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The Effect of Anti-tuberculosis Drugs on Liver Enzymes in Iraqi Patients

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ABSTRACT

Tuberculosis is a national and world-wide spreading disease that many patients suffer from in addition to their battle with the disease itself, a new health challenging aspect is added which is the adverse effects of the anti-tuberculous drugs, as they have a hepatotoxic effect therefore this study has targeted the effect of anti-tuberculous drugs on liver enzymes. The study was conducted in three cities in Iraq (Baghdad, Samawah and diyala) 30 patients in total. All patients were registered in the national centers of infectious diseases according to their city. patients were monitored for four months for liver enzymes level (ALT, AST and ALP) , which were markedly elevated in the first two months then a promising recovery to normal levels in the later four months. Combined therapy of pyrazinamide, rifampicin, ethambutol and isoniazid has been used to all patients equally.

Patient and Methods : In descriptive study, a total of 30 cases aged from 7-65 years where collected from the national centers of tuberculosis centers in Iraq, from july 2018 to January 2019.pateints were treated for two months with combined drug formula (rifampicin, ethambutol, isoniazid and pyrazinamide) followed by isoniazid and rifampicin for the second two months. Blood samples were collected at 7 occasions, before treatment followed by 1 months, 2 months, 3 months, 4 months, 5 months and 6 months. Investigated for ALT, AST and ALP. Data were analyzed using SPSS ver. 23, results expressed as means and ± standard deviation, paired sample t -test study was used.

Inclusion and Exclusion: Patients included in our study were with pulmonary tuberculosis or extra pulmonary tuberculosis, planned and completed a full course of antituberculous. Any patient didn't complete the course and followed the treatment protocol was excluded.

Statistical analysis: Data is presented as means ± standard deviation (S.D) and were compared using paired sample t-test for continuous variables and Wilcoxon test. SPSS version 23.0 was used for analyzing the data, and p-values ≤ 0.05 were considered significant.

Key words: Anti-tuberculosis, Liver Enzymes, Iraqi Patients.

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INTRODUCTION

Tuberculosis (TB) is a standout amongst the most genuine irresistible illnesses worldwide and a main cause of death for almost 3 million passing's yearly. In 2013, an expected 9.0 million individuals were infected with tuberculosis, and 1.5 million passed on from this illness. In Iraq, there are an estimated 20,000 TB patients in Iraq. Estimated deaths due to TB are more than 4000 annually (1). TB is a very common incessant obliterating infection brought about by Mycobacterium tuberculosis. This microscopic organism is a stationary, commit oxygen consuming, corrosive quick facultative intracellular pole molded bacterium, with long age time and inclination to confine in macrophage and ordinarily influences the lungs (aspiratory TB) yet can influence different destinations just as additional aspiratory TB (2, 3). The most well-known strategy to identify TB is sputum smear microscopy. In this strategy, microorganisms are seen in sputum tests analyzed under a magnifying instrument. In regions with progressively prepared research centers, instances of TB likewise are analyzed through culture strategies (the reference standard technique). Following late advancement in TB diagnostics, fast atomic tests have been utilized for determination of TB and sedate safe TB (4). Medicines of tuberculosis include the utilization of a blend of medications to frustrate tranquilize obstruction. A piece of medications is exceedingly compelling in treating tuberculosis, yet it might likewise prompt improved danger and side effects. TB is treated with an underlying concentrated 2-month routine comprising of numerous anti-toxins, including rifampicin (RIF) 600mg, isoniazid (INH)250mg, pyrazinamide (PZA)1400mg, and ethambutol (EMB)1100mg daily, this is the fundamental treatment of dynamic tuberculosis, of which the initial three are hepatotoxic, after the two months treatment ,four months regimen with rifampicin 150mg and isoniazid 75mg is started, This regimen can cure TB in more than 90% of patients(10).impervious to at any rate isoniazid and rifampicin, requires our consideration since they requires the utilization of second-line medicates that are hard to acquire and are substantially more dangerous and costly than the main line routine (7, 8). Markers of hepatocellular capacities that typically are tested in clinical toxicology contemplates are the proteins alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Changes in centralizations of the exudation chemicals ALT and AST show changes in cell layer work, for example, changes in porousness or the more clear cell layer detachment (5, 9).In tuberculosis, numerous hematological and biochemical variations from the norm are normal, and they are highly helping to patients' administration what's more, determination. In accordance with our ongoing examinations on the impact of various mixes on liver function test, this examination was intended to watch the liver enzymes changes and related hazard factors in Tuberculosis patients experiencing treatment with standard protocol.

