



ISSN: 0975-833X

RESEARCH ARTICLE

CONTEMPORARY TRENDS OF DRUGS CAUSING FIXED DRUG ERUPTIONS

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ARTICLE INFO

Article History:

Received 22nd October, 2014
Received in revised form
10th November, 2014
Accepted 15th December, 2014
Published online 23rd January, 2015

Key words:

Fixed Drug Eruption,
Causality Assessment,
Severity Assessment,
Preventability Assessment.

ABSTRACT

Background: The extensive outgrowth of newer drug molecules not only improves the disease condition but also frequently changes the pattern of Adverse Cutaneous Drug Reaction (ACDR). The need for this study is to identify the current drugs responsible for fixed drug eruption (FDE) and to ensure safety of the patients.

Materials and Methods: The subjects with the diagnosis of FDE were included in the study for a period 12 months. The entire details such as patient's clinical history, drug reaction and detail drug history were noted down. Then the assessment of individual cases was done for causality, severity and preventability using validated scales.

Results: Out of the 38 ACDR cases the total number of fixed drug eruption cases were 18. Male: female ratio was 1.25:1. The mean time between the drug intake and the appearance of eruption was on average of 7.25. The most common suspected drug was paracetamol and fluoroquinolones. Causality assessment showed that 17 cases were of probable category and one was of possible category. Severity assessment showed that 16 were of moderately severe category and two of mildly severe. Preventability assessment analysis has shown that 5 cases as definitely preventable category while the remaining were not preventable.

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INTRODUCTION

In this modern era, newer treatments have brought significant changes in controlling the diseases and provided more benefits to the society. In spite of that it sometimes causes many adverse drug reactions (ADR) which are often preventable but at times it may lead to disability or even death. So the patients who are more prone to these ADR requires careful monitoring. At times it will be very difficult to distinguish between an ADR and that of patient's other disease as they act through the same physiological and pathological pathways. ADR are one among the factors of economic burden to the patient as well as the society (Farcas and Bojita, 2009). One of the most common and typical adverse cutaneous drug reactions (ACDR) is fixed drug eruption (FDE) (Brahimi *et al.*, 2010). This specific drug induced reaction was at first described by Bourns in the year 1889 (Bourns, 1889). FDE can appear anywhere on the skin and its specific feature is that the reappearance of the lesion at the same site when the causative drug is reintroduced (Segal *et al.*, 2007). FDE can appear within a day to a few weeks after the intake of the causative drug depending on the drug and the individual. The most common sites involved are the limbs, tongue, penis and perianal areas. These pruritic lesions are usually well-demarcated, mostly solitary and at times multiple edematous papules or plaques with the colour varying from

dusky red to violet. Post inflammatory residual pigmentation of the lesion may persist for years (Stern and Wintroub, 1999). The FDE can be diagnosed with the help of a rechallenging test which still remains the gold standard for diagnosis of FDE. The test should be performed depending on the severity of the initial reaction. The patient should be given symptomatic treatment and the suspected causative drug should be immediately withheld (Segal *et al.*, 2007). The most common drugs causing FDE are the antimicrobial agents and NSAIDs. Among the antimicrobials the sulfonamides and tetracyclines were commonly involved. Recently, many cases due to ciprofloxacin has also been reported (Sharma *et al.*, 2001) but FDE due to newer generation fluoroquinolones like ofloxacin are rarely reported (Bose, 1995). Due to frequent changes in the treatment schedules and subsequent marketing of newer drug molecules there will be always a change in the drug groups causing FDE. So this study was done to identify the current changes in the drugs that cause FDE in the Puducherry population.

MATERIALS AND METHODS

This is a descriptive, cross sectional study done by the department of Pharmacology with the collaboration of dermatology department for a period of 12 months from June 2009 onwards. After getting approval from Institutional Human Ethical Committee [IHEC], subjects were enrolled into the

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study. Subjects who attended the outpatient department of Dermatology in our tertiary care hospital and diagnosed by two independent dermatologist as having FDE were enrolled into the study.

The subjects were given information about the study and written consent was taken from them. The following were noted down in the Central Drugs Standard Control Organization (CDSCO) Suspected ADR Reporting form - Subject's demographic details, clinical history, detailed drug history, history of drug allergy, family history and history of any skin disease (included only if documented data was available), drug reaction history. The entire data was then entered in Excel sheet for analysis. All the documented data were analyzed for various risk factors causing FDE, common causative drugs etc. Each case was analysed for causality assessment using the Naranjo's causality assessment scale (Naranjo *et al.*, 1981), severity assessment using Modified Hartwig and Siegel scale (Hartwig *et al.*, 1992), preventability assessment by using modified Schumock and Thornton scale (Schumock and Thornton, 1992). Statistical analysis was done using SPSS 17.0 version. Descriptive analysis was done to assess the mean, median and the frequencies of multiple factors like age group, gender, causative drug, intake of multiple drugs, onset of reaction. The enrolled subject were given appropriate treatment by the consulting dermatologist.

