Detection the effect of rifampicin concentration on the level of hepatic enzymes in white rats

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Abstract
The present paper aimed to detect the effects of rifampicin on the enzymatic activity of some liver enzymes (GPT, GOT, ALP). 40 adult male rats were used in this study, randomly divided into four equal groups for each drug, control group and three groups administrated GöTric dose - Low, medium and high (50, 100, 150 mg / kg) for a period of 28 days, and the rat's weights averaged from 225 - 260 g at the age of 5 months, after which blood was drawn from animals for the purpose of obtaining the serum for the required functional tests, which is to measure the level of liver enzymes GPT, GOT, ALP. The results of the current study recorded a significant increase (P <0.05) in the level of enzymes (GPT, GOT, ALP) in groups of rats treated with rifampicin drug compared with the control group.

Keywords. Rifampicin ,GPT , GOT , ALP

1- Introduction Rifampicin is a semisynthetic compound derived from Streptomyces spp that is used as consider as bactericidal antibiotic drug of the rifampicin group. It for the treatment of respiratory infections and disorders (2,17), many metabolic and morphological abnormalities produced by Rifampicin in the liver because the detoxification functions of the liver for drugs(1). Many studies reported that there the effect of rifampicin on lipid peroxidation there was a noticeable increase when the experimental models treated with rifampicin(20 mg/kg) for four weeks (4). Other papers demonstrated that there was increasesin serum GOT and GPT levels after treatment of rats with rifampicin. Increasing the levels of GOT and GPT were reported after treatment with rifampicin (200 mg /kg b.w./day) for four weeks (2,7).

Liver enzymes are clinically important, as their level in the blood is a standard for the duration of damage in the liver cells, which leads to their leakage into the blood, these enzymes are ALP, GPT and GOT, the ALP enzyme, it is produced mainly in the liver and bones, and in a small amount in the intestine and kidney, where the liver also manufactures this enzyme in more quantities than bone and other organs, therefore the level of concentration of these enzymes in the blood gives a picture of the level of their activity in the liver and the rest of the aforementioned organs (3,5).

While the GPT enzyme is produced mainly in the hepatocytes, that is why this enzyme is the most specialized in the diagnosis of liver disease, it is also found in some other tissues, but in small amounts such as the heart, pancreas, lung, skeletal muscles and spleen (11,16). The GOT enzyme, it is found in the mitochondria and the cytoplasm of the hepatocytes, in addition to the cells of some other organs, such as the skeletal muscles, the heart, the kidneys and the brain (10,14).
For above mentioned, the present paper designed to investigate the effect of rifampicin on the liver enzymatic represented by enzymes (GOT, GPT, ALP).

2- Materials and methods In this study 20 adult white male rats (Rattus norvegicus) were used, whose average weights were 225 - 260 g and at the age of 5 months, they were placed in metal cages for rats. The cages were spread with sawdust and the animals of the experiment were subjected to appropriate laboratory conditions at a temperature of 20 - 25 ° C. and for 12 hours lighting and 12 hours dark, the animals were given free water and food (ad lebtum) and the animals were left for ten days to adapt to those laboratory conditions as care continued in cleaning cages and sterilizing them with a 70% ethanol alcohol disinfectant once a week for the duration of the experiment. The study included the effect of different concentrations of rifampicin (50, 100, 150 mg / kg of body weight) on the level of liver enzymes GPT, GOT and ALP.

The experiment animals were divided according to dose into four groups for each concentration of drug. Each group included five animals, as follows: first control (group 1): Dose the physiological solution by 1 ml for a period of 28 days, second (group 2) low dose of rifampicin solution at a concentration of (50 mg / kg b.w./ daily) orally for 28 days, third (group 3) medium dose of rifampicin solution at a concentration of (100 mg / kg b.w./daily) orally for 28 days, while the fourth (group 4) high dose of rifampicin solution at a concentration of (150 mg / kg b.w./daily) orally for 28 days. The animals were sacrificed 24 hours after the GOT dose and drawn blood from the heart by means of a (heart puncture). Then the blood was drawn with a 5 ml centrifuge syringe and blood samples were stored in sterile gel tubes to accelerate the clotting process and then centrally discarded at 3000 rpm for 10 minutes to separate serum to perform the required functional tests, which are measuring the level of liver enzymes GPT, GOT and ALP.