PATIENT AND METHODS

In descriptive study, a total of 30 cases aged from 7-65 years where collected from the national centers of tuberculosis centers in Iraq, from july 2018 to January

2019.pateints were treated for two months with combined drug formula (rifampicin, ethambutol, isoniazid and pyrazinamide) followed by isoniazid and rifampicin for the second two months. Blood samples were collected at 7 occasions, before treatment followed by 1 months, 2 months, 3 months, 4 months, 5 months and 6 months. Investigated for ALT, AST and ALP. Data were analyzed using SPSS ver. 23, results expressed as means and ± standard deviation, paired sample t -test study was used.

Inclusion and Exclusion: Patients included in our study were with pulmonary tuberculosis or extra pulmonary tuberculosis, planned and completed a full course of antituberculous. Any patient didn't complete the course and followed the treatment protocol was excluded.

Statistical analysis: Data is presented as means ± standard deviation (S.D) and were compared using paired sample t-test for continuous variables and Wilcoxon test. SPSS version 23.0 was used for analyzing the data, and p-values ≤ 0.05 were considered significant.

RESULTS

A total of 30 patients were selected from 3 different cities in Iraq (Baghdad, Diyala, Samawah) for our study, all the patient followed the protocol with caution for 6 consecutive months .we have noticed a significant changes in liver enzymes (AST,ALT,ALP).

As for ALT, The means were significantly increased comparing before treatment (33.8 ± 2.2) with that of 1st months of treatment (47.3 ± 3.1) followed by a further increase in the 2nd month (57.2 ± 6.9) then a slight decrease for the following 4 months after till reached an approximate normal level.16 patient's showed an increase of 1.5 folds in the second month of that in initial.

AST on the other hand, results have shown a significant increase in the 1st month (19.0 ± 3.0) and 2nd month (57.2 ± 9.2) compared to that of before treatment (15.5 ± 2.5) last 4 months also showed dramatic return to normal values.13 patients had more than 3 folds increase in the second month of that in initial.

ALP has the same scenario as the previous liver enzymes ,before treatment value (70.6 ± 11.4) then inclined to (100.3 ± 15.8) in the 1st month ,2nd month (132.3 ± 17.6) followed by dramatic decrease back to normal values.6 patients results in an increase of 1.9 folds in the second month of that in initial.

The three liver enzymes results were significant in the first month to that of before treatment (p value < 0.05).

Table.1 Showing the results of the effect of antituberculous drugs on liver enzymes.

Parameters	Before Treatment Mean ± SD	Antituberculous Treatment Duration (Months)					
		1st Month Mean ± SD	2nd Month Mean ± SD	3rd Month Mean ± SD	4th Month Mean ± SD	5th Month Mean ± SD	6th Month Mean ± SD
ALT (U/L)	33.8 ± 2.2	47.3* ± 3.1	57.2* ± 6.9	38.7* ± 2.3	28.6* ± 2.5	26.8* ± 1.4	24.1* ± 2.0
AST (U/L)	15.5 ± 2.5	19.0* ± 3.0	57.2* ± 9.2	19.2* ± 2.3	14.2 ± 2.6	11.8* ± 1.2	16.3 ± 2.0
ALP (U/L)	70.6 ± 11.4	100.3* ± 15.8	132.3* ± 17.6	73.7 ± 18.0	63.7 ± 14.1	50.3* ± 12.1	60.5* ± 15.6

*Results were significant of that before treatment P value <0.05

Table 2. Alanine transferase level during 6 months compared to initial (bar number 1).

