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TOXICITY ASSESSMENT OF ANTIBACTERIAL DRUGS- PYRAZINAMIDE AND RIFAMPICIN IN RATS

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ABSTRACT

Pyrazinamide is a medication used to treat tuberculosis. For active tuberculosis, it is often used together with rifampicin, isoniazid and either streptomycin or ethambutol. Rifampicin also known as rifampin, is an antibiotic used to treat several types of bacterial infections. This includes tuberculosis, leprosy, and Legionnaire's disease. Tuberculosis (TB) remains a global major health Problem, especially in developing countries. Since 1993, World Health Organization (WHO) has declared TB as a public health emergency. Recommended standard treatment includes a combination of isoniazid (INH), rifampicin (RIP), pyrazinamide (PZA) and ethambutol (EMB) for 6-9 months. Although this treatment regimen has been highly effective, treatment-related adverse effects including hepatotoxicity, skin reactions, gastrointestinal and neurological disorders account for significant morbidity leading to reduced effectiveness of therapy. Hepatotoxicity is the most important and serious one. The biochemical mechanism and pathogenesis of drug-induced hepatotoxicity (DIH) remain unclear for the most offending drugs.

Keyword: Tuberculosis; leprosy; legionnaire's disease ; hepatotoxicity ; drug- induced hepatotoxicity (DIH)

INTRODUCTION

Pyrazinamide is a drug used to treat tuberculosis. In case of active tuberculosis, it is often used together with rifampicin, isoniazid and either streptomycin or ethambutol. It is not generally recommended for the treatment of latent tuberculosis. Pyrazinamide was first made in 1936 but did not come into wide use until 1972. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. Pyrazinamide is a synthetic pyrazinoic acid amide derivative with bactericidal property. Pyrazinamide is particularly active against slowly multiplying intracellular bacilli. Its bactericidal action is dependent upon the presence of bacterial pyrazinamidase enzyme, which removes the amide group to produce active pyrazinoic acid. Pyrazinamide is an important component of multidrug therapy for tuberculosis. Rifampicin, also known as rifampin, is used to treat several types of bacterial infections. This includes tuberculosis, leprosy and Legionnaire's disease. It is almost always used along with other antibiotics. Rifampin is a semi-synthetic antibiotic produced from *Streptomyces mediterranei*. It has a broad antibacterial spectrum including activity against several forms of *Mycobacterium*. In susceptible organisms, it inhibits DNA-dependent RNA polymerase activity by forming a stable complex with the enzyme. It thus suppresses the initiation of RNA synthesis. Rifampin is bactericidal and acts on both intracellular and extracellular organisms.

REVIEW OF LITERATURE

Tuberculosis (TB) remains a global major health problem, especially in developing countries. Since 1993, World Health Organization (WHO) has declared TB as a public health emergency. [1] In 2014, there was an estimated 9.6 million new cases reported to WHO and 1.5 deaths around the world. [2] In Morocco, TB remains the leading cause of

