HEPATOTOXICITY TO DIFFERENT ANTITUBERCULOSIS DRUG COMBINATIONS

Pages with reference to book, From 290 To 294

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ABSTRACT

Hepatotoxicityto different combinations of anti-tuberculosis drugs containing, Rifampicin (R), Streptomycin (5), lsoniazid (H), Pyrazinamide (Z) and Myambutol (E) is described in 47 patients who completed 6 to 9 months therapy. Seven cases (15%) showed signs of toxicity and in 4 patients (8.5%) the drugs had to be withdrawn. Two patients developed hepatitis, one with jaundice and the other with fever and deranged liver functions, while others 2 developed severe hypersensitivity reactions. Burning palms, difficulty in micturition, itching and giddiness ware complained of by one patient each, which sealed in due course without recourse to withdrawal of drugs (JPMA 40: 290, 1990).

INTRODUCTION

Treatment of tuberculosis has undergone rapid change in the last few years, with older drugs being replaced by newer and more effective ones. Treatment regimens are now available which, when taken regularly and in correct doses produce almost 100% cure[1-3]. Depending upon the combination of drugs, both for initial and continuation phase, daily or intermittently, the cost and duration of treatment can also be reduced considerably. In Pakistan the use of rifampicin and pyrazinamide alongwith isoniazid has become popular, and vast majority of patients, even in the Government hospitals are being treated with these effective but relatively more toxic and expensive drugs. Since the level of toxicity differs in different races, and little data is available in the Pakistani population, this study was undertaken to evaluate the tolerance and toxicity of different combinations of antituberculosis drugs in a cross section of patients belonging to the lower socio-economic group taking treatment for 6 to 9 months.

PATIENTS AND METHODS

Patients with pulmonary tuberculosis (new and with previous history of treatment) attending the chest outpatients department of K.V.S.S. Site Hospital, Karachi, irrespective of age and sex, were included in the study. This is a social security hospital serving mostly the labour class of the main industrial estate in Karachi. The workforce consists of almost all ethnic groups. Amongst those attending the chest outpatients, Pathans predominate. Diagnosis of pulmonary tuberculosis was based on positive sputum for AFB whcrever possible, but some cases diagnosed on clinico-radiological grounds were also in-cluded. On inclusion each patient had complete blood picture, ESR, liver function tests including proteins and calcium levels were done before starting the treatment. These investigations were repeated initially at 2 weeks and then every 6 weeks till the completion of treatment. Sputum if initially positive was tested for AFB every 4 weeks till it became negative; among those who were negative on three occasions, no further sputa were examined. All patients received 3 or 4 drugs in the initial phase, followed by 2 drugs. All drugs werc prescribed as a single daily dose atleast half an hour before breakfast. Those receiving streptomycin combination were advised to take injections daily at the same time either in the morning or evening. Depending upon the body weight the dosage of the drugs varied as Rifampicin (R) 450-600mg, Pyrazinamide (Z) 1500-2500mg, Streptoniycin (5) 75G-1G, Ethambutol

(E) 1200mg and Isoniazid (H) 300mg. Patients were clinically examined weekly (on Sundays) as outpatients. Of 46 cases, 36 received 4 drugs and the rest 3 drugs during the initial 2 months, followed by 2 drugs for further 4 to 7 months. All received isoniazid. Rifampicin was given to all except 4 patients, while 40 received ethambutol, 36 pyrazinamide, and 16 streptomycin. One case who had been treated with various combinations for the past 5 years but still had positive sputum for AFB was given 5 drugs (SHRZE) daily for one year. X-ray chest was done before starting treatment and then after 3 months and, lastly, at the completion of the therapy.

RESULTS

A total of 95 patients with pulmonary tuberculosis were included in the study. Thirty eight came once only and were, therefore, excluded. Of the remaining 57 cases, 47 completed 6 to 9 months of therapy, 8 defaulted at 8th and one each at 14th and 20th weeks. Of 47 patients completing the study, 35 were males and 12 females with a mean age of 29±10 years (Range 10-60 years). Majority were in 20-40 years age group. There were 40 new cases and 7 had antituberculosis treatment in the past. Twenty five (53%) cases had positive sputum On direct smear while one was culture positive. Disease was of moderate to advanced degree in majority of the cases, one had miliary infiltration. Initial liver functions, i.e., alkaline phosphatase, aspartate and alanine amino transferase and total proteins, though variable, were within normal limits in all cases. Toxicity was observed in 7 (15%) cases (Table 1).

TABLE I. Toxicity to anti tuberculosis drug.

