Anti-Tuberculous induced Hepatitis

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تأثير أدوية التدرن على الكبد

الخلاصه :

دراسة تاثيرادوية التدرن سريريا و مختبريا على الكبد لمرضى التدرن الرئوي في محافظة واسط
خمسون مريضا من البالغين المصابين بالتدرن الرئوي لأول مرة تمت متابعتهم سريريا ومختبريا اثناء زياراتهم الى عيادة التدرن وردهة العزل في مستشفى الكرامة التعليمي في محافظة واسط . لوحظ وجود ارتفاع في انزيمات الكبد في بداية العلاج(73%) وغير مصحوب باعراض وعلامات سريرية مهمة وأن ا نزيمات الكبد عادت الى معدلاتها الاعتيادية(88%) بعد شهرين من بداية العلاج، عدا حالتين ظهرت اعراض شديدة استوجب ايقاف العلاج مؤقتا. اظهرت الدراسة ان نسبة 4% فقط من المرضى الذين يأخذون ادوية التدرن يعانون من تأثيراتها المهمة على الكبد وهي نسبة أقل بكثير مما سجل سابقا في بعض البلدان الاسيوية

Abstract

This study is about anti-TB induced hepatitis , clinical and biochemical follow up of 50 adult patients with active pulmonary TB(sputum-positive for acid bacilli) in Wassit Province , Iraq ,during their visit to TB-outpatient clinic and infectious ward in Al-Karama Teaching Hospital in Wasit Province. There was an elevation in liver enzymes (Alanine aminotransferase, Aspartate aminotransferase and Alkaline Phosphatase) at the start of anti-TB therapy (73%), but with no significant clinical or laboratory derangement in liver function tests, apart from 2 young females who needed cessation of therapy till settlement of their condition .In most patients there were no significant clinical complaints and liver enzymes returned to normal (88%) after two monthsof anti-TB therapy. The percentage of clinically significant hepatitis (jaundiced) was only 4% which is considered low in comparison with that reported in some Asian countries

INTRODUCTION

Tuberculosis (TB) is a common communicable disease, caused by *Mycobacterium Tuberculosis (MBT*),that is still prevalent in our country despite all efforts for its control and its incidence may be under-estimated. It carries a lot of sequences if not diagnosed earlyor treatedpromptly.Although TB-infection can involve any organ in the body, but its main target system is the respiratory system. It can be mild form flu –like illness to severe miliary fatal type, which can be missed and discovered atpostmortem. That is why any longstanding cough especially if accompanied by hemoptysis should alert for exclusion of TB. It may present as ill health, loss of weight, pyrexia of unknown origin (PUO) or involve many organs giving to a tray of presentations as dysfunction of systems such as meningitis, pericarditis, orchitis, peritonitis, lymphadenitis and osteomyelitis.

First line anti-Tb drugs include: Isoniazid (INH), Rifampicin, Ethambutol (ETB) Streptomycin and Pyrazinamide. Most cases of Tuberculous infections are treated for six months therapy by the standard first line anti-TB drugs, except few conditions which needs more pronged period (as in the central nervous infection), or when there is drug resistance .The regimen of anti-TB

therapy consist of two months consolidation phase with 3-4 drugs (INH, Rifampicin ,ETB , ±Pyrazinamide or streptomycin) and continuation phase of 4 months of (INH & Rifampicin) .Most drug side effects appear early in the first two months of therapy[1], especially drug induced hepatitis by INH and Rifampicin[2,3,4].It is well documented in previous literatures that both INH and Rifampicin are the most famous causatives of anti-TB induced hepatitis[2,3,4,5].
In this study we monitored the main side effects of anti-Tb drugs on the liver clinically and biochemically through their regular follow –up visits and during their admission in the infectious ward in Al-Karama Teaching Hospital in Kut City of Wassit Province

MATERIAL AND METHODS

This study consists of clinical and laboratory follows up of patients with active pulmonary TB during treatment. Fifty patients with active pulmonary TB were selected in this study from Kut city and it's peripheries in Wassit Province, Iraq, when they first diagnosed during the period between January 2007 and June 2009.Patients age rangefrom 18to 63 years. Twenty three female patients with mean age 27 ±2.4 SD, 27 males with mean age 29 ±2.1 SD.Twenty healthy persons wereincluded as a control group in the study.Full clinical examination and laboratory tests carried out for them before starting anti –TB therapy including: liver enzymes: Alanineaminotransferase (ALT) ,Aspartate aminotransferase (AST) and Alkaline phosphates), total serum bilirubin (direct and indirect) ,blood urea,serum creatinine, blood sugar, hemoglobin, total serum protein, to exclude pre – existing disease. Patients with history of liver disease ,alcohol intake , previous anti-TB therapy , chronic use of non-steroid drugs use or who had diseases such as renal impairments, diabetes mellitus and cardiac problems were excluded from the study. All patients received thestandard anti – TB drugs from TBoutpatient clinic (as recommended by Ministry of Health) in the usual doses :INH, ETB, Rifampicin±Streptomycin or pyrazinamide. Liver function tests ALT , AST, Total serum bilirubin, Alkaline phosphates) carried out for all patients before commencing treatment, after one week, two week and two months from starting anti –TB therapy. Regular clinical examination fallow up on their visits to the outpatientclinics and in the infectious wards

