CASE SERIES

Adverse cutaneous drug reactions to fixed dose combination tablet of antituberculous drugs: a case series

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Abstract

Tuberculosis, an infectious disease caused by *Mycobacterium tuberculosis* is very common in India. The treatment of tuberculosis consists of multiple drugs which are given as fixed dose combinations with all the drugs in a single tablet. Adverse drug reaction to these drugs is common and rechallenging is the only way to find the incriminating drug. But in a few cases, no drugs were found as the incriminating agent and the patients completed the treatment with individual component drugs without any adverse drug reaction. The reason is probably the excipients like colouring agent added to the fixed dose combination which could have provoked the allergic reaction. This case series reports four such cases in which excipient would have caused the adverse drug reaction.

Keywords: Anti-tuberculous Treatment, Drug Reaction, Excipients

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* that affects almost all the organs of our body [1]. In developing countries like India, it is one of the causes of morbidity and mortality [2]. Globally, India leads the world in the total number of TB cases [1]. The treatment and control of Tuberculosis is organized under the Revised National Tuberculosis Control Program (RNTCP) [3]. The treatment involves multidrug therapy which consists mainly of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E) daily for new TB cases. These are given in Fixed Dose Combinations (FDC) with all the drugs in a single tablet, with the number of tablets taken based on the age and weight of the patient. The treatment is divided into two phases- Intensive Phase (IP) and Continuation Phase (CP). The fixed combination of the above four drugs (HRZE) are given for 8 weeks during the intensive phase and FDC of three drugs (HRE) are given for 16 weeks during the continuation phase [4]. The Antituberculous Treatment (ATT) can cause many adverse cutaneous drug reactions ranging from pruritus to toxic epidermal necrolysis which may require discontinuation of drugs. Since the treatment is given as FDCs, re-challenging the component drugs sequentially is the only possible way to find out the incriminating drug [5]. Re-challenge of the drugs were performed after the drug free wash out period lasting 5 elimination half-lives of each drug [6]. The component drugs of FDC were reintroduced one by one, starting at one-fourth of the recommended dose on the first day, half on the second day and full dose on the third day. If no drug reaction is found to the

rechallenged drug, subsequent drugs were added one by one. In this case series, we report four cases who presented with adverse cutaneous drug reaction to FDC of ATT and were rechallenged with individual drugs without any adverse effects.

Case 1

A 50 year old male presented with generalized pruritic maculopapular rash of one day duration. There was no history of fever or mucosal involvement or jaundice. He was treated for sputum positive pulmonary tuberculosis with fixed drug combination for the past three days. ATT was stopped and the lesions subsided with systemic steroids and antihistamines. After the complete subsidence of the reaction and stopping of antihistamines and systemic steroids, patient was rechallenged with ATT drugs one by one in increasing doses in the order – isoniazid, rifampicin, pyrazinamide and ethambutol. When no reaction was noted with the first drug, subsequent drugs were added to it. As no adverse reactions were noticed, the patient was rechallenged with a single tablet of FDC following which he developed pruritic maculopapular rash in two hours after which the FDC was stopped. After complete subsidence of the reaction, ATT was restarted as individual drugs patient tolerated 6 months course of ATT as individual drugs.

Case 2

A 60 year old male with sputum positive pulmonary tuberculosis presented with generalized itching after taking FDCs. ATT was stopped and individual drug was rechallenged one by one, without any adverse reactions. He did not develop any reactions. Patient completed ATT course with individual drugs.

Case 3

A 56 year old male with microbiologically confirmed pulmonary tuberculosis presented with generalized itching which started one hour after intake of FDC and lasted till evening. On stopping the drug combination, itching subsided. After complete subsidence of symptoms, he was rechallenged with individual drugs without any adverse reactions and was managed further with individual drugs.

Case 4

A 47 year old male patient with sputum positive pulmonary tuberculosis on 5 tablets of FDCs presented with generalized itching after taking FDCs for one month. Investigations were normal except for high ESR (120 mm per hour) and a high absolute eosinophil count (410 cells per mm^3). It was stopped and was rechallenged one by one after complete subsidence of itching. He did not develop any itching with individual drugs and the treatment was continued with individual drugs.

Discussion

All the four patient developed drug reaction to fixed drug combination of ATT but on rechallenging, no reaction to individual drugs were found. This implies, the culprit is not any of the individual drugs but probably the excipients added to the fixed dose combination. The excipients include the colouring agents, red oxide of iron and titanium dioxide. But titanium dioxide is present in rifampicin also. So the most probable agent which produced drug reaction in these cases could be red oxide of iron.

A medicine consists of two parts- active drug and excipients [7]. Drug as well as excipients can produce adverse reactions. Case reports on excipients causing drug reaction are very few in

literature [8]. Euser *et al*. has reported a case of urticaria due to excipient [9]. The incidence of adverse cutaneous drug reaction in patients on antitubercular therapy is 5.7% as per Tan *et al*.[10]. In a retrospective study conducted by Sharma *et al*. [5], ethambutol was found to be the most common offending drug and no cases were mentioned with excipient as the probable agent.

Whenever a drug reaction due to ATT is observed, it is always better to rechallenge wherever possible to find out the culprit drug. If no drug reaction is found to the individual drugs, then the probable cause might be excipients. This will help to continue the ATT treatment without any change in the regime.

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