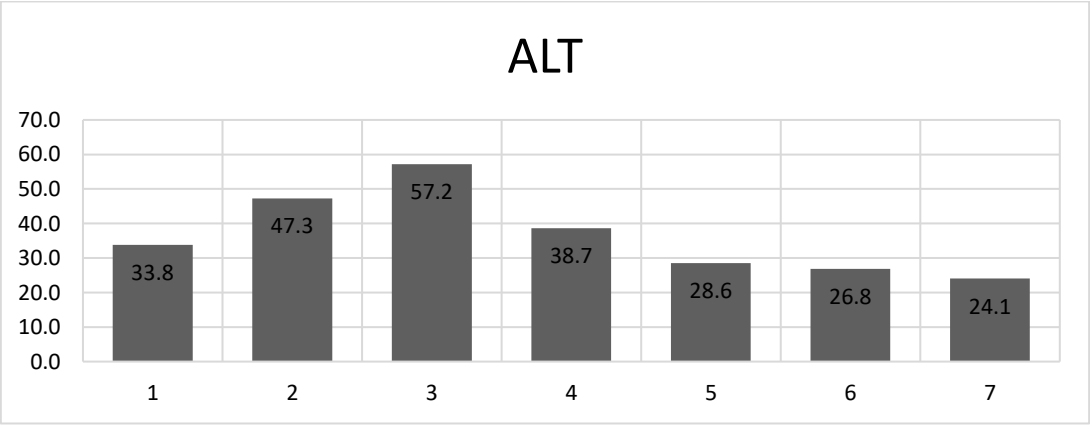


Table 3. Aspartate Aminotransferase levels during 6 months compared to initial (bar number 1).

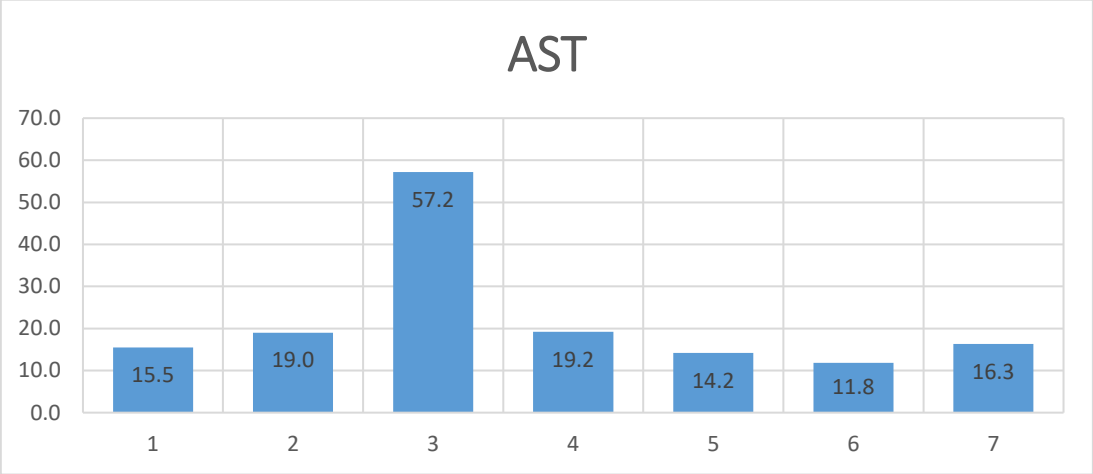
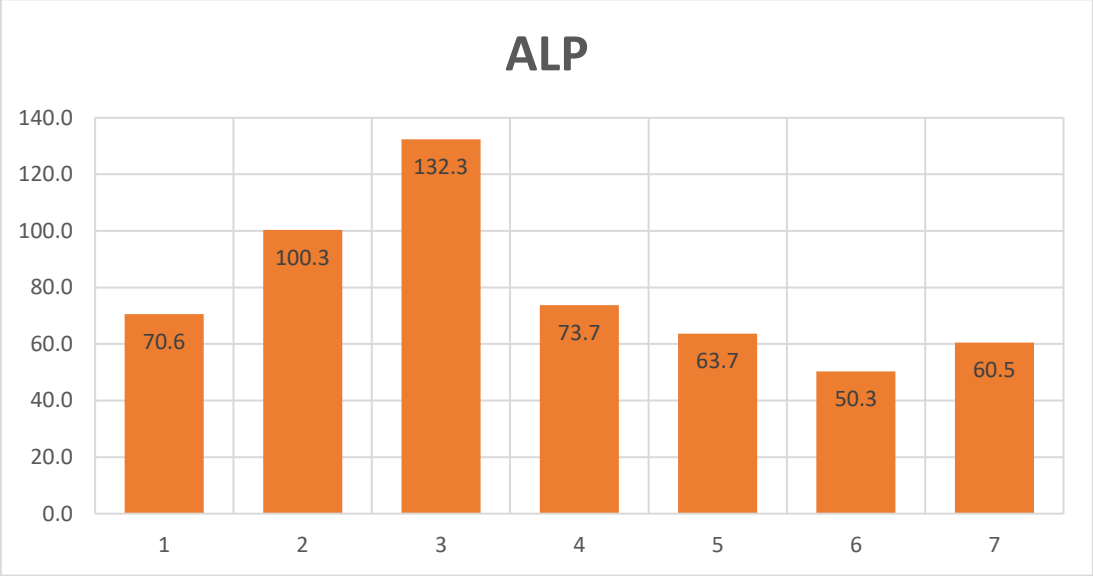


