

## THERAPY IN TUBERCULOSIS

Pages with reference to book, From 320 To 322

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Developments in the last few years have greatly changed the therapy of tuberculosis. Primary drugs are highly effective, relatively simple to take, and are well tolerated, parenteral treatment is not necessary, nor is the long protracted treatment in the sanatorium. New cases can safely be treated at home without any risk to the family, there is little risk of being infected after chemotherapy has begun<sup>1-4</sup> If cases have to be admitted for diagnosis or complications they can be managed in the chest ward of a general hospital.

Effective drug therapy for pulmonary tuberculosis depends upon appropriate drugs, in adequate doses for adequate period. There are over 10 drugs available (table).

### Drugs for Tuberculosis

	Drug	Dose (Kg/day)	Maximum/day
Primary	Isoniazid	5-10mg	300mg
	Rifampicin	10mg	450-600mg
Secondary	Ethambutol	15-20	800-1200mg
	Pyrazinamide	25-40mg	3g
	Streptomycin	15mg	.75-1g
	Para aminosalicylic acid	.2g.	10-12g
Tertiary	Thiacetazone	2-3mg	150mg
	Ethionamide	15mg	.75-1g
	Cycloserine	15mg	1g
	Kenamycin	15mg	.75 - 1g
	Caperomycin	15mg	.75 - 1g

Primary drugs i.e. Isoniazid and Rifampicin are most effective with low toxicity, secondary drugs are

more toxic and less effective, while tertiary are least effective and most toxic.

Newly diagnosed cases can be treated with a combination of at least 2 drugs, depending upon the extent of the disease and drug resistance (Primary). Treatment will have to be modified in special medical situations like acquired and primary resistance, pregnancy, renal and hepatic insufficiency. There is a practice of using 3 drugs also, but there are indications that Isoniazid, Rifampicin combination produces earlier conversion of sputum than standard 3 drug regimen<sup>5</sup>. There are many combinations of drugs and different regimens of short and long courses are available. However in special situations selection of a treatment regimen or its successful completion may prove difficult

### **DRUG RESISTANCE**

Treated cases who relapse may be due to drug resistance, though most give a history of non-compliance. In Pakistan resistance has not been investigated fully, some earlier reports regarding standard drugs showed acquired resistance of 41.9% (16.5% to one, 14.8% to two and 1% to three)<sup>6</sup> to 38.3%<sup>7</sup> increasing to 71% in the same locality<sup>8</sup> which was much higher than others reported at that time (Britain 1960 5.1%, East Africa 1960 5.1%, Nigeria 1960 12%). There is no data available for Rifampicin and other newer drugs, though primary resistance of 8% has been suggested (Iqbal personal communications). Relapse should ideally be treated according to the drug sensitivities, though cultures take a long time. Methods of rapid testing of drug susceptibility, that measures the incorporation of radioactive label, by multiplying bacteria have recently been described<sup>9-10</sup> but have not found general favour. Detailed history of previous treatment should be taken, and drugs not previously used should be prescribed. Under no circumstances should one new drug be added to previously used therapy. The regimen can be re-adjusted once the sensitivities are available.

### **RENAL DISEASE**

With decreased renal function the drugs which are excreted in the urine are the cause of increased blood levels. Among the antituberculosis drugs Ethambutol and Kanamycin are most problematic. Since Ethambutol is almost all excreted in the urine, reduced renal functions will increase the blood levels, and should be avoided in chronic renal failure. If it has to be used the recommended dose is 9mg/kg/day<sup>11</sup>. Ophthalmic, examination and liver functions should be monitored during the therapy. Even though 50-80% of Isoniazid is excreted in urine with normal renal functions in 24hours, part of it is excreted in unchanged form but mainly as acetylisoniazid and isonicotinic acid plus a small amount of isonicotinic acid conjugate as isonicotinoyl hydrazon<sup>12</sup>. The usual dose of Isoniazid like that of Rifampicin is quite safe in renal disease<sup>13</sup>. No data is available for pyrazinamide, but renal excretion may be significant and dose should be modified to 12-20mg/Kg/day.

The incidence of tuberculosis is increased 10-12 times greater than the general population<sup>10,14</sup> in patients on long term dialysis for end stage renal disease, particularly extra pulmonary disease. It is suggested that impaired cellular immunity associated with Uraemia due to advanced renal failure may predispose to increased incidence. There is limited data about the dosage of antituberculosis drugs for dialysis. Isoniazid, Kanamycin, Ethambutol are all dialyzable. Isoniazid<sup>15</sup> and Rifampicin should be given in normal dosage and if Ethambutol must be used it should not exceed 9mg/kg.<sup>11</sup> The drugs should be administered immediately after dialysis.

### **LIVER DISEASES**

The treatment of patients with liver dysfunction is difficult, since most of the effective drugs are potentially hepatotoxic.

Least toxic regimens like Streptomycin, Ethambutol, and Isoniazid should be prescribed. In severe hepatic failure the drugs should be given in reduced dosage.<sup>16</sup>

### **PREGNANCY**

The drugs of choice in pregnancy are Ethambutol and Isoniazid, both are well tolerated by mother and<sup>17-18</sup> fetus. Rifampicin is also relatively safe, but experience with this is more limited and should

not be given in first trimester. Streptomycin causes fetal ototoxicity<sup>19</sup> and is best avoided, Ethionamide is teratogenic.<sup>20</sup> Since all drug exposure should be avoided in pregnancy diagnosis must be confirmed before starting antituberculosis treatment. Some antituberculosis drugs i.e. Streptomycin, Isoniazid and Rifampicin are excreted in breast milk<sup>21</sup> which should also be taken into consideration during the postpartum stage.

### **INTERACTIONS**

During treatment, with other medications antituberculosis drugs may cause problems. The complete list of drugs apart from antituberculosis being received by the patient should be reviewed, since many antituberculosis drugs interfere with others reducing or potentiating their effects. Isoniazid interferes in the excretion of phenytoin and may cause toxicity in a patient stabilised on a dose,<sup>22</sup> the dose will have to be reduced accordingly to maintain the same therapeutic level. Rifampicin, a hepatic mixed-function oxidase inducer, is likely to interact with other drugs. Since oxidase enzyme system helps in clearance of many drugs, various Rifampicin interactions may be expected. To date it has been implicated in accelerating the metabolism of coumarin type of anticoagulants,<sup>23</sup> reducing the effects of oral contraceptives<sup>20-24</sup> so patient of antituberculosis should use other contraceptive methods. The therapeutic effects of corticosteroids<sup>25</sup> Methadone<sup>26</sup> oral Hypoglycaemic agents<sup>27</sup> and Digoxin<sup>20</sup> are also effected by Rifampicin, and dosage will have to be modified accordingly.

Tuberculosis therapy now is so effective that once the patient has completed a full course of drugs faithfully relapse is so infrequent that he should be discharged from supervision with the instructions to seek medical advice for such symptoms as persistent cough, protracted fever, and Haemoptysis.<sup>28,29</sup>

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