Ciprofloxacin and metronidazole induced fixed drug eruption

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Abstract
Fixed drug eruption(FDE) is delayed type of hypersensitivity reaction that occurs as lesions at the same skin site due to repeated intake of an offending drug.FDE can be an adverse event to different fixed dose combinations (FDC)of antiprotozoal and an antibacterial drug.A 40 years old female patient developed Blackish hyperpigmented skin lesions all over body andfluid filled skin lesions over legs and arms with itching following ingestion of Inj.Ciprofloxacin 200mg iv BD and Inj. Metronidazole 500mg iv TDS. Drug was prescribed for acute infective diarrhea and vomiting. After provisional diagnosis of Ciprofloxacin and Metronidazole induced FDE by dermatologist patient was asked to withdraw the drug immediately.The reaction was treated withInj.Pheniramine maleate 1 cc i.v. stat,Inj.Dexamethasone 1cc iv OD, Inj.Ceftriaxone 1g iv BD,Tab. levocetirizine 5mg 1OD,Tab.Betamethasone forte 1mg TDS, for local application calamine lotion, Fusidic Acid cream and Liq. Paraffin was given.Patientrecovered subsequently.It is important to report ADRs,which can help,detect and prevent drug reactions and in turn decrease the cost of treatment and adverse drug reaction causing mortality and morbidity also decreases.Concerted efforts are needed to discourage over-the-counter sales and purchase of nonprescription drugs in order to limit the occurrence of this adverse cutaneous drug eruption.

Keywords: Fixed Drug Eruption, Hypersensitivity, Cross-reactivity.

Introduction
Cutaneous adverse drug reactions (ADRs) are seen in about 1–2% cases. Fixed drug eruption (FDE) is accounts for 10% of all ADRs.It is a delayed type of hypersensitivity reaction that occurs as lesions at the same skin site due to repeated intake of an offending drug. The most common drugs causing FDE areCotrimoxazole (25%), Non SteroidalAntiinflammatoryDrugs (NSAID) (21.7%),Tetracyclines (11.7%), Ciprofloxacin (6.7%) Amoxycillin (5%) and Metronidazole (3.3%).[1]

Diarrheal disorders are quite common in all age groups and are mostly of infective origin.FDE can be an adverse event to many drugs like different fixed dose combinations (FDC)of antiprotozoal and an antibacterial drug whichare marketed in India for the treatment of diarrhea.[2]It is generally believed that if an individual develops FDEs to a particular drug, exposure to structurally similar drugs from the same pharmacological group should preferably be avoided.

Case History
A 40years old female patient was brought to Emergency Medicine Department of a tertiary care hospital with chief complaints of severe diarrhea which was sudden, watery 10-15 times per day, not stained with blood or mucus associated with vomiting which was sudden, non projectile, non bilious, not stained with blood, 3-5 times a day.Patient was completely asymptomatic before 2days.Provisional diagnosis made by physician was acute infective diarrhea.Patient was known case of Hypertension and Diabetes since 3years.On Admission hers vitals were normal except Blood Pressure was 194/110mmhgand HbA1-C was 6.6%. For hers chief complaints following treatment was given:

Inj. Ciprofloxacin 200mg iv BD, Inj. Metronidazole 500mg iv TDS, Cap. Doxycycline 100mgthree Tab stat, Inj. Normal Saline1L iv 40ml/hr, Inj. Labetalol20mg iv slowly over 10min, ORS sachets once after each stool, Tab. Telmisartan+Chlorthalidone 40/12.5mg BD. She was on treatment ofTab. Metformin500mg OD and Tab. Glipizide 2.5mg OD.

Following above therapy, she suddenly developed reddish skin lesions all over body associated with itching. She was immediately given Inj. hydrocortisone ivTDS and Inj.Pheniramine maleateone ampule iv TDS. The most culprit drug causing FDE was identified by physician and Inj. Ciprofloxacin 200mg, Inj. Metronidazole 500mg were immediately stopped and then she was transferred to skin ward. On cutaneous examination lesions were multiple, well defined, discrete, annular, few small and few large centrally hyperpigmented and peripherally erythematous patches present over chest, back, abdomen, buttock, and both upper limb and lower limb.Multiple discrete small fluid filled vesicles present on left and right side of arm and feet. (See Fig. 1and3)Noinvolvementofthe genitaliaandfacewerepresent.Routineblood investigations were normal. Dermatologist diagnosed that case as Ciprofloxacin and Metronidazole induced FDE. For that cutaneous reaction following treatment was given:

Inj. Dexamethasone 1cc iv od for 1week, Inj. Ceftriaxone 1g iv BD, Inj. Ranitidine2cc iv BD, Tab.levocetirizine 5mg 1OD, Tab. Betamethasone forte

1mg given TDS for 3days,calamine lotion local application for 21days, Fusidic Acid cream local application for 21days, Liq. paraffin local application for 21 days from day 10 of reaction Tab. Prednisolone 20mg 1 OD with milk. Patient's condition started improving and her lesions recovered within after 20to25 days by taking above mentioned drug (See Figure:2and4) and was discharged and prescribed to continue Tab. Prednisolone 20mg 1 OD for 15 days, Tab. Levocetirizine 5mg 1 OD for 15days, Calamine lotion Local application for 15days, Fusidic Acid cream local application for 15days.