RESULTS

Among the 12,764 patients who attended the dermatology outpatient department 38 cases were diagnosed to have ACDR. Out of these 38 cases, 18 cases were of fixed drug eruption. The median age of the subjects with FDE was 32 ranging from 16 to 64 years. Slight male preponderance was found with a male: female ratio of 1.25:1. The suspected drugs list that caused FDE were given in Table 1.

Table 1. DRUGS causing FDE

DRUGS	Number of cases
Fluoroquinolones	4
Cotrimoxazole	3
Diclofenac	1
Ofloxacin + Omidazole	2
Ferrous sulphate	1
Fluconazole	1
Hydroxychloroquine	1
Paracetamol	4
Ibuprofen	1

The time period between the drug intake and the appearance of eruption was on average of 7.25 days ranging from 1 to 37 days. Out of total 18 subjects, 7 had history of allergy, 3 had history of pre-existing diseases such as bronchial asthma, systemic lupus erythematosus and diabetes with renal failure, 10 subjects were taking multiple drugs and 5 of the subjects have taken over-the-counter (OTC) drugs. Of the 18 subjects 5 had history of intake of same drug prior also which was confirmed by the left out strips of medication.

Causality assessment by using WHO scale showed that 17 cases were of probable category and one was of possible

category. Severity assessment showed that 16 were of moderately severe category with the severity level of 3 and two of mildly severe category with the severity level of 1 for one case and 2 for the other case as per the assessment by Hartwig *et al* scale. Preventability assessment analysis has shown that 5 cases as definitely preventable category while the remaining were of not preventable ADR.

DISCUSSION

In our study there was a slightly higher male prevalence which was controversial to the existing data which says that the ACDR are more common in females and female gender is considered as one of the risk factors for the hypersensitivity reactions (Riedl and Casillas, 2003). Antimicrobials were the most common cause of FDE and this finding was well correlated to other studies. The most common offending agents were fluoroquinolones and paracetamol. But this is unlike the prospective observational study done by Raksha *et al* for a period of 10 years from July 1997 to June 2006 in 200 patients with ACDR which has shown that the most common causative agent of FDE was cotrimoxazole (Raksha and Marfatia, 2008). In another study done in Chandigarh by Sharma VK *et al* they have predicted that the most common offending agent to produce FDE was the sulfonamide group of drugs (Sharma *et al.*, 2001). In this study we found that equal number of cases of FDE was due to both paracetamol and fluoroquinolones. This was similar to a study done in France for a period of 3 years by Brahimi N *et al* who found that the paracetamol was the most common offending agent (Brahimi *et al.*, 2010). This may be due to the common prescribing pattern and self-medication habits among the local population. In this study it was interesting to note that 4 cases of FDE were due to fluoroquinolones which may be due to increased use of quinolones over co-trimoxazole.

The most common route of administration of drugs to produce hypersensitivity reactions were topical, intramuscular, and intravenous routes. The oral route is considered safe and less likely to produce hypersensitivity reactions (Riedl and Casillas, 2003). But in our study the picture shows that the most common route of administration of drug to cause FDE was the oral route (90%). In this era of modern therapeutics, per oral preparations have replaced the need for systemic route of administration of many medications and this may be claimed as the reason for more ACDR cases due to oral route of administration. We have also found rare cases of FDE due to ferrous sulphate and fluconazole. Due to ethical issues we have not done re-challenge test to confirm the findings. Most of the cases (64%) were with single lesions and the remaining 36% had 2 or more lesions. In our study nearly 20% of subjects developed FDE due to self-medication. This shows that proper instruction and increasing the awareness is a must to all the subjects for prevention of the adverse reaction in future. FDE due to self-medication of ofloxacin and ornidazole combination was reported in two cases and it shows that improper use of such irrational combination of drugs by the patients. So rigorous steps should be taken to overcome the self-medication practice among the society. The major limitation of this study is that we have not done the re-challenge test due to ethical issues, to identify and confirm the findings and hence it is

reported only as suspected drug rather than causative drug. Hence the causality assessment also showed that majority were of probable category.

Conclusion

ADRs cause a significant problem for patients and also increase their risk of morbidity and mortality.

The ADRs also result in substantial financial burden to the patient as well as the society. Over half of them are definitely or potentially avoidable ADRs and steps should be taken to introduce strategies to reduce their impact for the well-being of the people. Prompt recognition of ADR, adequate and effective clinical management of their outcome are mandatory in promoting patient's safety. Healthcare professionals should definitely consider and analyse the benefit as well as the risk of a drug when making therapeutic choices for a particular disease depending on individual patients. Necessary and strict actions should also be taken regarding the procurement of the over the counter drugs by the people and they also should be educated about the endangerment of self-medication practice.

Acknowledgement

The first author would like to acknowledge the Dermatology department for their valuable support for this study.

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