Assessment of protective role of polyherbal preparation, Livina, against anti-tubercular drug induced liver dysfunction

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The present study evaluated the possible protective role of Livina (a polyherbal preparation) against anti-tubercular therapy (ATT)-induced liver dysfunction in patients of pulmonary tuberculosis. Patients were given intensive phase treatment with 4-drugs (rifampicin, INH, pyrazinamide and ethambutol) used for anti-tubercular therapy for 2 months, followed by a 4-month continuous phase treatment with 2 drugs (rifampicin and INH) under clinical advice and supervision. Both qualitative and quantitative measures of liver function were assessed, at different time intervals, before and after ATT. Analysis of data showed that the incidence of qualitative manifestations of liver dysfunction were greater in the placebo treated group as compared to the test drug group. None of the patients of either group showed clinical jaundice. Most significant changes ant were observed in the SGOT and SGPT levels in the placebo group, wherein the levels of both enzymes were higher at 4 and 8 weeks post–ATT, as compared to the respective baseline (0 week) values. When Livina (2 capsules twice daily) was given with ATT drugs, incidence of qualitative manifestation of liver dysfunction was insignificant and SGOT and SGPT levels were also significantly lower than the placebo+ATT drugs treated group. These results indicate that the test drug (Livina) was efficacious, against ATT-induced hepatic dysfunction in patients of pulmonary tuberculosis.

Keywords: Anti-tubercular therapy, Hepatoprotection, Liver dysfunction, Livina, Polyherbal preparation

Pulmonary tuberculosis (TB) is a commonly occurring respiratory infection and its incidence has increased globally in the past few years. Chemotherapy, with long term use of potent antimicrobial agents, is the mainstay in the management of this complex disease\textsuperscript{1,2}. However, anti-tubercular therapy (ATT) is associated with a plethora of adverse effects like hepatic dysfunction which often interferes with the course of antimicrobial therapy, that leads to lack of patient compliance and resultant discontinuation of ATT. This in turn could contribute significantly to inadequate cure and rising incidence of MDR-TB. Thus, it is of paramount importance to device strategies to ensure the successful completion of such chemotherapy. Further, there is also a pressing need to monitor and prevent occurrence of such drug-induced hepatic dysfunction and currently available modalities to counteract this problem are not satisfactory\textsuperscript{3,5}.

Herbal drugs are fast emerging as alternate therapy in a variety of pathophysiological states and some phytopharmaceuticals have widely been reported to act as hepatoprotective agents. For example, medicinal plants like Picrorrhiza kurroa (kutki), Phyllanthis niruri (bhuyumamlaki), Andrographis paniculata (kalmegh), and Selebium marainum, have shown to confer differing degrees of protection to liver during chronic exposure to hepatotoxic agents\textsuperscript{6-14}. Thus, hepatoprotective agents used in conjunction with ATT therapy may provide effective protection against liver dysfunction and enable TB infected patients to continue the entire course of ATT, that may result in lower morbidity and mortality rates. The present study was, thus, designed to study the possible protective effect of a polyherbal preparation, Livina, against ATT induced liver dysfunction in patients of pulmonary tuberculosis. Efficacy of Livina was assessed on the basis of qualitative and quantitative liver function test parameters in patients of pulmonary tuberculosis on short term (6-month) chemotherapy.

Materials and Methods

The study was randomized, single blind, prospective, parallel design, and placebo controlled. The study protocol was approved by the Institutional Ethical Committee of the Vallabhbhai Patel Chest Institute.
Institute, University of Delhi, and conducted according to the guidelines of the Declaration of Helsinki.

Freshly diagnosed cases (18–60 years) of pulmonary tuberculosis attending the outpatients department of the Vallabhbai Patel Chest Institute, University of Delhi, were enrolled for the study. Written informed consent was taken from all participants after explaining to them in detail about the drug, the objectives of the study and the necessary procedures that they have to undergo during the trial. Patients were diagnosed on the basis of clinical, radiological (X-ray) and microbiological (two out of three consecutive sputum samples were positive for AFB) findings. The exclusion criteria were: extra pulmonary tuberculosis, abnormal liver function tests, pregnancy, presence of Hepatitis B or HIV, current alcohol use, any other systemic disease, use of corticosteroids, silymarin or other hepatoprotective or immunomodulators. Antitubercular drug regimen was given as per WHO recommended schedule and comprised of initial intensive phase therapy with four drugs for two months followed by a maintenance phase of four months using two drugs.

