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Nimesulide-induced Fixed Drug Eruption

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ABSTRACT

Nimesulide is a cyclooxygenase (COX) inhibitor with a high degree of selectivity to COX-2. Nimesulide is a nonsteroidal anti-inflammatory agent with antipyretic and analgesic properties. It is being commonly prescribed in India.[1] Some of the side effects reported with its use are Pruritus, urticaria, purpura, maculopapular rash and localized toxic pustuloderma.[2],[3] Due to severe hepatotoxicity and hemolytic anemia associated with its use, Nimesulide is likely to be withdrawn from the market in many countries.

Case report: The authors report a case of a patient with a history of antihistamine hypersensitivity that developed a bullous form of pigmented fixed drug eruption after Nimesulide. Patch tests performed on residual skin lesion were positive to Nimesulide, confirming that this was the culprit drug.

Keywords: Drug eruption, Fixed drug eruption, Lesion patch testing, Nimesulide, Nonsteroidal anti-inflammatory drugs

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INTRODUCTION:

A fixed drug eruption is an allergic reaction to a medicine that characteristically recurs in the same site or sites each time a particular drug is taken. The number of involved sites may increase over time. Usually just one drug is involved, although independent lesions from more than one drug have been described. Cross-sensitivity to related drugs may occur and there are occasional reports of recurrences at the same site induced by drugs that appear to be chemically unrelated. Sometimes the inducing drug may be re-administered without causing reappearance of the patch (es), and there may be a refractory period during which no reaction can occur after the occurrence of fixed drug eruption. It is thought that an antigen from the drug activates cytotoxic T cells in the epidermis.

These release cytokines (inflammatory mediators), such as interferon- γ , granzyme B, and perforin. The cytokines, with helper T cells and neutrophils, destroy the local skin cells (keratinocytes and melanocytes). The cytotoxic T cells then remain in the epidermis, and release more cytokines when again exposed to the causative drug. Fixed drug eruption presents as well defined, round or oval patches of redness and swelling of the skin, sometimes surmounted by a blister. This then fades to a purplish or

brown colour and the blister shrinks and peels off. In mucosal sites (lips, vulva, penis), extensive ulceration can occur. The hands and feet, lips, eyelids, genitalia and perianal areas are common sites. [4]

CASE REPORT:

We report a case of a 40 year old healthy female referred to our Drug Allergy Clinic for several episodes of lesions after drug administered. Patient was apparently 3days back she developed pains all over the body for which they consulted RMP doctor and prescribed NIMESULIDE. Then patient developed high grade fever, vomiting, and Erythematous lesions after using nimesulide, then lesions gradually increased development of multiple fluid lesions at the same site and developed lesions all over the body. Multiple bullae distributed over hands, thigh region, and forearms. Multiple flaccid bullae of ranging from 2*2cm to 3*5cm.hyperpigmentation over abdomen, thigh region, neck.

Eyes: Erythematous lesions over both upper eyelid surfaces

Nails: yellowish discoloration

Past history: Patient had similar complaints in the past 10years back for which she got treated at SRGH & SRMC

Past medication history: Use of medicines NSAIDS from local RMP doctor



FIXED DRUG ERUPTION DUE TO NIMESULIDE

RESULTS & DISCUSSION:

Nimesulide is a commonly used nonsteroidal anti-inflammatory drug with a reliable safety profile. CADR due to Nimesulide is unusual and is generally of fixed type.[5] Bullous variant is still rarer. Systemic manifestations have also been described in patients with FDE. In our patient, the temporal correlation with the drug, history of a similar episode and the quick improvement led us to a diagnosis of bullous FDE due to Nimesulide. Applying Naranjo's algorithm [6] a causality score of 8 was obtained and was categorized as probable reaction to Nimesulide.

In appropriate clinical settings, other differentials to bullous FDE include blistering disorders, bullous lupus erythematosus, linear IgA bullous

dermatosis and bullous pemphigoid. FDEs may exhibit anatomical preferences to genitalia, lips, and sacrum.[7] In some patients FDE could be a result of cross-sensitivity if the drugs are closely related, however it does not follow an all or none reaction.[8] A repeat exposure at times may not result in FDE owing to refractoriness, and it could vary from weeks to months.[9] Oral rechallenge is the most reliable technique of identifying the causal agent but can be potentially disastrous. A positive patch test over the previously affected area is a relatively safe method. Lymphocyte transformation tests useful in many types of drug eruptions yield poor results in cases of FDE. [10] Discontinuation of the culprit drug is the main aspect of the management of FDE.



Fig: 2 A large red plaque on the cheeks



Fig: 3 The elbow of a young lady with fixed drug eruption



Fig: 4 Plaque with small blisters on elbow

Naranjo’s adverse drug reaction probability scale

	Yes	No	Do not know
Are there previous conclusive reports on this reaction	+1	0	0
Did the adverse event appear after the suspected drug was administered	+1	-1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered	+1	0	0
Did the adverse event reappear when the drug was re-administered	+1	-1	0
Are there alternative causes that could on their own have caused the reaction	+2	-1	0
Did the reaction reappear when a placebo was given	-1	+2	0
Was the drug detected in blood in concentrations known to be toxic	-1	+1	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased	+1	0	0
Did the patient have a similar reaction to the same or similar drug in any previous exposure	+1	0	0
Was the adverse event confirmed by any objective evidence	+1	0	0

Adapted from Naranjo’s method for estimating the probability of adverse drug reactions

WHO-UMC causality assessment system

Causality term	Assessment criteria (All points should be reasonably complied with)
Certain	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/likely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/unclassified	<ul style="list-style-type: none"> • Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/unclassifiable	<ul style="list-style-type: none"> • Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

CONCLUSION: They are common cutaneous drug reactions and misdiagnosed. The detailed anamnesis & physical examination is the key to suspect this condition.

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