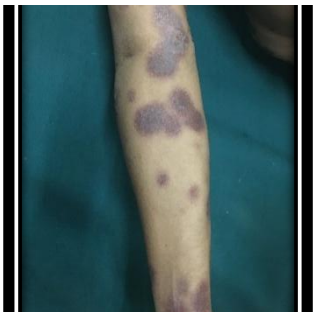

Fig. 1: FDE on forearm at the time of admission

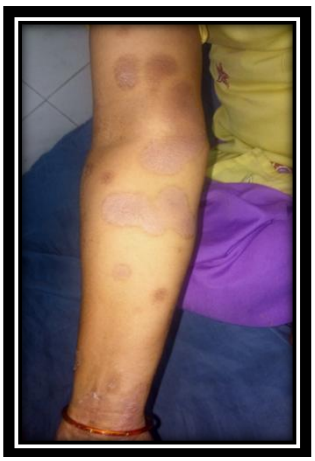

Fig. 2: Healed lesions at the time of discharge

Fig. 3: FDE on buttocks at the time of admission

The causality assessment was carried out using the Naranjo ADR probability scale.3This adverse drug reaction (ADR) after excluding other causative factors categorized under " Possible " category and reported via vigiflow to the National coordinating centrePvPI for ADR monitoring with reference ID:2018-35192.

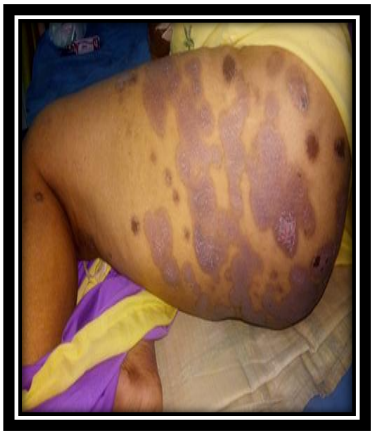

Fig. 4: Healed lesions at the time of discharge

Discussion

The term FDE was first introduced by Brocq in 1894.[4]It is a delayed type of hypersensitivity reaction that occurs as lesions recurs at the same skin site due to repeated intake of an offending drug.The exact mechanism for this FDE is still unclear but, it has been postulated that FDE is due to a delayed classical type IV hypersensitivity reaction mediated by $CD8^+$ T cells.

The drug binds with basal keratinocytes and stimulates the inflammatory process by causing the release of lymphokines, mast cell and antibodies, which in turn cause damage to basal cells. $CD8^+$ on activation causerelease of interferons and cytotoxic granules.[5]A genetic susceptibility to develop a FDE with an increased incidence of human leukocyte antigen-B22 is also a possibility.Histologically, FDE is characterized by marked basal cell hydropic degeneration with pigmentary incontinence. Scattered keratinocyte necrosis with eosinophilic cytoplasm and pyknotic nucleus (civatte bodies) are seen in the epidermis. Infiltration of lymphocytes, histiocytes, and neutrophil polymorphs is evident in the upper dermis.[6]The peak incidence is usually between 21 and 40 years of age which is similar to the our case report.

The list of causative drugs is long, including nonnarcotic analgesics, antibacterial agents, antifungal agents, antipsychotics, other miscellaneous drugs. Even ultraviolet radiation, emotional and psychiatric factors, heat, menstrual abnormalities, pregnancy, fatigue, cold, and undue effort can lead to FDE. It presents mainly as sharply marginated, round or oval itchy plaques of erythema and edema becoming dusky violaceous or brown and sometimes vesicular or bullous lesions on the lip, hip, sacrum, or genitalia.Several variants of FDE have been described, based on their clinical

features and distribution of lesionsincluding pigmented, generalized,linear,nonpigmenting, bullous, eczematous, urticarial erythema dyschromicumperstans, vulvitis, psoriasiform or cellulitis.Most of the reactions occur within 30 min to 1day of drug exposure. In our case it was after two days of therapy.Subsequent reexposure to the medication results in a reactivation of the site, withinflammation occurring within 30 min to 16 h.The lesions may be solitary or multiple. The most common sites are the genitalia in males and the extremities in females.Lesions may persist from days to weeks and then fade slowly to residual oval hyperpigmented patches.The reactivation of old lesions also may be associated with the development of new lesions at other sites. The severity of reactions in FDE may increase after repeated exposures to the drug and very rarely progress to a clinical state called generalized bullous FDE. It may be clinically misdiagnosed as Steven Johnson's Syndrome (SJS) and Toxic epidermal necrolysis (TEN).[7]A diagnostic hallmark is the reappearance of the lesions over the previously affected sites, when the offending drug is reused.Treatment includes stopping the offending drug with oral and topical steroids, emollients, and oral antihistamines. Though usually not fatal, FDE can cause enough cosmetic embarrassment especially when they recur on the previously affected sites leaving behind residual hyperpigmentation.In this case, the patient was prescribed Fixed Drug Combinations of fluoroquinolone and nitroimidazole for treating infective diarrhea of sudden onset.Therefore, this rare case is presented to create awareness about the various side effects associated with this type of very commonly prescribed antibiotics.[8]

Conclusion

Pharmacovigilance for detecting and diagnosing ADR by practicing physicians, general practitioners and family physicians is an essential knowledgefor theirclinical practice. It is also important to report ADRs, which can help, detect and prevent drug reactions and in turn decrease the cost of treatment and adverse drug reaction causing mortality and morbidity also decreases.Educating medical practitioners and other health-care workers such as pharmacists and nurses about this ADR with Ciprofloxacin and Metronidazole, in treatment of diarrhea is important.Appreciating the magnitude of this condition and limiting it's occurrence and recurrence is important for prescribing physicians**.**Concerted efforts are needed to discourage over-the-counter sales and purchase of nonprescription drugs in order to limit the occurrence of this adverse cutaneous drug eruption. The public will also benefit from awareness campaigns on the dangers of over-the-counter and nonprescription drugs that includes FDEs and life-threatening conditions such as Steven Johnson's Syndrome (SJS) and Toxic epidermal necrolysis (TEN).

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