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CASE REPORT

A Case of Drug-induced Toxic Epidermal Necrolysis: Pharmacovigilance in Action and Lessons to learn

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ABSTRACT

Pharmacovigilance refers to the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems. During the pharmacovigilance activities undertaken by us, a case of toxic epidermal necrolysis provided us with a setting for discussing various aspects of pharmacovigilance—the process itself, important signal generators that it may yield for practice, research and policy-related matters.

Keywords: Toxic epidermal necrolysis, TEN, Pharmacovigilance, Paracetamol, Metoclopramide, Antihistaminics, Multivitamins.

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INTRODUCTION

A 42-year-old woman was referred by a private practitioner to the PGIMER emergency medical outpatient department (EMOPD) with extensive epidermal detachment along with ocular, genital and oral lesions. Based on the morphology of skin lesions, diagnosis of toxic epidermal necrolysis (TEN) was made. TEN is commonly drug-induced and at the time of presentation she was found to be on two (!) antihistaminics (cinnarizine and dimenhydrinate), paracetamol plus metoclopramide and multivitamins besides an unknown antihypertensive drug. The patient was stabilized and transferred to the dermatology ward where she had an uneventful recovery.

We are not presenting the details of the case as it is being published elsewhere. So why we have chosen it for discussion in the JPMER and what is the link between this case and pharmacovigilance?

Knowledge of clinical pharmacology is fundamental for rational prescribing and topics like pharmacovigilance, evidence-based medicine and rational drug use are within the scope of clinical pharmacology. The WHO defines 'pharmacovigilance' as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems'. In 2007[1] and 2008,[2] by means of two published articles, we stressed upon the need for pharmacovigilance and suggested ways of initiating the same. As a part of the same effort, we started monitoring for adverse reactions to drugs in several departments. Our department had earlier also been involved in adverse drug reaction monitoring in in-patients,[3] hypertension clinic,[4] medical emergency[5] and intensive care unit.[6]

This process is not easy though and lack of motivation and shortage of working hands often lead to the discontinuation of regular monitoring and surveillance of such adverse drug reactions (ADRs). The efforts are usually renewed followed by discontinuation and then the whole cycle restarts. This is the case not only in India but is the typical scenario all over the world with the result that we keep on missing adverse reactions to drugs.

As an important step to avoid the pitfalls of ADR monitoring, the governments in various countries have put the onus on the pharmaceutical companies marketing the products, a process which has legal backing. This has resulted in the marketing authorization holder/pharmaceutical companies to monitor the adverse effects of their products. However, this process mostly includes newly marketed drugs and does not preclude monitoring of ADRs by physicians, clinical pharmacologists, pharmacists and nurses.

In the current ADR monitoring project, which was started a couple of years back, we laid particular stress on cases of drug-induced Stevens Johnsons syndrome (SJS) and TEN in our hospital. TEN is a serious idiosyncratic cutaneous ADR characterized by epidermal detachment of more than 30%. Acute skin blisters and erosions on the mucous membrane occur and the condition is associated with significant morbidity and has high mortality rates of up to 30%.[7] Seventy percent of the cases of TEN are drug induced, most commonly implicated drugs being anticonvulsants, antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs).[8,9]

The most important aspects of management are early diagnosis and stopping the suspected drug. There is no specific treatment and supportive therapy in the form of intravenous fluids, topical antibiotics and proper wound care is advisable. Apart from the conventional supportive treatment intravenous glucocorticoids, intravenous immunoglobulin, N-acetylcysteine, cyclosporine and cyclophosphamide have all been used for treatment of TEN[10] but clear-cut evidence for their efficacy and safety is not yet available.

The case presented here is a part of the renewed pharmacovigilance effort initiated by our team. Additionally, it has some important lessons to be learned for health care providers which we intended to highlight in the current article.

Toxic epidermal necrolysis is classified as a serious, potentially fatal adverse drug reaction. In our hospital, about 6% of all visits to the medical emergency are likely to be drug-related[5] many of which are life-threatening. The majority of them are caused by drugs considered relatively harmless by most lay persons as well as some practitioners. Drugs which have been most commonly implicated in the causation of the serious adverse reactions are antibiotics, NSAIDs, anticonvulsants, oral hypoglycemics and antitubercular drugs.

