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Hiding in Plain Sight: Revisiting a Case of Antitubercular Drug Induced Chromaturia

Ebisha Pauline[1], Girish Joseph[2], Prabhjot Kaur[3], Neena Bhatti[4], Dinesh Badyal[5]

[1]Student, Phase III Part 2, Christian Medical College & Hospital, Ludhiana

[2,4]Assistant Professor, Department of Pharmacology, Christian Medical College & Hospital, Ludhiana

[3]Pharmacovigilance Associate, AMC, Christian Medical College & Hospital, Ludhiana

[5]Professor & Head, Department of Pharmacology, Christian Medical College & Hospital, Ludhiana

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Abstract

India being a developing country has a high burden of Tuberculosis (TB). It is a communicable disease and a major global heath challenge. Considering the impact of this illness on both individual patients and public health, it is critical to comprehend the effectiveness and adverse pharmacological profile of the medications. Although most patients on a daily ATT regimen do not encounter the documented ADRs listed below, doctors and patients should be concerned about them. For example, rifampicin induced discoloration of body fluids is often overlooked as it is "innocuous". Nonetheless, Adverse drug reaction (ADRs) reports on these drugs are scarce in proportion especially in regards to the most common ADRs like antitubercular treatment (ATT) induced chromaturia.

Keywords: Chromaturia, Antitubercular Drugs, Adverse Drug Reactions

Introduction

India being a developing country has a high burden of Tuberculosis (TB). It is a communicable disease and a major global heath challenge. The causative agent for TB is mycobacterium tuberculosis. An estimated 10.6 million TB incident cases were reported in 2021, according to the Global TB Report 2022. By 2035, the World Health Organization's (WHO) End TB policy seeks to lower 95% of TB-related fatalities and 90% of new incident cases (Chauhan et al., 2023). Considering the impact of this illness on both individual patients and public health, it is critical to comprehend the effectiveness and adverse pharmacological profile of the medications recommended for use by the National Tuberculosis Elimination Program. (NTEP). Adverse drug reactions (ADRs) are defined by the WHO to be “a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function” (Siddhu et al., 2023). A recent descriptive study done to determine the ADR profile of daily ATT regimen found out that of all the ADRs reported as per WHO scale, hepatitis or asymptomatic elevated liver enzymes were the leading ADR reported followed by diminished vision (Michael et al., 2016). Although most patients on a daily ATT regimen do not encounter the documented ADRs listed below, doctors and patients should be concerned about them. For example, rifampicin induced discoloration of body fluids is often overlooked as it is "innocuous". Furthermore, rifampicin-induced reddish-orange urine is not even included in the list of ADRs observed in

TB patients with HIV who are on first-line anti-tubercular medications (Sankar et al., 2022). This case report aims to highlight an often-underrepresented ADR in the realm of Indian pharmacovigilance.

Case Report

A 38-year-old lady presented to the hospital on 1st April 2024 with right sided pleural effusion. She is a known case of pulmonary tuberculosis since January of 2024 which was diagnosed and confirmed by positive CBNAAT test and positive findings on chest x-ray. These investigations were done after high degree of clinical suspicion following the patient's symptoms of chronic dry cough and fever. Patient was started on category 1 treatment regimen (new TB case) on January 10th of 2024 which includes (Isoniazid+ Rifampicin + Pyrazinamide+ Ethambutol) for two months and (Isoniazid+ Rifampicin + Ethambutol) for the preceding four months. Along with these drugs the patient was prescribed tab. pyridoxine 100 mg and tab. paracetamol. Within a span of 10 days of starting the regimen the patient noticed reddish discoloration of her urine along with symptoms of irritation and urgency. Although her doctor had warned her of the red discoloration to be expected because of her ATT treatment, she presented to her doctor for investigation where no signs of abnormally elevated urine protein and no pus/red cells were found in urine. On arrival to the tertiary care hospital, chest x-ray, ECG, pleural tap was done. ECG was unremarkable except for the low t wave in V4. Pleural tap revealed no acid-fast bacilli. Patient is continuing on drug regimen and continues to have reddish discoloration of urine. The Naranjo's score was 5 (probable) and the causality assessment showed probable correlation with the current adverse event (Naranjo et al., 1981).

Discussion

Chromaturia or an abnormal coloration of urine as reported by this patient along with discoloration of any body fluids such as saliva, sweat and tears is estimated to be present in at least 80% of those taking rifampicin. Therefore, rifampicin induced chromaturia is an augmented/ dose dependent adverse drug reaction (Coleman & Pontefract, 2016). Such reactions can be understood on the basis of their pharmacology. Since its addition to the antitubercular treatment regimen in 19637, rifampicin was found to have a potent bactericidal action against M. tuberculosis with its inhibition of prokaryote DNA dependent RNA polymerase (RNAP) (Rothstein et al., 2024). Rifampicin is mostly linked to plasma proteins (80%) and has a wide volume of distribution after its quick absorption from the gastrointestinal system. The remaining unbound portion is nonpolar accounting for its ability to cross the blood-brain-barrier (BBB). Following enterohepatic circulation, rifampicin is deacetylated in the liver and is excreted through bile. While the majority is eliminated in the bile, only 30% is eliminated via urine.9 Rifampicin and its metabolites are chromogens which are responsible for imparting their reddish orange color to body fluids like urine during elimination (Sotgiu et al., 2015). It is important to note that rifampicin is a potent inducer of P450 isoenzymes (Beloor et al., 2024). In other words, in doing so rifampicin increases the elimination of other drugs like contraceptives and NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors) which ultimately can lead to therapeutic failure. One rare case report found that a smear positive TB patient had sudden absence of reddish orange urine for two months after three weeks of treatment when being on therapy with isoniazid, rifampicin, and pyrazinamide. Reddish orange chromaturia reappeared after withdrawal of pyrazinamide. It was concluded that rifampicin and pyrazinamide both being potent enzyme inducers had resulted in increased metabolism of rifampicin to which could mostly be eliminated in bile and not in the urine (Morgan et al., 1993). Therefore, rifampicin induced chromaturia provides information regarding the metabolism and elimination of rifampicin. Moreover, urine colorimetry studies have been done

using such an ADR to check treatment adherence and pharmacokinetic parameters (Szipszky et al., 2021). It is important to note that chromaturia is not a phenomenon exclusive to rifampicin. In fact, red chromaturia can also be seen in patients on therapy with phenazopyridine, hydroxocobalamin, other rifamycin derivatives along with haematuria and benign conditions like beet root consumption. More importantly, Rifampicin induced chromaturia should not be taken lightly as rifampicin, although rare, has been known to cause acute renal failure (Koratala et al., 2018).

Conclusion and Suggestions

Rifampicin induced reddish orange chromaturia is equally significant to report as an ADR just as other ADRs of all the antitubercular drugs employed through DOTS. More importantly, Chromaturia can also serve as vital assessment tool for pharmacokinetic studies. At the patient bedside level, however, other causes for red chromaturia must be evaluated as done in this patient.

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