Review Article

The Effect of Combination Therapy (İsoniazid, Streptomycin, Rifampin, Ethambutol) Used in Tuberculosis Patients on Liver Function

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ABSTRACT

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Tuberculosis (TB) is a significant cause of morbidity and mortality worldwide, particularly in developing countries. In recent years, there has been a renewed increase in its incidence. We aim to present an approach to the use of combination drugs, which play a significant role in TB treatment, from the past to the present. The methodology used in this review is to evaluate a biochemistry dissertation entitled "The effects of combination therapy for tuberculosis on liver function tests" in conjunction with current research. In the treatment of TB, drugs such as isoniazid, rifampicin, streptomycin, and ethambutol are primarily used for at least 6 months. The most significant side effect of these drugs, hepatotoxicity, should be detected mainly through liver enzyme tests. When liver enzymes are mentioned, the ones that come to mind are ALT (alanine aminotransferase), AST (aspartate aminotransferase), GGT (gamma-glutamyl transpeptidase), and ALP (alkaline phosphatase). Because drug resistance develops in TB treatment, multiple drug therapy should be applied. On the other hand, hepatotoxicity to the liver should be continuously monitored, and drug dosages should be adjusted as needed based on enzyme analyses.

Keywords: *Tuberculosis, combination therapy, liver function; hepatotoxic.*

ÖZET

Bu çalışmanın amacı, Tüberküloz (TB), özellikle gelişmekte olan ülkelerde olmak üzere, dünya çapında önemli bir morbidite ve mortalite nedenidir. Son yıllarda, görülme sıklığında yeniden bir artış olmuştur. Bu derlemede, TB tedavisinde önemli rol oynayan kombinasyon ilaçlarının kullanımına ilişkin geçmişten günümüze bir yaklaşım sunmayı amaçlıyoruz. Bu derlemede kullanılan metodoloji, "Tüberküloz için kombinasyon tedavisinin karaciğer fonksiyon testleri üzerindeki etkileri" başlıklı bir biyokimya tezini güncel araştırmalarla birlikte değerlendirmektir. TB tedavisinde, izoniyazid, streptomisin, rifampin ve etambutol gibi ilaçlar öncelikle en az 6 ay süreyle kullanılmaktadır. Bu ilaçların en önemli yan etkisi olan hepatotoksisite, esas olarak karaciğer enzim testleri yoluyla tespit edilmelidir. Karaciğer enzimlerinden bahsedildiğinde akla gelenler ALT (alanin aminotransferaz), AST (aspartat aminotransferaz), GGT (gama-glutamil transpeptidaz) ve ALP (alkalin fosfataz)'dır. TB tedavisinde ilaç direnci geliştiği için çoklu ilaç tedavisi uygulanmalıdır. Öte yandan, karaciğere hepatotoksisite sürekli olarak izlenmeli ve enzim analizlerine göre ilaç dozları gerektiği gibi ayarlanmalıdır.

Anahtar Kelimeler: *Tüberküloz, kombinasyon tedavisi, karaciğer fonksiyonu; hepatotoksik.*

INTRODUCTION

Treatment typically involves the primary use of medications such as isoniazid, streptomycin, rifampin, and ethambutol for at least six months. Due to the development of drug resistance, multidrug therapy is often employed. The drugs used in tuberculosis treatment have a significant potential for side effects. Hepatotoxicity is the most common side effect. If hepatotoxicity occurs, it is recommended to interrupt drug treatment and resume it only after the liver involvement has subsided (Ateş, G., Yıldız, T., Akyıldız, L., 2008).

The liver is the largest and most important metabolic organ in our body, performing numerous functions including protein synthesis, detoxification, and the production of enzymes essential for digestion. Liver enzymes include ALT, AST, GGT, and ALP. The first two enzymes are synthesized in hepatocytes, while the latter two are synthesized in the epithelial cells of the bile ducts. These enzymes are not exclusive to the liver and bile ducts. ALT and especially AST are also synthesized in skeletal muscle and cardiac muscle, GGT in the kidneys, and ALP in bones and intestinal epithelial cells (Kantar, D.F.H., 2017; Ersoy, O., 2012).