All selected patients received rifampicin (450 mg) + isoniazid (300 mg) + ethambutol (800 mg) + pyrazinamide (1500 mg) as short course, intensive chemotherapy for 8 weeks. Forty eight patients were enrolled and divided in two groups and administered either placebo or the test drug (Livina), as per a computer generated randomization chart. There were 6 dropouts from the study at different stages of treatment. Out of the 42 remaining patients who completed the study, 22 patients had received the test drug, Livina, and 20 patients had received the placebo. Baseline liver function tests were done at the time of entry (0 week). Subsequently, all patients on anti-TB drug therapy receiving either Livina or placebo were assessed qualitatively and quantitatively for liver functions at 4 and 8 weeks after initiation of anti-TB drug therapy. At every visit, clinical examination was carried out for symptoms and signs of liver dysfunction and complaints like loss of appetite, fever, abdominal discomfort, pallor, icterus, edema, cough, breathlessness, chest pain, hemoptysis were recorded. General examination like temperature, body weight, pulse rate, blood pressure, and respiratory rate were carried out in addition to other systemic examinations. After completion of 8 weeks intensive phase ATT, the patients were assessed for the efficacy of the drug treatment. On the basis of clinical and laboratory assessment (X-ray and sputum tests becoming negative) the patients were put on a further 16 weeks of continuance phase of anti-TB therapy, i.e. rifampicin + INH, to complete the course of ATT therapy.

The drug, Livina (developed and pharmacognostically certified by R&D Division of Dey’s Medical Stores, Kolkata) was a polyherbal preparation comprising extracts (50 mg each) of Picrorhiza kurroa (kutaki), Phyllanthus niruri (bhuyamaalaki), Andrographis paniculata (kalmegh), Cichorium intybus (kasni), Tephrosia purpurea (sharphaunka), Solanum dulcamara (kakamarchi), Crenum aciaticum (macchaka), Astonia seholanis (saptaparna), - and 25 mg each of Holarrhena antidysenteric (indiriyava), Tinospora cordifolia (guduchi), Terminala chebul (Haritaki), Asteracantha longifolia (kakilakshya). Thus, the total quantity of plant extract in each capsule was 500mg. The dosage schedule was 2 capsules given 2 times daily after meals for six months i.e. the complete duration of ATT. The placebo was in the form of a capsule, similar in color, size, shape etc. like the study drug, containing an inert substance and was specifically developed for this purpose. The study drug and placebo were stored in a secure area under the supervision of the investigator as per GCP guidelines and were dispensed by or under the supervision of the investigator. All drugs under study were accounted for during the clinical trial as per standard guidelines laid down for this purpose.

Efficacy of the test drug (Livina) or placebo was assessed by performing liver function tests (serum bilirubin, SGOT, SGPT and alkaline phosphatase by Synchron CX5 autoanalyser from Beckman Coulter) at 0, 4 and 8 weeks of ATT treatment. Differences between these qualitative and quantitative data of Livina and placebo treated groups were evaluated and analyzed on the basis of the above efficacy variables.

Data of different variables tested for Livina and placebo groups were compared by appropriate statistical tests. Quantal data was analyzed using Chi-Square test with Yate’s modification, whereas, the quantitative data was expressed as mean ± SD and analyzed by the paired Wilcoxon’s test. P value of at least 0.05 was considered as the level of significance in all statistical tests.

**Results**

Patients of the test drug and placebo groups were compared for the differences in incidence and
intensity of qualitative signs and symptoms of liver disease. Most patients had an uneventful course of ATT. Generally disappearance of fever and cough was seen within 4 weeks of initiation of treatment. Hemoptysis was reported by three patients which disappeared after 2 weeks of initiation of ATT. There was a general tendency for increase in appetite and gain in weight in all patients. Analysis of the data showed that there was a 8% increase in body weight in the test drug (Livina) group as compared to 5.6% in the placebo group, a difference that was not statistically significant (data not shown). A general feeling of well being was also reported in both test drug and placebo groups.

Most significant changes were observed in the liver function test (LFT) data. There was 92 and 113% increase over 0 week basal data in SGOT levels, respectively at 4 and 8 weeks after initiation of ATT in the placebo group, whereas these levels were increased by only 27 and 36% in test drug group at these respective time intervals (Table 1). Similarly, the elevations in SGPT levels in the test drug group were far less i.e. by 51 and 40% at 4 and 8 weeks, respectively as compared to the corresponding data of 116 and 179% over 0 week data in the placebo group (Fig. 1 A, B). Further, alkaline phosphatase levels were elevated by 64 and 86% respectively at 4 and 8 weeks as compared to basal values in the placebo group, whereas the magnitude of these elevations were 16 and 11% in test drug (Livina) group (Table 1).

The comparative effects of placebo and Livina groups at 4 and 8 weeks post ATT, respectively, are summarized in Fig 1A, B. Serum bilirubin levels were also elevated in group receiving placebo by 41 and 59% after 4 and 8 weeks of ATT, respectively. However, no such rise in serum bilirubin level was observed in Livina treated group. A comparison of the total protein data showed that there was no significant difference at any time interval (4 and 8 weeks) in either placebo or Livina treated group (Table 2).