Table 4. Alkaline Phosphatase levels during 6 months compared to initial (bar number1).



DISCUSSION

Tuberculosis (TB), which is caused by bacteria of the *Mycobacterium tuberculosis* complex, is one of the oldest diseases known to affect humans and a major cause of death worldwide. Recent population genomic studies suggest that *M. tuberculosis* may have emerged ~70,000 years ago in.

Africa and subsequently disseminated along with anatomically modern humans, expanding globally during the Neolithic Age as human density started to increase. Progenitors of *M. tuberculosis* are likely to have affected pre-hominids. This disease most often affects the lungs, although other organs are involved in up to one-third of cases. If properly treated, TB caused by drug-susceptible strains is curable in the vast majority of cases. If untreated, the disease may be fatal within 5 years in 50–65% of cases. Transmission usually takes place through the airborne spread of droplet nuclei produced by patients with infectious pulmonary TB. More than 5.7 million new cases of TB (all forms, both pulmonary and extra pulmonary) were reported to the World Health Organization (WHO) in 2013; 95% of cases were reported from developing countries.9 million (range, 8.6–9.4 million) new cases of TB occurred worldwide in 2013, 95% of them in developing countries of Asia (5 million), Africa (2.6 million), the Middle East (0.7 million), and Latin America (0.3 million). It is further estimated that 1.49 million (range, 1.32–1.67 million) deaths from TB, including 0.36 million among people living with HIV infection, occurred in 2013, 96% of them in developing countries. *M. tuberculosis* is most commonly transmitted from a person with infectious pulmonary TB by droplet nuclei, which are aerosolized by coughing, sneezing, or speaking. The tiny droplets dry rapidly; the smallest (<5–10 μm in diameter) may remain suspended in the air for several hours and may reach the terminal air passages when inhaled. (11)

There may be as many as 3000 infectious nuclei per cough. Studies conducted in various countries before the advent of chemotherapy showed that untreated TB is often fatal. About one-third of patients died within 1 year after diagnosis, and more than 50% died within 5 years. The 5-year mortality rate among sputum smear–positive cases was 65%. Of the survivors at 5 years, ~60% had undergone spontaneous remission, while the remainder were still excreting tubercle bacilli. With effective, timely, and proper chemotherapy, patients have a very high chance of being cured. (11)

Normal liver enzymes range values are affected significantly by the antituberculous drugs ,AST normal range 10–45 U/L,ALT normal range 10–50 U/L and ALP normal range 40–125 U/L (12).the liver metabolize the anti-tuberculous drugs as a result it is the most affected organ in the body.

Isoniazid is a prodrug activated by a mycobacterial catalase–peroxidase (KatG). Isoniazid targets the enzymes acyl carrier protein reductase (InhA) and β-ketoacyl-ACP synthase (KasA), which are essential for the synthesis of mycolic acid. Inhibiting mycolic acid leads to a disruption in the bacterial cell wall. Hepatitis is the most serious adverse effect associated with isoniazid. If hepatitis goes unrecognized, and if isoniazid is continued, it can be fatal. Rifampin blocks RNA transcription by interacting with the β subunit of mycobacterial DNA-dependent RNA Polymerase Rifampin is generally well tolerated. The most common adverse reactions include nausea, vomiting, and rash.