The most important indicator of acute hepatocellular damage is an increase in serum transaminases. Biochemically, the most important function of transaminases is to catalyze the transfer of alpha-amino groups from alanine and L-aspartic acid to the alpha-keto group in ketoglutaric acid. When the hepatocyte cell membrane is damaged, transaminases are released into the bloodstream, and serum levels increase. AST is both a cytosolic and mitochondrial enzyme. Besides the liver, AST is found in the heart and skeletal muscle, kidney, brain, pancreas, lung, leukocytes, and erythrocytes. ALT, on the other hand, is a cytosolic enzyme. ALT is most abundant in the liver, therefore it is more specific than AST in indicating liver damage (Yılmaz, R., 2012; Dong, M.H., Bettencourt, R, Brenner, D.A., 2012; Bayraktar, V., Coşar, A.M., 2019)

Elevated serum transaminase levels are observed in cases of damage to tissues rich in transaminases and in situations where there are changes in cell membrane permeability. Necrosis of hepatocytes is not necessary for the release of transaminases from the liver. Furthermore, elevated transaminase levels do not correlate with the degree of liver damage. Transaminase elimination generally occurs via the reticuloendothelial system; small amounts may pass into the bile, but there is no excretion in the urine. AST has a slightly faster half-life than ALT (Ersoy, O. 2012).
(Bayraktar, V., Coşar, A.M., 2019)

Transaminase levels below the normal reference range have no clinical significance. It is particularly noted in kidney patients undergoing hemodialysis and in cases of vitamin B6 deficiency. Transaminase values above 1000 u/L should clinically suggest viral hepatitis, ischemic hepatitis and toxic hepatitis. Less commonly, autoimmune hepatitis, acute Budd-Chiari syndrome, fulminant Wilson's disease, and acute biliary obstruction should also be considered. AST/ALT Ratio (De Ritis Ratio): This ratio Guides physicians in differential diagnosis of liver diseases. If the De Ritis Ratio is less than 1 (ALT > AST), this is usually seen in conditions such as chronic viral hepatitis or non-alcoholic fatty liver disease. If the ratio is greater than 2 (AST > 2 x ALT), this strongly suggests alcohol-related liver disease. Serum AST and ALT ratios can also be diagnostic in certain specific situations, particularly in alcoholic hepatitis. An AST value below 300 U/L and an AST-to-ALT ratio >2 suggest alcoholic liver disease, while a ratio >3 strongly suggests alcoholic liver damage. This is because individuals with alcoholic liver disease have decreased pyridoxal 5'-phosphate levels. Pyridoxal phosphate is required in greater quantities for ALT synthesis than for AST synthesis. Elevated gamma-glutamyl-transpeptidase enzyme levels are also an important finding in alcoholic liver disease. The AST-to-ALT ratio also increases in muscle diseases. In muscle diseases, AST levels are usually <300 u/L. However, in rare cases such as rhabdomyolysis, serum transaminase levels can reach values similar to those seen in acute hepatocellular damage. Initially, the AST/ALT

ratio is >3, but due to the shorter half-life of AST, the ratio rapidly approaches 1:1. In chronic muscle diseases, the AST/ALT ratio is close to 1. Serum creatinine kinase and aldolase levels are other tests that aid in the diagnosis of muscle disease. While the AST/ALT ratio is <1 in chronic viral hepatitis and non-alcoholic fatty liver disease, it may become >1 with the development of cirrhosis (Bayraktar, V., Coşar, A.M., 2019; Yazar, H., Kayacan, Y., Ozdin, M., 2022; Demir, B., Özsoy, F., 2021).

METHOD

The methodology used in this review is to evaluate a biochemistry dissertation entitled "The effects of combination therapy for tuberculosis on liver function tests" in conjunction with current research.

