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Original Research Paper

Zoology

EFFECT OF DELAMANID DRUG ON THE HEPATIC ENZYMES IN ALBINO RATS

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ABSTRACT Tuberculosis is a deadly disease for the last many decades which was somehow managed by potent drugs but nowadays cases of drug resistance have increased on average in India, especially in dense states like Uttar Pradesh. As we know Tuberculosis and Multidrug-Resistant Tuberculosis drugs are quite toxic and have an impact on various organs of the body. The side effects of Delamanid are still not fully defined but as this drug has been started to being administered in India now, research and more trials are the need of the hour especially as we have started this drug in the treatment of children. In the light of present evidence available on the side effects of the drug, it is clear that more research is required to make the available facts clearer. The drug affects vital organs like the heart. Ample studies have been done on cardiac side effects, plus other effects that need to be evaluated in our environmental conditions, taking our living habitat at Agra City in particular. Keeping these points in view, the present study is designed to assess the hepatotoxicity levels using a newly synthesized Delamanid drug in the animal model, an albino rat. We obtained a certain pattern of these hepatotoxic levels in which they increased and decreased.

KEYWORDS : Delamanid, Tuberculosis, Drug Resistance, Hepatic Enzymes

INTRODUCTION

Tuberculosis (TB) is a serious infectious bacterial disease. Humanity has been facing this disease for 5000 years. It is caused by *Mycobacterium tuberculosis* or *Koch's Bacillus* and has taken the lives of humans more than any other disease. It can be cured successfully by Chemotherapy but different factors may lead to negative outcomes. Inappropriately followed treatment may lead to the development of Multi-Drug Resistant Tuberculosis. According to Global TB Report 2022, 10.6 million people fell ill with TB in 2021. There were an estimated 1.6 million TB deaths in 2021 in HIV-negative people and 1,87,000 deaths among HIV-positive people. The burden of drug-resistant TB (DR-TB) is also estimated to have increased between 2020 and 2021 due to COVID-19 pandemic, reversing the declines of about 2% per year for most of the previous 2 decades, with 4,50,000 new cases of rifampicin-resistant TB (RR-TB) in 2021.

The emergence of multidrug-resistant tuberculosis, or tuberculosis caused by strains of *Mycobacterium tuberculosis* that are resistant to isoniazid and rifampin, with or without resistance to other drugs, has been a major factor in efforts to combat the global tuberculosis epidemic over the past two decades. Approximately 440,000 cases of MDR-TB occur worldwide each year, accounting for approximately 5% of all TB cases worldwide. A line drug is administered for up to two years. MDR-TB has a lower cure rate and a higher mortality rate than drug-sensitive TB, even with the most effective treatments (WHO, 2008).

The liver is a critical organ that plays a role in regulating important biochemical and physiological activities such as homeostasis, growth, energy and nutrient supply, detoxification of drugs and other xenobiotics, and fighting infections. (Zimmerman *et al*., 1999). As such, it is highly susceptible to damage by hepatotoxicants.

Delamanid is the active substance in a new TB drug treatment. Formerly called OPC-67683 it is also known by its trade name of Deltyba. It is the first in a new class of TB drugs called nitroimidazoles. It is currently being developed by the Otsuka pharmaceutical company as a treatment for MDR TB. Delamanid is given to adults with TB that is affecting the lungs, and which is multi-drug resistant (Orenstein *et al*., 2009). This means that it is resistant to at least isoniazid and rifampicin, two standard anti-TB drugs. It is used together with other standard medicines, and it must not be taken on its own. It is used when other drug combinations cannot be used either because the TB bacteria are resistant to the other drugs or because of the side effects of these other drugs (Leimane *et al*., 2010). Its common side effects include headache, dizziness and nausea. Its primary safety concern is its side effects reported on the heart.

Hence in the present research work, the effect of the antituberculosis drug Delamanid has been assessed on hepatic enzymes viz. acid and alkaline phosphatases and aspartate and alanine aminotransferases in albino rats to implicate results on mammalian species.

MATERIALS AND METHODS

The present investigation has been made on acclimatized specimens of albino rats, *Rattus norvegicus* (Berkernhout) under good laboratory conditions. The colony of albino rats were breed in the animal house of the Zoology Department, School of Life Science, Khandari Campus, Dr. Bhimrao Ambedkar University, Agra. Thirty healthy male albino rats of equal size and weight 110 ± 12gm and eight weeks aged were selected for the present investigations. The albino rats were housed in polypropylene cages measuring 45×25×15 cm and maintained controlled temperature (25±2□c), humidity (45±10%) and proper circadian rhythm. The cages were regularly cleaned to avoid obnoxious odour and infection. They were fed with green vegetables and tap water. The albino rat was maintained under good laboratory practices (GLP) and guidelines of the committee for the purpose of control and supervision of experiments on animals (CPCSEA) were followed. Group 1 was treated as a control group and given normal water while groups 2-6 were treated with Delamanid drug (0.625 mg /kg body wt.) for 7, 15, 30, 45 and 60 days respectively.