Hepatitis and death due to liver failure are rare. However, the drug should be used judiciously in older patients, alcoholics, or those with chronic liver disease. There is a modest increase in the incidence of hepatic dysfunction

When rifampin is co-administered with isoniazid and pyrazinamide. When rifampin is dosed intermittently, especially with higher doses, a flu-like syndrome can occur, with fever, chills, and myalgia, sometimes extending to acute renal failure, hemolytic anemia, and shock.

Pyrazinamide is a synthetic, orally effective short-course agent used in combination with isoniazid, rifampin, and ethambutol. The precise mechanism of action is unclear. Pyrazinamide must be enzymatically hydrolyzed by pyrazinamidase to pyrazinoic acid, which is the active form of the drug. Some resistant strains lack the pyrazinamidase enzyme. Pyrazinamide is active against tuberculosis bacilli in acidic lesions and in macrophages. The drug distributes throughout the body, penetrating the CSF. Pyrazinamide may contribute to liver toxicity. Uric acid retention is common, but rarely precipitates a gouty attack. Most of the clinical benefit from pyrazinamide occurs early in treatment. Therefore, this drug is usually discontinued after 2 months of a 6-month regimen. Ethambutol is bacteriostatic and specific for mycobacteria. Ethambutol inhibits arabinosyl transferase, an enzyme important for the synthesis of the mycobacterial cell wall. Ethambutol is used in combination with pyrazinamide, isoniazid, and rifampin pending culture and susceptibility data. Ethambutol distributes well throughout the body. Both the parent drug and its hepatic metabolites are primarily excreted in the urine. The most important adverse effect is optic neuritis, which results in diminished visual acuity and loss of ability to discriminate between red and green. The risk of optic neuritis increases with higher doses and in patients with renal impairment. Visual acuity and color discrimination should be tested prior to initiating therapy and periodically thereafter. Uric acid excretion is decreased by ethambutol, and caution should be exercised in patients with gout.

A baseline hepatic enzyme measurement is a must in the treatment of tuberculosis with anti-tuberculous drugs, as stated by table "1" below.

Table.5 Major adverse effects of anti-tuberculous drugs.

DRUG	ADVERSE EFFECTS	COMMENTS
Ethambutol	Optic neuritis with blurred vision, red-green color blindness	Establish baseline visual acuity and color vision; test monthly.
Isoniazid	Hepatic enzyme elevation, hepatitis, peripheral neuropathy	Take baseline hepatic enzyme measurements; repeat if abnormal or patient is at risk or symptomatic. Clinically significant interaction with *phenytoin* and *carbamazepine*.
Pyrazinamide	Nausea, hepatitis, hyperuricemia, rash, joint ache, gout (rare)	Take baseline hepatic enzymes and uric acid measurements; repeat if abnormal or patient is at risk or symptomatic.
Rifampin	Hepatitis, GI upset, rash, flu-like syndrome, significant interaction with several drugs	Take baseline hepatic enzyme measurements and CBC; repeat if abnormal or patient is at risk or symptomatic. Warn patient that urine and tears may turn red-orange in color.

CONCLUSION

After 6 months of our study about the effect of anti-tuberculous drugs on liver enzymes in Iraqi patients, we can finally declare that anti-tuberculosis drugs do have an adverse effects on liver enzymes following a standard regimen protocol. The samples were collected in Baghdad, Samawah and Diyala showed a promising findings specially in the first two months of intensive combined treatment yet none of the patients did develop a critical hepatotoxicity.

RECOMMENDATION

As our results have shown that liver enzymes are highly affected by the anti-tuberculous drugs, therefore we highly recommend that all patients diagnosed with tuberculosis and planned to start anti-tuberculous medication must have an initial liver enzymes test before starting the treatment and follow up to detect and monitor any adverse effects in the 6 month treatment regimen.

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