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A Case Report on Isoniazid Induced Bullous Drug Reaction

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ABSTRACT

The term bullous drug reactions also known as fixed skin eruptions refers to adverse drug reactions that result in fluid-filled blisters or bullae. Blistering can be due to various medications, prescribed or over-the-counter, natural or synthetic. Blistering may be localized and mild, or widespread and severe, even life-threatening. Blisters may be the major feature of the reaction or may be only seen sometimes or in localized areas of a more extensive rash[1]. Management challenges including Adverse Drug Reactions (ADR), complex drug interactions, overlapping toxicities and tuberculosis-associated immune reconstitution inflammatory syndrome. The spectrum of tuberculosis-associated ADR ranges from minor to life-threatening, including delayed-type cutaneous adverse drug reactions (CADR),immediate type hypersensitivity reactions, drug induced liver injury, nausea and vomiting, arthralgia, peripheral neuropathy, vertigo, and psychosis[2].Wepresent a case of 70 years old male patient who developed bullous drug eruptions over the lower limbs following isoniazid for the treatment of pulmonary tuberculosis.

INTRODUCTION

About one-third of the world's population has latent tuberculosis, caused by Mycobacterium tuberculosis infection. From this pool, roughly 9 million cases of active tuberculosis emerge annually, resulting in 2-3 million deaths. Treatment for tuberculosis using more than one drug is based on two principles, preventing acquired drug resistance and enhancing efficacy. Treatment that uses a combination of drugs has been shown to accelerate the response of the disease to treatment and to shorten the length of treatment required to cure. Rifampicin and isoniazid are the main drugs used today, rifampicin being the more important agent in terms of reducing the duration of treatment and assuring favorable outcomes. Nine-month regimens using rifampicin and isoniazid, together with an introductory phase of streptomycin or ethambutol, or both, have been predicted to cure 95% or more patients[4] the drug isoniazid is known to interfere with various metabolic pathways essential for neuronal functioning. INH causes vitamin B_6 deficiency by increasing its excretion. INH also inhibits brain *pyridoxal-5-phosphate* activity, which leads to decreased brain levels of GABA and some other synaptic neurotransmitters[3], if pyrazinamide is included in the treatment for the first two months, the length of treatment could be reduced to six months and still retain cure rates of 95% or more[4].

Isoniazid (INH), which was introduced by Robitzek more than half a century ago in 1952, is still one of the primary drugs used in the treatment of *Mycobacterium tuberculosis* infection. It is both safe and effective. Isoniazid inhibits the synthesis of mycolic acids, an essential component of the bacterial cell wall. At therapeutic levels isoniazid is bactericidal against actively growing intracellular and extracellular Mycobacterium tuberculosis organisms[6]. The common side effects of INH are peripheral neuropathy, hepatitis, and rash. Rarely, psychosis, convulsions, and even death have been reported on conventional doses of this drug[3]. The majority case of adverse drug reactions is skin reaction[5], Cutaneous eruptions, the most frequent adverse reaction to isoniazid (2% of patients), include acneiform eruption, urticaria, purpura, lupus erythematosus-like syndrome, pellagra-like syndrome, exfoliative dermatitis, toxic epidermal necrolysis, and Stevens-Johnson syndrome and bullous eruption caused by isoniazid[2] followed by hepatotoxicity, then gastrointestinal reactions.[7] severe joint pain and peripheral neuropathy[8] Majority of cutaneous hypersensitivity reactions occurred within two months after the initial dose[9], Gastric related adverse drug reactions are common with pyrazinamide[10]. Common causes of skin reactions due to anti-tuberculosis drugs are isoniazid and rifampicin, rarely in use of pyrazinamide and ethambutol[11].

CASE REPORT

A 70 years old male patient was brought with complaints of bullous formation over the both lower limbs since 5days due to on usage of ATT cat-1(pyrazinamide-750mg, Ethambutol-600mg, isoniazid-300mg, Rifampicin-450mg three times per a week) drugs since 10 days for the treatment of pulmonary tuberculosis. On taking of those drugs, patient experienced bullous formation on 5^{th} day of the treatment Laboratory investigations such as hemoglobin decreased in condition, complete blood count shows increased neutrophils count and blood sugar level was found to be within normal limits. Bullous were well-circumscribed, 2-5 cm in size with a burning sensation without itching. There was no history of similar complaints in the past he had history of smoking habit since 38 years. Hence, the provisional diagnosis of bullous drug reaction was made.

Isoniazid-induced bullous drug reaction is shown in figure 01. The probability of bullous drug eruptions cannot be ruled out after applying Naranjo's scale of WHO ADR assessing scale karch and lasagna results were shown in table 01. We also assessed the severity, predictability and preventability as a part of management through modified hart wig and Siegel severity scale, schomok and Thornton preventability scale.