The albino rats were anaesthetized under light chloroform anaesthesia and dissected carefully. The blood samples were collected directly from the left ventricle of the heart using 5.0 ml disposable syringe and 20 swg. hypodermic needle and stored in sterilized centrifuge tubes for further assessment. The fresh blood was taken in the sterilized centrifuge tubes and kept undisturbed in a vertical position for about fifteen minutes at room temperature. When the blood starts clotting

the centrifugation was done at 2000 rpm for about thirty minutes. Now the supernatant serum was separated from the clotted blood by a fine rubber bulb pipette. The serum samples thus obtained were used for the estimation of biochemical parameters *viz.* acid phosphatase, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. The serum acid phosphatase in the serum was estimated by King's method (1959). The alkaline phosphatase in Serum was estimated by the method of Kind and King's (1954). The aspartate aminotransferase and alanine aminotransferase were estimated by the method of Reitman and Frankel (1957).

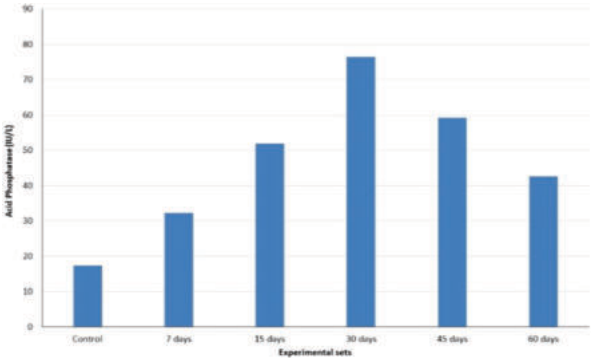
The data obtained from biochemical studies have been tabulated and statistically analyzed using computer software Ky plot version 3.0.

RESULTS AND DISCUSSION

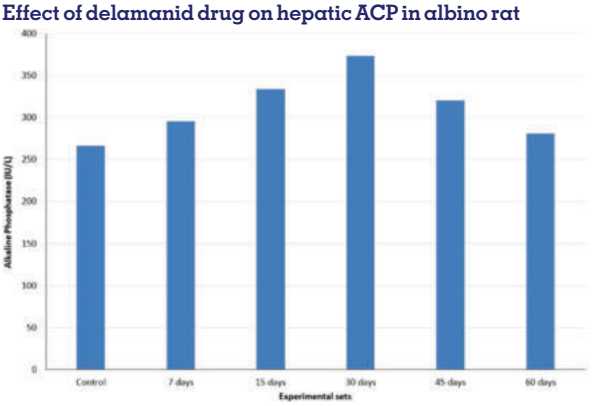
The results show alteration in liver enzymes viz. acid phosphatase (ACP), alkaline phosphatase (ALP), aspartate aminotransferase (AST and alanine aminotransferase (ALT) after treatment with the drug Delamanid in albino rats as shown in table-1 and graph 1-4 below-

Table 1: Effect of Delamanid drug on hepatic enzymes in albino rat

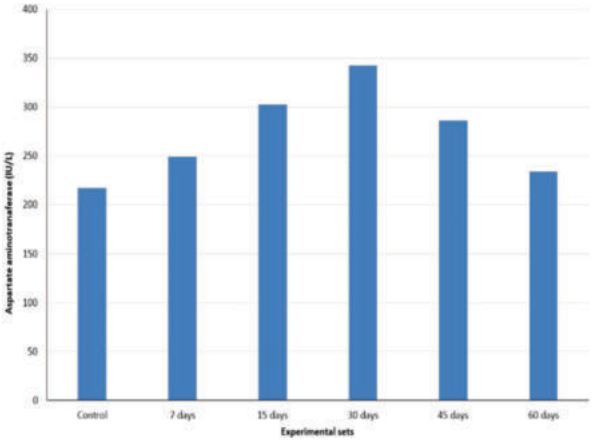
Group	Experimental Sets	ACP (IU/L) Mean±S.Em.	ALP (IU/L) Mean±S.Em.	AST (IU/L) Mean±S.Em.	ALT (IU/L) Mean±S.Em.
1	Control	17.36±0.65	266.66±2.90	217.33±2.90	51.33±1.76
2	7 days	32.33±1.27*	295.66±2.02*	249.0±2.88***	78.0±3.46**
3	15 days	51.83±1.67**	334.33±2.60**	302.66±5.20***	101.66±2.02***
4	30 days	76.53±1.45**	373.33±3.71**	342.66±2.90***	124.66±1.76***
5	45 days	59.20±2.10**	320.66±5.20**	286.66±2.40**	99.33±3.71**
6	60 days	42.56±2.16**	281.33±3.52*	234.33±3.48NS	67.30±1.76*