Results

This study showed that most clinical side effects of anti- TB drugs were mild and transient, except in 2 young females who suffered severe symptoms and signs of epigastric pain, nausea with tender enlarged liver and Jaundice, for these reasons: cessation of therapy, till recovery after 3 weeks, and resumption of treatment in low doses gradually. The main complaints of patients taking anti – TB drugs were epigastricdiscomfort (85%), indigestion (47%), nausea, vomiting (24%) [Table 1].Most of these problems became mild or disappeared when the drugs taken with food.Jaundice appeared clinically only in two young females (4%) and disappeared after two months with continuing drugs but adjusting the doses.
Laboratory finding showed that liver enzyme elevation in ALT, AST were more than the increase in alkaline phosphatase and serum bilirubin [table 2]. These liver enzymes returned to near normal values after two months of anti-TB therapy with no significant clinical complaints. Serum level of ALT was significantly elevated in the first and second week of therapy reaching six fold of pre-start therapy (p=value o.oo1) with more than five folds elevation of AST (p=value 0.002) in the most severe case, but only mild elevation in serum bilirubin (2.2 mg /100ml),

alkaline phosphatase rise was only minimal [table 2] .There were no significant changes in serum albumin, creatinine or blood urea among patients during this follow up period

Discussion:

Drug induced hepatitis is among the main clinical problems during anti-TB treatment and sometimes may cause severe liver injury and non-compliance of patients especially at the beginning of treatment [6,7,8]. This study concentrates on liver problems during therapy of active pulmonary TB in the first two months of anti-TB therapy .The main clinical problems wereepigastric discomfort and indigestion as shown in(table 1). However, these symptoms were mild and disappeared when the drugs were taken with food and this may indicate gastric upset by the drugs [13,14,15].Liver enzymes were elevated during first two weeks (73%), but returned to normal range in most of patients (88%) after two months, as shown in[table2]. Liver enzymes elevation was not always associated or correlated with symptoms and many patients without complaint, exception to that is seen in 2 young females ,who developed severe symptoms of epigastric pain, jaundice and high liver enzymes necessitating cessation of drugs until clinical improvement after 3 weeks, then resumption of therapy with lower doses, gradually increasing the dose.According to the British Thoracic Society (1998) guides that if theaspartate aminotransferase and alanine transferase are two or more times normal, liver function should be monitored for two weeks, then two weekly until normal. If the aspartate aminotransferase and alanine transferase under two times normal, liver function should berepeated at two weeks,if the aspartate aminotransferase and alanine transferase level rises to five times normal or bilirubin level rises, rifampin, isoniazid and pyrazinamide should be stopped(13) , and this was only neede in the 2 young females with severe symptoms . Clinical improvement precedes the settlement of liver enzymes (16, 17).Many studies in Asian countries reported drug induced hepatitis by anti-TB drugs but variable degrees of liver insults [18,19,20] The percentage of clinically significant anti-TB induced hepatitis in this study was (4%) which is considered low in comparison with those reports in studies from Asian countries e.g.: Japan 18% China 14% Hon Kong 13% India 11.5%.

Although the sample of this study is small but it showed that most of patients tolerate well all the standard anti-TB drugs in their usual doses without any serious side effects. The results as compared with old studies indicate that these drugs are safe apart from minor adverse effects.Large sample studies are needed for confirmation of these results

Table 1: Symptoms and signs percentage in patients taking anti-TB therapy

	Symptom	% First and second weeks	% After two months
1	Epigastric pain	85	4
2	Indigestion	47	3
3	Nausea and vomiting	24	1
4	Malaise	4	1
5	Jaundice	4	-

6	Hepatomegaly	2	-
7	Other	1	-

Table 2: Mean values of liver enzymes during anti-TB drug therapy

Enzyme	Before treatment mean value	After one week mean value	After two weeks mean value	After two months mean value
ALT	35IU/L (N<40 IU/L)	65 IU/L	192 IU/L	50 IU/L
AST	24 IU/L (N<40)	58 IU/L	144 IU/L	45 IU/L
Alkaline phosphates	60 IU/L(N<70 IU/L)	82 IU/L	130 IU/L	66 IU/L
TSB	1.0 mg/100ml (N<1.1mg/100ml)	1.9mg/100ml	2.2 mg/100ml	1.3 mg/100ml

RECCOMENDTION

Although many literatures reported many side effects of anti-TB drugs , we found many of these adverse effect were mild and largely minimized by taking the drugs with food or reducing the dose if the patients develop symptoms early.

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