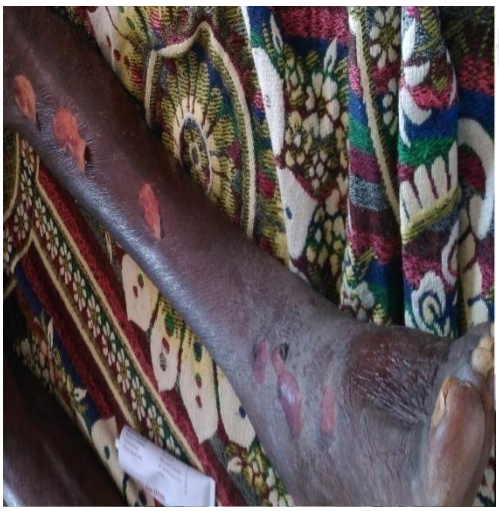

Figure 1: Isoniazid induced bullous drug reaction

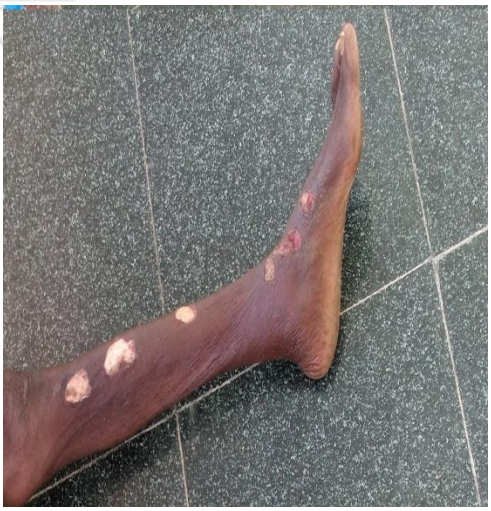

Figure 2: After the management of ADR

ADR Management:

Generally, management of ADR includes withdrawal/suspension, dose reduction of suspected drug and administration of supportive therapy. Here in this case report, the supportive therapy was administered. Those are Injection Pheniramine maleate 45.5mg IM once daily, Ointment

soframycin E/A twice in a day. Injection ceftriaxone 1gm IV twice in a day, Injection dexamethasone 2cc once in a day, Capsule Vitamin A&D 5400 IU p/o once in a day, tablet vitamin B complex 67.5mg p/o once in a day, tablet ranitidine 150mg p/o twice in a day. After 4 days usage of above medication patient under recovering condition than patient was discharged with tablet chlorpheniramine maleate 4mg once in a day, capsule vitamin A&D 5400 IU once in a day, ointment soframycin E/A twice in a day along with ATT-1 drugs.

ADR analysis:

Table 01: Causality assessment of suspected ADRs

Suspected drug and reaction	Naranjo's scale	WHO-probability scale	Karch & Lasagnas scale
Isoniazid-induced bullous drug reaction	Probable	Probable	Condition

SEVERITY: -Moderate level 4

PREDICTABILITY: -unpredictable

PREVENTABILITY: -Probably preventable

DISCUSSION

Bullous or blistering drug eruptions and drug-induced anaphylaxis and hypersensitivity syndromes are among the most serious types of adverse drug reactions. Based on the various mechanisms, bullous drug eruptions may be classified into the following categories are spongiotic or eczematous, Acute generalized exanthematous pustulosis, Fixed drug eruption Erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis. In our case, the patient has bullous formation on lower limbs bullous were well-circumscribed, 2-5 cm in size with a burning sensation without itching i.e., cutaneous surface. This case reflects a broad spectrum of events in bullous drug eruptions. Solitary or multiple, round to oval erythematous patches with dusky red centers, some of which may progress to bulla formation are indicative of active phase bullous drug eruptions, whereas the leaving a pigmentation mark; recovery phase shown in figure: 2.

Table-2: Different Types of Skin Reactions

Symptoms	Skin reaction
Small pustules on erythematous patch	Acute generalized exanthematous pustulosis.
Annular hyperpigmented patch	Fixed drug eruption
Target or iris lesions on palm	Erythema multiforme
Coalescing eroded patches	Stevens-Johnson syndrome
Crusted erosions on scalp	Drug-induced pemphigus

Counseling of patients by a health care professional for timely prevention of ADRs is necessary as the treatment adherence can be achieved. Proper education should be given to the patients about the ADRs caused due to ATT which may reduce defaulter rates and would enhance medication adherence. Monitoring of ADRs induced by ATT in all RNTCP/DOTS centers should be explored. Implementation of spontaneous reporting system in the RNTCP/DOTS program can be useful in identification of new ADRs to ATT[12].

The assessment of ADR is done by means of Naranjo's ADR scale. A score of >9 is indicative of definite ADR. A score of 5-8 is indicative of probable ADR[11]. Our patient had a score of 5, thus indicative of bullous drug reaction. The present case shows a temporal relation between the isoniazid and the presence of bullous drug eruption.

CONCLUSION

Pharmacovigilance for detecting and diagnosing ADR by practicing physicians, general practitioners and family physicians is an essential armament for future avoidance of the medication are essential to reduce morbidity and mortality. If a medication is necessary, careful monitoring of severe reactions is important. It is also important to report ADRs, to decrease the cost treatment. Isoniazid is commonly used anti-TB drug, it is important for prescribing physician to keep in mind that it can also lead to bullous drug reaction. This case report concluded that there is a need of a system for proper monitoring of ADRs caused by anti-TB drugs.

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