medicine. This common dermatological condition is often being ignored for its causative agent as well as the patient's sufferings sometimes become unpredictable.

Aims The objective of this large population study is to identify the causative agents responsible for fixed drug eruption.

Materials & Methods The study is comprised of 120 suspected patients of fixed drug eruption. History, classic clinical features of well circumscribed erythema, edema, and violaceous pigmentation, and the recurrence of the eruptions on the same sites upon re-administering drug were used as diagnostic criteria. The drug(s) causing allergic reactions were confirmed by provocation tests.

Results The incidence of drug eruption was found distributed in 0.62% amongst all dermatology outpatient attendees. The male to female ratio recorded was 7:2. The highest number of cases was observed within in the age group of 21–35 years. The provocation tests were positive in 92 among 120. The genitalia and lips/face were the most commonly affected site for fixed drug eruption.

Discussion The drug sulphonamide (including co-trimoxazole) accounted for the highest number of cases of eruptions (28.33 %). The other drugs, in order of frequency, responsible for the cause of eruptions were identified as nonsteroidal anti-inflammatory drugs, tetracycline, metronidazole, herbal medicine, paracetamol, fluconazole, penicillin, Griseofulvin, and homeopathic medicine, etc.

Conclusion Drug reactions are very frequently experienced by dermatologists in their day-to-day practice. The patients are often ignorant of the drugs consumed and often do not accept them as an etiologic factor. A detailed drug history as well as the complaints will be helpful before undertaking the provocation test.

Introduction

Fixed drug eruptions (FDEs) are defined as recurrent lesions occurring at the same skin or mucosal sites following repeated intake of the causative agent.¹ Allergic drug reactions are recognized as the most frequent and important adverse reactions brought about by a drug. About 30% of all adverse reactions to drugs cause involvement of the skin.² Skin can get involved in two ways: dermatitis medicamentosa due to locally applied medicine; and drug eruptions due to systemically administered drug. Researchers indicated that systemically administered drugs could produce a variety of reaction patterns. Pruritus, the only frequent manifestation of a drug reaction has been encountered to precede the eruption.³ Other commonly encountered reactive patterns include: (i) urti-

caria and angioedema; (ii) exanthematous eruptions, including macular, papular, papulovesicular, papulosquamous, vesiculobullous, and purpuric eruptions; (iii) erythema multiforme; (iv) Stevens–Johnson syndrome; (v) toxic epidermal necrolysis; (vi) exfoliative dermatitis; (vii) lupus erythematosus-like syndrome; (viii) lichenoid eruptions; and (ix) FDEs.

Fresh FDE lesions are well-defined round or oval patches of redness and swelling of the skin, sometimes surrounded by a blister. With age, the lesions fade to a purplish or brown color. They are usually developed within 30 minutes to 8 hours following intake of drugs and are sometimes solitary at first. With repeated attacks, new lesions may appear, and the existing one may increase in size. Lesions are found more common on the limbs than the trunk, hands, and feet. Genitalia (glans

penis) and perianal areas are favorite sites. Lesions may occur around the mouth or eyes. The genitals or inside the mouth may get involved in association with skin lesions or on their own. As healing occurs, crusting and scaling are followed by a persistent dusky brown color at the site. This may fade but often persists between attacks. Pigmentation tends to be more extensive and pronounced in people with darker skin. Pigmentation from FDE fades away as the causative drug is withdrawn. Local or general symptoms accompanying an FDE are mild or may be absent. The objective of the present study is to determine FDE episodes in outpatients in Bangladesh and evaluate the provocation test with the suspected drug for proof in establishing the diagnosis of drug eruptions.

Materials and methods

The study comprises 120 patients seen in the outpatient Department of Dermatology and Venereology at the Community Based Medical College (Bangladesh) suspected of developing drug reaction eruptions.

Case history

A detailed history was taken for every case with special emphasis on timings and dosages of all the drugs taken by the patient and exact timings of the onset of drug eruption and its subsequent evolution. Besides, they were asked about the duration of the present episode, any aggravating factor(s), and treatment already taken. The timings of withdrawal of any such drug(s) and the effect of the withdrawal with respect to his/her symptoms were carefully evaluated.

Provocation test

Bearing in mind the necessary preventive measures, when the patient was symptom free clinically after one month, they were subjected to the provocation test done with all the suspected drugs taken by them. On the first day, the patient was given one-fourth to half of the therapeutic dosage. If there was no reaction during 24 hours, the patient was given full therapeutic dosage on the second day. If still there was no reaction, the patient was given one day's full therapeutic dosage. At this stage if there was again no reaction, the drug was considered safe. In this manner, each patient was tested with all drugs suspected to be responsible for the eruptions. Patch tests were not done in any of the cases.

Results

Table 1 demonstrates the result of number and percentage of patients that reacted to different drugs and were found to develop FDE. It is revealed that sulfur drugs and non-steroidal anti-inflammatory drugs created the greatest number of reactions with 34 patients (28.33%) followed

Table 1 The drugs causing FDE in patients

Kinds of drugs causing FDE	No. of patients (n) reacted and developed FDE	% of patients with FDE
Sulfur drugs (cotrimoxazole, sulfasalazine, dapsone)	34	28.33
NSAIDs (naproxen, indomethacin, diclofenac, mefenamic acid, ibuprofen, aspirin)	17	14.16
Tetracycline/doxycycline	09	7.50
Metronidazole	08	6.66
Herbal medicines	07	5.83
Paracetamol	05	4.16
Fluconazole	05	4.16
Penicillin	05	4.16
Griseofulvin	03	2.50
Homeopathic medicines	03	2.50
Sedatives (benzodiazepine)	02	1.66
Ciprofloxacin	02	1.66
Chloroquine/hydroxychloroquine	02	1.66
Pseudoephedrine	02	1.66
Albendazole	02	1.66
Hyoscin- <i>M</i> -butylbromide	01	0.83
Clindamycin	01	0.83
Citirizine	01	0.83
Rifampicin	01	0.83

by the NSAID group with 17 patients (14.16%) exhibiting eruptions. Tetracyclines and metronidazole were found to be the next common drugs involved in causing FDE. It is interesting to note that herbal medicines as well as homeopathic medicines could also lead to FDE.