For instance, paracetamol has been considered potentially safe and is one of the most widely used drugs. With respect to dermatological adverse effects, it is considered to be even safer as there have been few reported cases of hypersensitivity[11,12] and just two cases of TEN in the literature.[13,14] However, a more thorough literature search including non-English articles showed that paracetamol has previously been shown to be related to increased incidence of TEN in certain regions of the world with a relative risk of 9.3.[8]

This patient was also prescribed metoclopramide and there has been one case report associating TEN with metoclopramide,[15] which makes this drug also a potential candidate for causing TEN.

We could not find any case reports of antihistaminics causing TEN. This patient was prescribed not one but two antihistaminics. So, can we exclude antihistaminics as a causative factor for TEN? Unlikely, for, in order to prove that antihistaminics definitely do not lead to TEN, we would need to rechallange the patient, which will be unjustified ethically in such severe reactions?

There are a few important lessons to be learnt from this case study. Foremost, the prescriptions written by local practitioners need serious attention. In the setting described here, the pertinent question is did the patient's index symptoms warrant the use of paracetamol, metoclopramide, two antihistaminics and multivitamins? It is a common notion that unless a practitioner gives some medication to the patients, patient would not be satisfied. Keeping in view the possibility of such serious reactions as the present case occurring with seemingly innocuous medications, the practice of irrational prescribing should be discouraged. How to do this is a challenge as not many will be willing to accept. This is not only because of the enormity of task involved but also because of the existing variety of systems of medicine all of which prescribe 'allopathic' medicines, many of which are difficult if not impossible to bring under control.

The WHO has given a set of 12 core interventions to promote more rational use of medicines (Panel 1).

Twelve core interventions to promote more rational use of medicines (WHO) are as follows:[16]

1. A mandated multidisciplinary national body to coordinate medicine use policies
2. Clinical guidelines
3. Essential medicines list based on treatments of choice
4. Drugs and therapeutics committees in districts and hospitals
5. Problem-based pharmacotherapy training in undergraduate curricula
6. Continuing in-service medical education as a licensure requirement
7. Supervision, audit and feedback
8. Independent information on medicines
9. Public education about medicines
10. Avoidance of perverse financial incentives
11. Appropriate and enforced regulation
12. Sufficient government expenditure to ensure availability of medicines and staff.

The reason for which antihistaminics and vitamins and an antiemetic were given to this patient is not clear. Not only was the prescription a cause of significant morbidity, but also cost the patient more than ₹ 25,000/- for medications, investigations, hospital stay and loss of wages.

This brings us to the issue of polypharmacy. In spite of all the criticisms of polypharmacy, it remains rampant. This may not be such a big problem here in PGIMER, but is definitely so elsewhere. Even in our setup, it is possible to come across same class of drugs prescribed twice by two different specialists on different OPD cards, most commonly seen would be proton pump inhibitors (PPIs) and NSAIDs. Otherwise, it is not uncommon to see a single prescription with two NSAIDs.

The next lesson is again for practitioners. Though paracetamol was one of the implicated medications, the 'paracetamol paradox' has wider implications. It often continues to be administered in these cases as patients are often febrile. One must keep in mind this possibility while giving paracetamol to these patients. To further confuse the issues, it must be mentioned that this does not imply that paracetamol is not the preferred drug in such cases. It merely highlights the need to take careful drug history. If paracetamol is one of the drugs which had led to the condition, then it should not be administered and certainly not if the condition continues to deteriorate.

Hardly has anything been said here that is not known. Despite that many prescribers fail to adhere to these simple

guidelines. At the cost of sounding a little pessimistic we do not see the situation improving in future as shown by a recent study[17] demonstrating that the fear of being sued for medical malpractice is pervasive, leading 91% of physicians across all specialty lines to practice defensive medicine—ordering more tests and procedures (we may add drugs) than necessary to protect themselves from lawsuits. We wish to publish such cases in future with a view to not only continue with pharmacovigilance practice in our institute but also to recognize knowledge gaps in rational prescription of drugs and identify lacunae in existing evidence-based practice. Through this publication, we also seek the support of everyone concerned to detect and, if possible, prevent adverse reactions to drugs.

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