3- Measurement of levels of liver enzymes GPT, GOT, ALP in serum levels of liver enzymes (GPT, GOT, ALP) in blood serum were measured by the RX DAYTONA and automatic analysis device supplied by British RANDOX company, where the serum is placed in the Hitachi cup and then placed in the place designated for it inside the device and after that the device is instructed through the computer connected to the device and after the completion of the test results appear on the computer screen through the device's program.

4- Results and discussion With regard to the GPT enzyme, the results of the current study (Table 1, figure1) reported that noticeable increasing (P <0.05) in the level of the GPT enzyme in the groups of rats treated with rifampicin respectively, compared with the control group. The results were (29.43±0.02 at control and 42.16±0.03 at low dose of rifampicin, 45.06±0.03 at medium dose of rifampicin and 60±0 at the high dose of rifampicin).

| groups   | GPT       | GOT       | ALP       |
|----------|-----------|-----------|-----------|
| control  | 29.43±0.02D | 80.46±0.03D | 114.5±0.02D |
| low      | 42.16±0.03C | 112.86±0.02C | 247.3±0.04C |
| medium   | 45.06±0.03B | 119.46±0.03B | 276.1±0.03B |
| high     | 60±0A     | 121.86±0.03A | 287.8±0.02A |
| LSD<0.05 | 0.103     | 0.128     | 0.084     |

- LSD : least significant difference
- Different letters denotes to the significant differences (P<0.05)
While GOT, the results of the present study were recorded (Table 1, Figure 2) recorded a significant increase (P < 0.05) in the level of the GOT enzyme in the groups of rats treated with rifampicin (80.46±0.0, 112.86±0.02, 121.86±0.03) respectively, compared with the control group (80.46±0.03).

Results of the present study (Table 1, Figure 3) indicated significant increase (P < 0.05) in the level of the ALP enzyme in the groups of rats treated with rifampicin (247.3±0.04, 276.1±0.03, 287.8±0.0) respectively compared with the control group (114.5±0.02).
5- Discussion  A complex system of antioxidants in mammals has been developed to reduce oxidative stress. However, reactive types that derive from oxygen and nitrogen continue to lead to oxidative damage to tissues and organs, and oxidative stress is a contributing factor to the initiation and development of liver injury (12,13). There are many factors that stimulate oxidative stress in the liver, and among these factors are drugs, radiation, environmental pollutants and alcohols, and this leads to severe liver disease and severe liver damage and thus high levels of liver enzymes, as they leak into the blood as a result of damage to the liver cells (9,11).

The results showed a marked increasing in the level of enzymes, and this increasing can be referred to the high leakage of liver enzymes in large quantities of liver cells into the blood serum, and this leak reflects the extent of damage to the liver tissue as a result of liver cell degeneration in addition to necrosis processes and cell death, and these results are compatible with a many of previous studies (8,18) that indicate signs of rifampicin damage in liver tissue and liver cells. The results of the current study showed that the treatment of male rats with doses with gradient concentrations of rifampicin has led to a noticeable increase in the level of these enzymes for this increase can be referred to the leakage of these enzymes in large quantities from hepatocytes to the blood serum and this leak reflects the damage to the liver tissue as a result of liver cell degeneration in addition to necrosis and cellular death processes, and these results are agree with previous studies that reported signs of damage caused by amoxicillin drug in liver tissue in general and hepatic cells in particular (6,13).

6- References

(1) AïtMoussa L, El Bouazzi O, Serragui S, SoussiTanani D, Soulaymani A, Soulaymani R.( 2016): Rifampicin and isoniazid plasma concentrations in relation to adverse reactions in tuberculosis patients: a retrospective analysis. TherAdv Drug Saf; 7: 239-47.
(2) Bliven-Sizemore EE, Sterling TR, Shang N, Benator D, Schwartzman K, Reves R, Drobeniuc J, Bock N, Villarino ME; TB Trials Consortium.( 2015): Three months of weekly rifampicin plus isoniazid is less hepatotoxic than nine months of daily isoniazid for LTBI. Int J Tuberc Lung Dis; 19: 1039-44.
(3) Bouazzi OE, Hammi S, Bourkadi JE, Tebaa A, Tanani DS, Soulaimani-Bencheikh R, Badrane N, et al. (2016): First line anti-tuberculosis induced hepatotoxicity: incidence and risk factors. Pan Afr Med J; 25: 167.