In the hematological parameters, ESR was elevated in most patients at baseline evaluation (0 week), which was normalized after 2 months of ATT schedule. All sputum AFB positive cases were negative after the 2 months treatment with 4 drugs, viz. rifampicin, isoniazid, pyrazinamide and ethambutol. Further, radiological evidence (X-ray chest) of pulmonary TB was also cleared after this intensive phase of chemotherapy.

Adverse reactions in both groups were assessed to compare the tolerance and safety in Livina treated and
various forms of liver disease and they not only prevent occurrence but also, in some instances, induce regression and promote recovery.\textsuperscript{8,9,11,14}

In the present study, a randomized, single blind, placebo controlled study was conducted to compare the safety and efficacy of Livina and placebo. Analysis of the compliance data of two groups indicates better tolerance of ATT in Livina treated group, resulting in completion of course of chemotherapy. Analysis of the data of change in body weight showed that Livina tended to increase body weight more as compared to placebo group, and though these changes were marginal, it indicates the possible better efficacy of Livina as compared to the placebo. SGOT and SGPT are reliable markers of liver function and are known to be elevated in a variety of clinical conditions associated with liver damage.\textsuperscript{15,16,21} In this study, the elevations in these enzymes were apparent in placebo treated group at both time intervals (4 and 8 weeks) of assessment, whereas the same was not seen in the Livina treated group. In fact, the values of SGOT, SGPT and alkaline phosphatase were higher than the reference normal range in the placebo group, whereas they were maintained within the normal range in the Livina treated group. Earlier studies and some pilot experiments had shown that derangement of liver function was most apparent at 4 weeks after initiation of therapy in most patients,\textsuperscript{22} and thus, 4 and 8 week time intervals were selected for measurements in this study. Alkaline phosphatase, along with SGOT and SGPT, is also a sensitive marker of liver damage and the fact that these levels were less affected in the presence of Livina, suggested that this polyherbal agent was exerting a protective effect against ATT-induced hepatic dysfunction in these patients of pulmonary tuberculosis. The analysis of ADR profile, from among the patients who completed the treatment, showed that Livina and placebo differed marginally in general and hence both treatments could be termed as equally safe and tolerable. However, the fact that most of the dropouts were in the placebo treated group suggested that Livina enhanced the compliance to ATT in patients. The overall observation was that on the basis of the various efficacy parameters measured, it was apparent that Livina was more effective as compared to the placebo when tested for their potential to protect against ATT induced hepatic damage.

From the present study, it could be inferred that the polyherbal agent, Livina, prevented ATT-induced

| Table 2—Comparison of bilirubin and total protein levels in serum after Livina and placebo in patients of pulmonary TB on antitubercular chemotherapy |
|-----------------|-----------------|-----------------|
| Parameter/Group | At 0 week (mg/dl) | At 4 week (mg/dl) | At 8 week (mg/dl) |
| Bilirubin | Placebo 0.92 ± 0.8 | Livina 1.02 ± 0.2 | 1.30 ± 0.4 | 1.10 ± 0.4 | 1.46 ± 0.5 | 0.95 ± 0.3 |
| Total Protein | Placebo 7.01 ± 0.4 | Livina 7.65 ± 0.7 | 7.43 ± 0.4 | 7.04 ± 0.7 | 7.82 ± 0.5 | 7.98 ± 0.9 |

placebo groups. Anorexia, nausea, fatigue and weakness were amongst the commonly reported adverse events during therapy, particularly in the placebo group. Most patients complained of high/orange coloured urine which was understandably due to rifampicin. None of the patients showed frank icterus and/or hepatomegaly. Among the total of six drop out cases, five were from placebo group (20% incidence), whereas only one patient from Livina treated group (4.3% incidence) discontinued treatment.

Discussion

Antitubercular chemotherapy is prone to induce hepatic dysfunction as liver plays a central role in the metabolism and detoxification of these agents. This is more likely to occur in the initial intensive phase therapy with four drugs, viz., rifampicin, isoniazid, pyrazinamide and ethambutol. Such drug induced liver dysfunction poses a major problem for effective completion of the course of ATT and hence could influence compliance. Poor compliance may result in stoppage of therapy which not only precipitates recurrence of disease, but also results in the development of drug resistance and MDR-TB. Incidence and nature/extent of hepatotoxicity with antitubercular therapy depends on a plethora of factors and the spectrum of liver dysfunction varies from slight elevation in serum enzyme levels to severe liver damage.\textsuperscript{15,16} Several factors could contribute to anti-TB drug induced liver injury and different strategies have been proposed to combat this long standing problem of increasing significance.\textsuperscript{17-20} Hepatoprotective agents are therefore, of great importance with respect to the control of the disease and its effective chemotherapy. Herbal hepatoprotective agents have been tried effectively in various forms of liver disease and they not only
elevations of the biochemical markers of liver function tested and maintained them within normal range, which was not seen in the case of the placebo group. Thus, Livina could be an effective and safe chemotherapy to enhance compliance to ATT, thereby preventing the occurrence of MDR-TB.

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References