	Reactions	No. of cases	Drug	Outcome
1.	Hepatitis	2	RHEZ	R+Z withdrawn
2.	Rash-cutaneous rash	1	SHRE	S withdrawn
3.	Giddiness	1	RHEZ	R Settled
	Burning palms & soles	1	SHRE	Settled with pyridoxin
	Difficulty in micturition	1	RHEZ	Settled with alkaline mixture

R = Rifampicin H = Isoniazid E = Ethambutol, Z = Pyrazinamide
S = Streptomycin

Drugs were withdrawn in 4 (8.5%) cases, because of hepatitis in 2 (4%), and hypersensitivity reactions in another two. One case who was very ill and had severe anaemia developed jaundice in the 6th week of therapy with very high transaminases, the other developed fever with deranged liver functions in the 2nd week. Both were on RHEZ combination. R in one and Z in the other was found to be the offending drug and was, therefore, withdrawn. Itching developed in one case which was traced to R, and was withdrawn. Two attempts to reintroduce the drug brought on the symptoms, which promptly disappeared on its withdrawal. Streptomycin was responsible for rash and itching in one case necessitating its withdrawal. Other complaints were minor, e.g. burning of palms, difficulty in micturition, (which settled with pyridoxin and alkaline mixture) and antituberculosis treatment was

continued. Liver functipn profile remained within normal limits even in patients with associated coqditions like anaemia and malnutrition. When compared with the base line values, there was a slight increase in the total bilirubin in most cases in the first 2 Weeks, but the values remained well within normal limits and as4reatment progressed thevalues reverted to normal (Table II).

TABLE II. Liver functions profile before, during and after completion of antituberculosis drugs.

	Bilirubin (mg %)					Transferase (IU/L)	
	Total	Direct	Indirect	Protein (G90)	Alkaline phosphatase (IU/L)	Aspar-tate (Ast)	Alanine (Alt)
Initial	10.1±5.22	6.0±3.15	4.0±2.72	7.3±0.64	37±23	34±19	30±15
(57)	(4.15-28.3)	(2.08-15.8)	(0-12.5)	(5.8-8.8)	(13-172)	(8-122)	(4-103)
2 weeks	13.2±9.1	8.3±7.89	4.9±3.02	7.2±1.0	38±18	35±20	29±17
(57)	(3.3-60)	(2-56)	(0-16.7)	(3.6-8.9)	(2-92)	(2-130)	(3-109)
6 months	9.69±5.1	5.59±3.7	3.98±2.66	7.41±0.48	38±16	31±12	28±15
(47)	(4.15-28.3)	(2.08-14.2)	(0-14.1)	(6-8.3)	(13-94)	(5-72)	(2-83)
9 months	12.2±8.37	7.1±5.13	4.9±3.7	7.4±0.47	36±18	30±15	28±14
(38)	(4.15-46.5)	(2.08-28.3)	(0-18.2)	(6.7-8.8)	(10-110)	(5-66)	(2-78)

DISCUSSION

Anti-tuberculous drugs i.e. Pyrazinamide (Z), Isoniazid (H), Rifampicin (R), Ethambutol (B) and Ethionamide have various forms of toxicity varying from mild G.I. disturbances, hypersensitivity reactions to hepatotoxicity. Almost all drugs are hepatotoxic with the exception of streptomycin. [4] Damage to liver ranges from slight asymptomatic increase in aspartate aminotransferase levels to severe frank necrosis. Pyrazinamide which now forms a necessary part of first line of drugs, due to its ability to act intracellularly in acidic environment, [5-7] has been reported to cause hepatitis[8-10]. The percentage developing hepatitis ranges from 6.6[11] to 10%6. Hepatitis was so frequent that regular use of pyrazinamide was thought inadvisable. In doses of 30-40mg/kg body weight per day, 8% had increased alaninetransferase[12]. However none of the patients developed hepatitis with the same dosage in Madras[13]. Pyrazinamide when used alone in non-alcoholics as a monotherapy showed excellent tolerance. [14] Pyrazinamide-induced hepatitis, however, is generally considered to have high mortality[15]. The drug also increases the serum uric acid levels causingjoint pains[16-19]. Isoniazid, a weak amine oxidase inhibitor, is the cheapest and most potent of the antituberculosis drugs which has been associated with severe hepatotoxicity. In one outbreak 19 of 2231 receiving isoniazid prophylactically for positive tuberculin test developed hepatitis; of these 13 developed jaundice and 2 died. [20] Toxicity is higher in older age group and amongst females. Rapid acetylators are said to be more susceptible[21]. Hepatitis resolves rapidly if the drug is discontinued but when jaundice develops, a mortality of 10% is reported[22]. Hepatic reactions are mild when isoniazid is used in combination with other antituberculosis drugs in doses not exceeding 30mg/kg/day[23,24]. Other untoward effects include peripheral neuritis, pyrexial reactions[25], cutaneous hypersensitivity[26,27] difficulty in starting micturition in males[28,29]. Peripheral neuritis rarely develops when small doses are used[30-34] but is more frequent with larger dosage[35-40]. Overt reactions are very[41,42] low and clinicaljaundice is rare[43]. Very high dosage produces toxic liver damage in animals[44] and humans[36]. Associated features of hypersen sitivity like rash, fever, leukocytosis and eosinophilia have been reported in a majority of the