(4) Bright-Thomas RJ, Gondker AR, Morris J, Ormerod LP. (2016): Drug-related hepatitis in patients treated with standard anti-tuberculosis chemotherapy over a 30-year period. Int J Tuberc Lung Dis; 20: 1621-4.

(5) Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; (2015): United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology; 148: 1340-52.e7.

(6) Chalasani N, Reddy KRK, Fontana RJ, Barnhart H, Gu J, Hayashi PH, Ahmad J, et al. (2017): Idiosyncratic drug induced liver injury in African-Americans is associated with greater morbidity and mortality compared to caucasians. Am J Gastroenterol; 112: 1382-8.

(7) Gourishankar A, Navarro F, Debroy AN, Smith KC. (2014): Isoniazid hepatotoxicity with clinical and histopathology correlate. Ann Clin Lab Sci; 44: 87-90.

(8) Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. (2014): Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol; 13: 231-9

(9) Jeong I, Park JS, Cho YJ, Yoon HI, Song J, Lee CT, Lee JH. (2015): Drug-induced hepatotoxicity of anti-tuberculosis drugs and their serum levels. J Korean Med Sci; 30: 167-72.

(10) Lin HS, Cheng CW, Lin MS, Chou YL, Chang PJ, Lin JC, Ye JJ. (2016): The clinical outcomes of oldest old patients with tuberculosis treated by regimens containing rifampicin, isoniazid, and pyrazinamide. ClinInterv Aging; 11: 299-306.

(11) Sekaggya-Wiltshire C, von Braun A, Scherrer AU, Manabe YC, Buzibye A, Muller D, Ledergerber B, et al. (2017): Anti-TB drug concentrations and drug-associated toxicities among TB/HIV-coinfected patients. J Antimicrob Chemother 2017; 72: 1172-7.

(12) Shamaei M, Mirsaedi M, Baghaei P, Mosaei H, Marjani M, Tabarsi P. (2017): Recurrent drug-induced hepatitis in tuberculosis-comparison of two drug regimens. Am JTher; 24: e144-e149.

(13) Shin HJ, Lee HS, Kim YI, Lim SC, Jung JP, Ko YC, Kwon YS. (2014): Hepatotoxicity of antituberculosis chemotherapy in patients with liver cirrhosis. Int J Tuberc Lung Dis; 18: 347-511.

(14) Simkins J, Abbo LM, Camargo JF, Rosa R, Morris M. (2017): Twelve-week rifampicin plus isoniazid versus 9-month isoniazid for the treatment of latent tuberculosis in renal transplant candidates. Transplantation; 101: 1468-72.

(15) Tweed CD, Wills GH, Crook AM, Dawson R, Dicon AH, Louw CE, McHugh TD, et al. (2018): Liver toxicity associated with tuberculosis chemotherapy in the REMoxTB study. BMC Med; 16: 46. [PMC free article]

(16) Usui T, Meng X, Saide K, Farrell J, Thomson P, Whitaker P, Watson J, et al. (2017): From the cover: characterization of isoniazid-specific T-cell clones in patients with anti-tuberculosis drug-related liver and skin injury. ToxicolSci; 155: 420-31.

(17) Ye YM, Hur GY, Kim SH, Ban GY, Jee YK, Naisbitt DJ, Park HS, Kim SH. (2017): Drug-specific CD4(+) T-cell immune responses are responsible for antituberculosis drug-induced maculopapular exanthema and drug reaction with eosinophilia and systemic symptoms syndrome. Br J Dermatol; 176: 378-86.

(18) Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. (2017): Treatment of latent tuberculosis infection: an updated network meta-analysis. Ann Intern Med; 167: 248-55.