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Pharmaceutical Conference-2019: Role of Antioxidants in the prevention of Hepatotoxicity induced by Antitubercular Drugs

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Tuberculosis is an emerging infectious disease in human beings in different countries and is the leading cause of deaths all over the world. Tuberculosis is caused by the bacteria known as mycobacterium tuberculi and is transmitted from person to person through the air. Transmission mainly occurs from the droplets of the saliva of an infected person. The drugs that are available for the treatment of tuberculosis are known as antitubercular drugs
like Isoniazid, Rifampicin, Ethambutol, Pyrazinamide,
streptomycin, etc. Antitubercular drugs are classified as first-line and second-line anti-tubercular drugs based on their safety profile, but drug-induced liver injury (DILI) or hepatotoxicity is the major adverse effect associated with the use of these antitubercular drugs and leading to discontinuation of therapy in almost 15% of patients. The risk of drug-induced liver injury (DILI) is very high with second-line anti-tubercular drugs when compared to first-line drugs. These drugs cause drug-induced liver injury (DILI) by the production of free radicals during their metabolism in the liver. To prevent the occurrence of drug-induced liver injury (DILI) we should neutralize the free radicals formed in the body. Apart from these antitubercular drugs, the mycobacterium also leads to the production of free radicals. Due to the presence of antioxidants like catalase and superoxide dismutase in
the mycobacterium itself, they mitigate the free radicals or reactive oxygen species (ROS) encountered inside the host phagocytes. Thus, the host immune response is corrupted and causes

oxidative stress-induced immune suppression. Due to these reasons, there will be excess free radical or reactive oxygen species (ROS) formation in the host. Whenever the concentration of free radicals is increased they will start damaging all types of biomolecules like lipids, proteins, carbohydrates, and nucleic acids, etc through a process is known as lipid peroxidation. Neutralization of the free radicals or reactive oxygen species (ROS) should be done to prevent such damage to the liver and lungs. Antioxidants like selenium, reduced glutathione, vitamin E, etc are the chemicals that can neutralize the free radicals. As there are no interactions between the antioxidants and the antitubercular drugs we can use them in tuberculosis patients without any risk. The concentration of free radicals or reactive oxygen species can be estimated by measuring the levels of malondialdehyde which is an end product of lipid peroxidation. Apart from that, we can use the spin trapping technique and electron spin resonance for the measurement of free radical concentration. Electron Spin Resonance (ESR) is an appropriate method for identifying the production of free radicals in the living system, and it has become an important tool for the detection and identification of free radicals, and the Spin Trapping Technique uses a few reagents for the detection of free radicals. In this method, oxygen radicals are trapped by 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) or alpha-phenyl-N-t-butyl nitrone (PBN), and the DMPO and PBN spin adduct signal were measured quantitatively by an ESR spectrometer. In a prospective observational study conducted at

government general hospital we have included 5 patients between the age group of 25-45 and analyzed for 4 months. We used selenium as antioxidants in all 5 patients and estimated the concentration of free radicals or ROS by measuring the serum malondialdehyde levels as it is the marker of lipid peroxidation, economical, and can be done easily at the site of clinical settings. Malondialdehyde is the most extensively studied and was used as a biochemical marker for the assessment of lipid peroxidation. Malondialdehyde reacts with thiobarbituric acid and produced red-colored products known as thiobarbituric acid reactive substances (TBARS) which were measured calorimetrically. The estimation of serum malondialdehyde was used to assess oxidative stress and free radical damage to the body. During the lipid peroxidation due to antitubercular drugs in the liver, the free radicals or ROS destroys liver cells and leads to leakage of liver enzymes into the bloodstream so apart from malondialdehyde, the levels of liver enzymes like alanine transaminase (ALT) aspartate transaminase (AST) and alanine phosphatase (ALP) as these liver enzymes often indicate damage to hepatocytes.

Selenium at a dose of 55 mg per day was used as an antioxidant to neutralize the free radicals or ROS. The levels of malondialdehyde and liver enzymes were very high when measured before starting of antioxidant therapy and their levels were malondialdehyde (MDA) = (2.93 – 6.47 nmol/ml), alanine transaminase & aspartate transaminase (ALT) & (AST) = (245-327 IU), and alanine phosphatase (ALP) (310-385 IU) were significantly higher than normal levels. The levels of malondialdehyde (MDA) and the liver enzymes started reducing from the 2nd week after starting treatment with

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antioxidants. And 4 months after follow-up of these patients the levels were found to be malondialdehyde (MDA) = (0.91-2.39 nmol/ml), alanine transaminase & aspartate transaminase (ALT & AST) = (14-54 IU) and alanine phosphatase (ALP) = (43-152 IU) which shows that the antioxidants can be very effective in neutralizing the free radicals or ROS. Finally, we conclude that the antioxidants when used along with antitubercular drugs can reduce the incidence or prevent the occurrence of drug-induced liver injury (DILI) and helps in the successful completion of therapy along with that of the hospital stay and cost also reduced.