cases. When used prophylactically it produces a slight rise in aspartate aminotransferase in 10-20% of the cases. Rifampicin can also cause asymptomatic rise in aspartate transferase in 20% cases[45] which is usually of bepatic type though cholestatic type is also seen. This often settles in time in spite of the continuation of drug, as the reaction is not of a serious nature. Isoniazid acts synergetically with rifampicin on the liver[46] resulting in jaundice and asymptomatic increase in aspartate amino-transaminase levels. [45] In B.T.T.A. studies in 512 patients on 3 different combinations of SHR & E for 9 months, with Zbeing used for the initial2 months as a part of 4 drugs regimens (SHRZ, EHRZ, EHR), 4% showed hepatitis; this frequency was the same as that in the control group. Mean bilirubin increase was 2m mols/L though it did not exceed the normal range[47]. Hepatitis presented in 3 different ways: (a) asymptomatic but persistently abnormal liver functions, (b) persistently abnormal liver functions with G.I. disturbances, and (c) jaundice. In another study by the same group in 802 patients with no associated disease or alcoholism, 3.6% (29 of 812) showed adverse reaction to R & H regimens, severe enough to warrant discontinuation of treatment. Fourteen of 29 had hepatotoxicity with raised transaminases and 8 had jaundice[47]. In Arkansas study 11% had adverse reactions of which 4% were major, 3% being hepatitis in R.H. group[48]. It was concluded that hepatic cirrhosis does not contra indicate the use of R & H or even Z[48]. In a study amongst alcoholics and patients with altered liver function tests, qualitative and quantitative improvement was observed after 2 months of intensive treatment with R, S, H, Z group and H, S, R, E combinations. Six months regimens studied in United States and Poland showed adverse reactions attributed to rifampicin or isoniazid or both in 5.2% (35/672) cases[49]. Ethambutol which has replaced PAS causes minimal toxic reactions[50] mainly of optic neuropathy causing diminution of visual acuity, narrowing of field of vision and colour blindness and, rarely, hepatitis[51,52]. Hyperuricaemia responsive to probenicid and not to salicylates unlike that of pyrazinamide[53] has also been described[54-56]. Gouty arthritis attributed to ethambutol has also been reported[57]. Streptomycin, which is more active in extra cellular alkaline environment58 and acts best on 6 rapidly multiplying bacilli[59], is mainly toxic to eight nerve. Vestibular damage i.e. vertigo, ataxia and nystagmus is much more common than auditory disturbances. Hypersensitivity reactions manifested by fever, rash or both usually appear within first 4 weeks of starting the treatment. Adverse reactions of 15% in the present study are similar to early reports when (PAS) was a regular part of therapy, [33,8] but higher than reported in other studies[61]. Drugs had to be withdrawn in only 0.8% in Lahore study[62] compared to 8.5% in ours. Hypersensitivity reactions were very mild in spite of 3 or 4 drugs used in the initial phase of 2 months. Of the 2 patients who complained of itching, one settled, but in the other R had to be withdrawn, and treatment completed with HEZ, followedby EH in con-tinuation phase. Hepatitis that occurred in two cases (4%) is similar to other reports[7,10,28]. It settled completely, on withdrawal of drugs and treatment was completed by substituting other drugs. In conclusion, antituberculosis combinations used are well tolerated even in the presence of associated anaemia and malnourishment. In most cases there is a slight increase in the serum bilirubin levels in the first 2 weeks though the values remain within normal range, and levels revert back to pre- treatment level, when the therapy is continued. In our opinion, if no associated liver disease is present, frequent estimation of transferases is not essential, since even weekly checks do not provide sufficient warning of impending hepatitis. On first sign of toxicity, i.e., fever, rash or G.I. disturbance, all drugs should be discontinued and transferases checked. Once the liver profile becomes normal, the test doses of most probable offending drug should be tried in turn, offending drug identified and avoided. Drugs producing hepatitis should never be used again. In case of hypersensitivity reactions when no choice is available, desensitization may be tried.

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