serious illness with an estimated incidence of 106 (97-105) per 100000 in 2014. [3] Recommended standard treatment includes a combination of isoniazid (INH), rifampicin (RIP), pyrazinamide (PZA) and ethambutol (EMB) for 6-9 months. Although this treatment regimen has been highly effective, treatment-related adverse effects including hepatotoxicity, skin reactions, gastrointestinal and neurological disorders account for significant morbidity leading to reduced effectiveness of therapy. Hepatotoxicity is the most important and serious one. It may result from the direct toxicity of the primary compound, a metabolite, or from an immunologically mediated response. Anti-tubercular drug-induced hepatotoxicity (ATDH) causes substantial morbidity and mortality and diminishes treatment effectiveness. There are many factors that contribute to the development of ATDH, which are advanced age, slow acetyl or status, malnutrition, HIV infection and pre-existent liver disease. Therapeutic drug monitoring (TDM) allows the clinician to make informed decisions in cases to avoid treatment failures or prevent the occurrence of adverse events. The relationship between ATDH and plasma drug levels has not been demonstrated. There are few reports on the correlation between basal plasma drugs levels and ATDH. The currently recommended first-line treatment for TB is a regimen of isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB) for 2 months, followed by 4 months of INH and RMP and/or EMB, Hepatotoxicity is one of the most frequent and serious adverse effects of anti-TB medications and may reduce treatment effectiveness by compromising treatment regimen. Among the first-line quadruple therapy drugs (INH, RMP, PZA, and EMB), INH, RMP, and PZA are metabolized mainly by the liver, and therefore, are potentially hepatotoxic. The incidence of anti-TB drug-induced hepatotoxicity (DIH) during standard multidrug TB treatment has been reported to be between 2% and 28%, depending on the definition of hepatotoxicity and the population studied . [4] However, the biochemical mechanism and pathogenesis of DIH remain unclear for the most offending drugs. Therapeutic drug monitoring (TDM) during TB treatment allows the clinician to make informed decisions in cases involving slow response to treatment, drug-resistant TB, drug-drug interaction risks, or severe underlying diseases. [5] However, whether DIH will develop more frequently with increasing serum drug levels is questionable. There are few reports on the direct correlation between basal serum drug levels and DIH, as it has not been well studied. RMP plasma levels were higher in cases with DIH than in controls and independently predicted subsequent development of DIH, according to one recent report. [6] The slow acetylator status of INH metabolites may be a risk factor for anti-TB DIH. [7, 8] Varying serum INH levels due to the different slow acetylator status may be a cause of hepatotoxicity. PZA has been shown to induce greater hepatotoxicity than other first-line anti- TB drugs. [3,9] Although the incidence of PZA-induced hepatotoxicity decreased considerably after reducing the recommended standard dose, PZA is still considered the most frequent cause of anti-TB DIH. However, little is known about the serum levels of anti-TB medications and the development of hepatotoxicity in TB. The aim of the present study was to evaluate the association between the basal serum levels of anti-TB drug and the development of hepatotoxicity. This study showed that neither the serum anti-TB drug concentration, nor the proportion of patients whose serum drug level exceeded the reference level for each anti-TB drug investigated, were different among the groups (hepatotoxicity group, mild LFT abnormality group, and non-hepatotoxicity group). Several commonly used anti-tubercular drugs are potentially hepatotoxic and can cause severe and even fatal, hepatitis. Apart from an estimated hepatotoxicity of 1%–0.1% , [10,11] the standard preventive treatment for latent tuberculosis infection (LTBI) with 6 months of isoniazid (6H) therapy often results in poor compliance. Less hepatotoxic preventive regimens of shorter duration that are not affected by isoniazid resistance were therefore sought . [12–13] In August 2003, after 48 reports confirmed severe liver injury related to 2RZ therapy, including 11 deaths (23% of the reports), the ATS and the CDC advised that 2RZ therapy should generally not be offered to persons with LTBI. This retrospective cohort study compared rates of hepatotoxic adverse effects

among patients in the Netherlands receiving either the preventive 2RZ or 6H regimens or the 2-month intensive-phase tuberculosis (TB) treatment, combining at least isoniazid, rifampin and pyrazinamide (2HRZ+). The goal was to determine relative rates of hepatotoxicity and whether 2RZ preventive treatment was more toxic than 2RZ therapy as part of a triple- or quadruple-drug curative regimen.

DISCUSSION

Hepatotoxicity is the most common adverse reaction of anti-TB treatment that leads to interruption of therapy. The exact mechanism of ATDH is not well defined but is due to toxic metabolites. The variation in the incidence of ATDH worldwide depends on several factors: study design, investigator's definition of ATDH, population studied and indiscriminate drugs. The difference in severe hepatotoxicity between the 2RZ and the 6H preventive treatments is likely attributable to the different drugs used. Contrary to other findings, previous use of isoniazid did not predispose our patients to hepatotoxicity during 2RZ treatment. [14] However, some Dutch TB physicians, prior to the first ATS/CDC warnings, chose the shorter regimen (2RZ) for patients with an elevated risk for liver injury (e.g., caused by alcohol abuse).