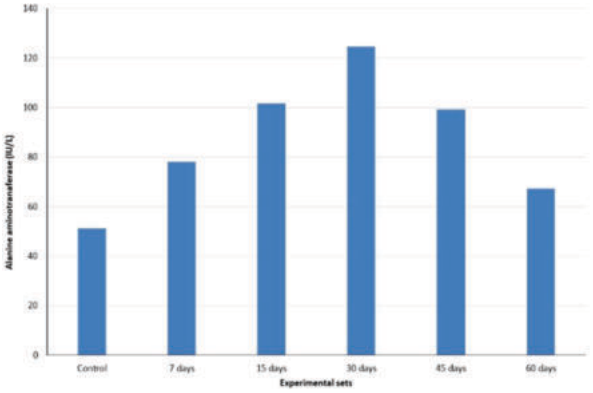
Effect of delamanid drug on hepatic ACP in albino rat



Effect of delamanid drug on hepatic ALP in albino rat



Effect of delamanid drug on hepatic AST in albino rat



Effect of delamanid drug on hepatic ALT in albino rat

Liver injury caused by certain drugs and toxic chemicals has been linked to the occurrence of oxidative stress that releases free radicals. The loss of balance between the production of free radicals and the antioxidant defence system results in oxidative stress which further disturbs cellular functions leading to various pathological conditions (Sabiu *et al.*, 2014). As a result, intervention with exogenous antioxidants strengthens the cellular defence system to counteract these ill effects at the cellular level (Poljsak *et al.*, 2013). Increased activities of serum enzymes viz. ACP, ALP, AST and ALT are often used as markers of hepatic injury as they indicate cellular leakage of intracellular enzymes and loss of liver cell membrane stabilization (Sabiu *et al.*, 2014). Destruction of the hepatocytes induced by Delamanid caused a significant alteration in hepatic enzyme levels. This agrees with the earlier studies which reported an increase in ALT and AST in rats administered with xenobiotic (Khan *et al.*, 2012; Dimkpa *et al.*, 2013).

Delamanid, a new antituberculous drug, is metabolized in vitro in plasma albumin to form a unique metabolite M1 by cleavage of the 6-nitro-2,3-dihydroimidazo[2,1-b]oxazole moiety. In this study, the probable mechanism behind the hepatotoxicity is the secondary metabolites of the drug. Eight metabolites (M1-M8) generated by cleavage of the imidazooxazole moiety of Delamanid were identified in plasma after repeated oral administration by liquid chromatography-mass spectrometry (Zimmerman, 1999). Delamanid is first catalyzed by M1 and then it is metabolized via three separate pathways, suggesting that M1 is the key starting point. The predominant pathway in humans was hydroxylation of the oxazole moiety of M1 to form M2, followed by oxidation to the ketone form (M3), primarily by CYP3A4. After repeated oral administration to humans, M1 showed the highest exposure among these eight metabolites, suggesting that M1 is the major metabolite (Mitnick *et al.*, 2003; Verma and Kaplowitz, 2013).

Levels of transaminases indicate restoration of the integrity of the plasma membrane and protection of hepatocytes after the recovery period against damage caused by hepatotoxin drug. This is in concurrence with the frequently recognized viewpoint that serum levels of transaminases come back to near normal with the healing of hepatic parenchyma and the regeneration of hepatocytes (Ikhajiangbe *et al*., 2014). In the present study the acid and alkaline phosphatase levels in the serum increase due to the toxic effect of Delamanid drug and can also be correlated with an increase in other related hepatic enzymes. Similar findings have also been observed by Singh *et al*., (2001) and Hanley *et al*., (1986) in rats due to the toxic effects of hepatotoxic xenobiotics increase these liver enzymes and also damage hepatocytes. Karman *et al*., (1995) reported that the reduction in the activities of the enzymes in the liver may be due to interference with protein metabolism in the cell or inhibition of these enzymes while; Naglaa *et al*., (2016) in rats due to hepatic injury with an interaction on the cellular enzymes.

The mechanism by which Delamanid causes serum aminotransferase elevations is not very clear in a lack of molecular-level studies but is likely due to the production of a toxic intermediate by its metabolism. Delamanid is metabolized by the liver via the P450 system (predominantly CPY 3A4) and it is susceptible to drug-drug interactions with agents that induce or inhibit CYP3A4 (Diacon *et al*., 2012).

We may conclude that while prescribing Delamanid, apart from heart issues, one must also consider its effects on lives, the parallel usage of other hepatotoxic drugs, or if the patient is already liver compromised.

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