Various sites of the body that have FDEs are shown in Table 2.

The genitalia and lips/face were the most commonly affected followed by trunk and limbs. However, the lesions were found more or less in almost all parts of the body.

It is evident from the result of the investigation as presented in Table 3 that of 120 patients subjected to a provocation test, 92 patients showed reactivation of their

Table 2 The clinical sites of involvement with FDE

Sites of involvement	No. of patients (n) with FDE	% of patients with FDE
External genitalia	39	32.50
Face	32	26.67
Trunk	26	21.67
Limbs	23	19.16
Total	120	100

FDE, fixed drug eruption.

Table 3 Provocation tests of patients with fixed drug eruption

Total no. of cases examined by provocative tests	No. and % of positive cases	No. and % of negative cases
120	92 (76.67%)	28 (23.33%)

lesions. A total of 28 patients did not develop any reaction with all possible drugs during provocation tests. Of positive reactors, six patients developed fresh lesions along with reactivation of the old lesions during provocation tests. Two patients developed blisters at the old reaction sites 2–24 hours after the last provocation dose of the drug. One patient developed depigmentation at the site of reaction.

Discussion

The principles behind the primary localization of lesions in FDE are still unknown. Studies investigating the predilection areas indicated drug-related, trauma-related, or inflammation-related specific site involvement in FDE. The present study showed that the group of drugs most often responsible for eruptions belonged to antimicrobial drugs followed by antipyretic–analgesic drugs. Of the antimicrobial drugs, sulfonamides were involved in the majority of cases, followed by tetracycline and penicillin. Similar observations were also reported by Metha *et al.*,⁴ Kauppinen *et al.*,^{5,6} and Hanumanthappa.⁷ However Mani *et al.*⁸ differed and reported that thiacetazone was the most common antimicrobial drug to cause eruptions. Oxyphenbutazone (13.3%) was the most frequent offending antipyretic–analgesic group to cause drug eruptions followed by analgin. Cotrimoxazole was found causing reactions in a considerable number of patients in the present study and was ascribed to the study conducted by Mehboob and Haroon⁹ in Pakistan. Similar findings were reported by Sehgal *et al.*¹⁰ from India and Konwar *et al.*¹¹ from Libya. This increase could be attributed to easy availability and indiscriminate use of drugs in rural as well as in urban areas in this region and low cost of the drug. In our investigation of drug series, the CNS depressant drug phenobarbital was responsible for eruptions in one case only. The incidence was very low compared to other workers.^{2,5,8} This difference apparently may be due to decreased use of barbiturates as other relatively safer drugs are easily available.

With respect to drugs associated with clinical types of eruptions, it was observed that sulfur produced the largest number of FDE (28.33%), followed by nonsteroidal anti-inflammatory drugs (14.16%), which were similar and in agreement with observations of Mani *et al.*⁸ In the drug

series of Alanko *et al.* from Finland, sulfonamides caused the largest number of exanthematous eruptions (12%).

Provocation tests were done in all cases with the suspected drugs and showed 92 cases with positive results. The likely cause of negative results in the remaining cases could be thought to be due to factors related to wrong diagnoses, smaller provocation test dosage, and patient in refractory period with temporary lack of response to the test dosage. These observations were more or less analogous with Kauppinen *et al.*⁶ and Alanko *et al.*² In this study, positivity of the provocation test was highest with FDE (76.66%), which was similar to the study carried out by Alanko *et al.*¹² The positivism may be due to a correct diagnosis and because it represents a type of eruption caused solely by drugs. Recently many newer drugs such as tinidazole, metronidazole,¹³ clarithromycin,¹⁴ and even cetirizine¹⁵ have caused FDEs. In this investigation, the provocation test is the only reliable method to detect causative agents and is often essential or even mandatory in the patient's interest. Although the provocation test is very safe, especially in fixed eruption, some workers are still unwilling to attempt it. If history suggests severe reaction, it may be safer to start with half the dose on the first day, followed by the full therapeutic dose on the next day provided there is no reaction to the first dose.

Conclusion

Drug reactions are very frequently experienced by dermatologists in their day-to-day practice. FDEs are usually not fatal, but they can lead to undesirable cosmetic embarrassments if present on exposed parts or there is recurrence of the reaction on previously affected sites or residual hyperpigmentation. When genitalia are involved, this is often misdiagnosed as venereal disease and thus creates a psychological problem for patients. The list of common drugs responsible for FDEs does not remain valid because of the introduction of newer additions, variations in use, and availability. Cotrimoxazole topped the list in the present series and was observed as a common offending agent.^{12,16} Patients are often ignorant of the drugs consumed and do not accept it as an etiologic factor. A detailed drug history as well as complaints will be helpful before undertaking the provocation test.

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