CONCLUSION

Pyrazinamide acts differently from common antibiotics by inhibiting multiple targets such as energy production, trans-translation and perhaps pantothenate /coenzyme A required for persister survival but Resistance to PZA is mostly caused by mutations in the *pncA* gene encoding pyrazinamidase involved in conversion of the prodrug PZA to the active form POA. Mutations in the drug target RpsA are also found in some PZA-resistant strains. Resistance to rifampicin (RIF) is a broad subject covering not just the mechanism of clinical resistance, nearly always due to a genetic change in the β subunit of bacterial RNA polymerase (RNAP), but also how studies of resistant polymerases have helped us understand the structure of the enzyme. In this case we can use combination therapy.

REFERENCES

1. Ramappa V, Aithal GP. Hepatotoxicity related to anti-tuberculosis drugs: mechanisms and management. Journal of Clinical and Experimental Hepatology. 2013 Mar; 3(1):37–49.
2. World Health Organization. Global Tuberculosis Report 2014. Geneva: World Health Organization; 2014.
3. World Health Organization. Moroccan Tuberculosis Report 2014. Geneva: World Health Organization; 2014.
4. Huiri A, Xueqiong W, Zhongyuan W, Jing X, Shaohua Z, Kun Wang. The clinical characteristics of anti-tuberculosis drug induced liver injury in 2457 hospitalized patients with tuberculosis in China. African Journal of Pharmacy and Pharmacology. 2013;7(13):710–714.
5. Tostmann A, Boeree MJ, Aarnoutse RE, et al. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol. 2008 Feb;23 (2):192–202.
6. Aouam K, Chaabane A, Loussaief C, Ben Romdhane F, Boughattas NA, Chakroun M. Adverse effects of antitubercular drugs: epidemiology, mechanisms, and patient management. Med Mal Infect. 2007; 37 (5):253–610.
7. Jeong I, Park JS, Co YJ, Yoon H, Song J, Lee CT, Lee JH. Drug-induced hepatotoxicity of anti-tuberculosis drugs and their serum levels. J Korean Med Sci. 2015 Feb;30 (2):167–172.
8. Jeong I, Park JS, Co YJ, Yoon H, Song J, Lee CT, Lee JH. Drug-induced hepatotoxicity of anti-tuberculosis drugs and their serum levels. J Korean Med Sci. 2015 Feb; 30(2):167–172.
9. Abera W, Cheneke W, Abebe G. Incidence of antituberculosis-drug-induced heptotoxicity and associated risk factors among tuberculosis patients in Dawro zone, South Ethiopia: A cohort study. Int J of Mycobacteriology. 2016 Mar; 5(1):14–20. Epub 2015 Oct 30.
10. Kopanoff DE, Snider DE, Cars GJ. Isoniazid-related hepatitis: a United States Public Health Service Cooperative Surveillance Study. Am J Respir Dis 1978; 117:991–1001.
11. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid

preventive therapy: a 7-year survey from a public health tuberculosis clinic. JAMA 1999; 281:1014.

12. Lecoeur HF, Truffot-Pernod F, Grosset JH. Experimental short-course preventive therapy of tuberculosis with rifampin and pyrazinamide. Am Rev Respir Dis 1989; 140:1189–93.
13. Grosset J, Truffot-Pernod C, Lacroix C, Ji B. Antagonism between isoniazid and the combination pyrazinamide-rifampin against tuberculosis infection in mice. Antimicrob Agents Chemother 1992; 36:548–51.
14. Hest NAH van, Trompenaars MC, Baars HWM. Severe hepatotoxic side-effects related to treatment of latent tuberculosis infection (LTBI) with two months of rifampin and pyrazinamide in the Netherlands. Int J Tuberc Lung Dis 2002; 6:S1286–7.