RESULTS

İzoniazid:

Tuberculosis, whose incidence has increased again in recent years, is a significant public health problem for our country. Isoniazid is one of the most frequently used antituberculosis drugs due to its low cost and effectiveness. It is generally well tolerated at the recommended doses. Systemic or cutaneous hypersensitivity reactions may occur in the first weeks of treatment. Drowsiness and lethargy can be resolved by changing the time of drug administration or by reassuring the patient. Peripheral neuropathy can be prevented by daily administration of pyridoxine (10 mg). Optic neuritis, toxic psychosis, and systemic convulsions may occur. They usually occur in the later stages of treatment and may require discontinuation of the INH. Limited elevations in liver enzymes are not clinically significant and may resolve during continued treatment. Symptomatic hepatitis is very rare but is a significant side effect. It requires discontinuation of the drug and can be fatal. Systemic lupus erythematosus-like syndrome, hypersensitivity reactions, pellagra, anemia, and arthralgia may occur. Monoamine poisoning from foods high in monoamine content is very rare (Dede, T., Yılmaz, H.L., Yıldızdaş, D.R., Aydemir, Ş., 2010).

Streptomisin:

Streptomycin is an antibiotic belonging to the aminoglycoside class. It was the first drug discovered in the aminoglycoside group and the first antibiotic used in the treatment of tuberculosis. Redness, swelling, or sterile abscesses may occur at the injection site. Hypersensitivity reactions may occur on the skin. Vestibular dysfunction is rare at currently recommended doses. Signs of vestibular nerve damage may include tinnitus, ataxia, vertigo, and deafness. This damage usually occurs within the first two months of treatment and reverses when the drug is discontinued or the dose is reduced. Streptomycin is less nephrotoxic than other aminoglycoside antibiotics. If urine output decreases, albuminuria occurs, or tubular casts are seen in the urine, streptomycin should be discontinued and renal function should be evaluated. Hemolytic anemia, aplastic anemia, agranulocytosis, thrombocytopenia, and lipoid reactions are rare side effects (Gürbüzler, L., Koç, S., Aladağ, İ., Soyalıç, H., Aksakal, C., & Göktaş, G., 2012).

Rifampin:

Rifampicin is an antibiotic from the rifamycin group with bactericidal effects. Side effects of rifampicin are generally due to its hepatotoxicity. Because it causes hepatotoxicity, rifampicin should not be used in patients with liver failure. It is generally well tolerated; some patients may experience gastrointestinal reactions with abdominal pain, nausea, and vomiting, and itching with or without rash. Other side effects, such as fever, flu-like symptoms, and thrombocytopenia, usually occur with intermittent drug administration. Moderate increases in serum bilirubin and transaminase levels may occur. Dose-dependent hepatitis may occur and can be fatal; therefore, it is important not to exceed a maximum dose of 600 mg (Dede, T., Yılmaz, H.L., Yıldızdaş, D.R., Aydemir, Ş., 2010; Gönlügür, U., Akkurt, İ., 2003).

Etambutol:

This antibiotic has a bactericidal effect at very high concentrations. Its most important side effect is optic neuritis. It can cause impairment of color vision and visual acuity in one or both eyes. Peripheral neuritis, arthralgia, and rarely hepatitis may occur. Dose-dependent optic neuritis can occur in one or both eyes. Visual toxicity is rare with 2-3 months of use at the recommended doses. Peripheral neuritis symptoms may develop in the legs. Other rare side effects include generalized skin reaction, arthralgia, and very rarely hepatitis (Dede, T., Yılmaz, H.L., Yıldızdaş, D.R., Aydemir, Ş., 2010; Varan, G., Şahin, A., 2020).

CONCLUSION

In conclusion, this study found that the hepatotoxic effects of drugs used in tuberculosis treatment are also mentioned in current guidelines. On the other hand, it appears that the combination therapy option is still the first choice. Furthermore, it is essential to note that liver enzyme monitoring should not be neglected when adjusting drug dosages. In our opinion, focusing pharmacological experimental studies on this subject, along with the increasing variety of new clinical trials, will enable the emergence of safer, more reliable, and more effective treatment options for TB.

Conflict of Interest: The authors declare that there is no conflict of interest.

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