A Study of The Type And Frequency of Adverse Effects of Anti-Tuberculosis Drugs Through The Application of DOTS Strategy in Basrah

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By

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وَيَسْأَلُونَكَ عَنْ الرُّوحِ قُلْ الرُّوحُ مِنْ أَمْرِ رَبِّي
وَمَا أُوتِيتُمْ مِنْ الْعِلْمِ إِلاَّ قَلِيلاً

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الإهـــداء

أهدي هذا الجهد المتواضع إلى

منبع الدفئ والحنان ...أمي الغالية

سندي في هذه الحياة...
زوجي العزيز ... د. مصطفى مجيد

فلذات كبدي ...أطفالي...

إخواني وأخواتي...

وكل من دعا لي بالنجاح والتوفيق...

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List of Abbreviations

1) TB	Tuberculosis
2) DOTS	Directly Observed Treatment, Short course
3) BCG	Bacillus Calmette Guerin
4) BMI	Body Mass Index
5) EDTA	Ethylene Diamine Tetra Acetate
6) ESR	Erythrocyte Sedimentation Rate
7) Hb	Hemoglobin
8) WBC	White Blood Cells
9) ALT (GPT)	Alanine aminotransferase (Glutamic pyruvic transaminase)
10) AST (GOT)	Aspartate aminotransferase (Glutamic oxaloacetic transaminase).
11) Cat	Category

Abstract

Monitoring of adverse effects is important in reducing morbidity and mortality caused by drugs. DOTS (directly observed treatment, short course) strategy, by ensuring patient compliance, provides a good opportunity to study the adverse effects of anti-TB drugs.

Eighty-three tuberculosis patients (61 diagnosed for the first time and 22 at various stages of their treatment) were followed according to a checklist of adverse effects, and investigated for liver transaminases (AST, ALT), serum uric acid, blood urea, hemoglobin, WBC, blood group, hemoglobin electrophoresis and others.

The overall incidence of adverse effects (as reported by patients) over a six-month period was 25.3%; most of them were minor (gastric upset and itching), Two thirds of those patients were females and were, on average, older than those without adverse effects. There was an increase in AST level above the upper normal limit (12 U/L) in 40% of those patients who had their baseline AST values measured (n= 61); 4 of these patients had more than double the upper normal limit. These increases occurred mainly during initial phase of treatment and tended to decrease during the continuation phase of treatment. They also occurred more in female patients and in those more than 35 years of age. ALT increased in 6 patients only.

Out of the 61 patients with baseline measurements; 37.7% had raised serum uric acid levels. These increases were mainly restricted to the initial phase where pyrazinamide was used.

None of our patients had jaundice, or peripheral neuropathy (though most patients received prophylactic pyridoxine).

All; except two, patients responded favourably to anti-TB drugs as judged clinically, radiologically and by sputum smear conversion, reduction in ESR and increase in body mass index.

In conclusion, the patients followed in the present study, appeared to tolerate anti-TB drugs well. Severe hepatotoxicity and peripheral neuropathy had not been encountered.

Chapter One: Introduction (Tuberculosis)

1.1 Definition of tuberculosis[1]

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. Its characteristic features include a generally prolonged latency period between initial infection and overt disease, prominent pulmonary disease (although other organs can be involved in up to one third of cases), and a granulomatous response associated with intense tissue inflammation and damage.

1.2 Epidemiology[1-11]

TB is considered, today, the most important re-emerging disease worldwide, with increasing global morbidity and mortality rate compared to any other single pathogen. It is estimated that one third of the world population is infected with Mycobacterium tuberculosis and that about 90% of infected individuals do not develop clinical disease.

The prevalence varies enormously between countries. About 8-10 million cases of active TB are diagnosed annually; most of them (95%) from developing countries. The global TB epidemic increased largely due to 20% increase in the African countries, which are affected by HIV/AIDS epidemic. If these trends continue, some 10.2 million new cases are expected each year by 2005.[10]

TB occupies the 4th place among major causes of death and comprises 26% of all avoidable death in developing countries. The vast majority of TB cases and TB deaths are in developing countries. About 3 million deaths occur each year in the world, one million of which in women and 170000 in children. The global ratio of female to male notified TB cases

is 1 to 1.5-2. It is unclear why more males than females are diagnosed with TB but the biological and social factors may be responsible for this difference. It is estimated that 75% of TB cases in developing countries are in economically productive age groups (15-50 years).

TB is an endemic in Iraq and the reported cases during the year 2000 are 25251, of which 19613 are pulmonary TB cases and 5638 extra-pulmonary TB cases.[11] Analysis of reported TB cases in Basrah TB center during 2001 showed that, total TB cases are 741, 70% of cases are pulmonary TB and 30% extra pulmonary TB cases; of them 66% were males and 34% were females.

1.3 Clinical features of TB[2]

TB is usually classified as pulmonary TB (around 85% of cases) and extra pulmonary TB (15% of cases). Pulmonary TB can be categorized as primary and post-primary (secondary) pulmonary TB. Out of all pulmonary TB cases, approximately 50-60% are sputum smear positive pulmonary cases; the rest are sputum smear negative pulmonary cases. Extra pulmonary TB affects any organ and tissue in the body, including pericardium, gastrointestinal system, genitourinary system, central nervous system, lymph nodes, bones, joints, skin, and eyes.

1.4 Diagnosis of TB in adult[3,12,13,14]

The following are the most important symptoms in the selection of TB suspects in adults (over 15 years of age): productive cough of more than 3 weeks, hemoptysis and significant weight loss. Patients with TB may also have other symptoms (which are more common but less suggestive) such as chest pain, breathlessness, fever, night sweats, tiredness, and loss of

appetite. The presence of these symptoms demands immediate radiological examination of lungs. If any abnormality is found, the microscopic examination of at least three specimens of sputum for tubercle bacilli should be done, using Ziehl-Neelsen method to stain the sputum. Sputum culture and tuberculin skin test (TST) can also be used to diagnose TB, but the TST is of limited value in the diagnosis of active TB because of its low sensitivity and specificity.

The application of polymerase chain reaction (PCR) in the direct detection of M. tuberculosis by specific gene amplification, was shown to be fast reliable and highly sensitive *.

1.5 Treatment of TB[2,15,16]

Drugs used to treat TB are classified as first line and second line agents. First line essential anti-TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin) are the most effective and are a necessary component of any short-course therapeutic regimen. Second line anti-TB drugs (e.g. ciprofloxacin, capreomycin, amikacin, kanamycin, para-aminosalicylic acid (PAS), thiacetazone, viomycin, ethionamide, and cycloserine) have a lower degree of efficacy and a higher degree of intolerability and toxicity. Therefore, these drugs are considered only:

(1) in case of resistance to the first line drugs.
(2) in case of failure of clinical response to conventional therapy.
(3) when expert guidance is available to deal with toxic effects.

1.6 The WHO and DOTS strategy[9,12]

In April 1993, the WHO declared that TB is a global emergency because TB is out of control in many parts of the world. The WHO has adopted new strategy for effective TB control. DOTS is the name of this strategy; it represents the abbreviation of Directly Observed Treatment, Short course strategy.

* (Saves, et.,al.,2002)

DOTS strategy combines five components:

1- Government commitment.
2- Case detection by sputum smear microscopy.
3- Standardized short course, treatment regimen that is directly observed for at least the first two months of treatment.
4- A regular drug supply.
5- A standardized recording and reporting system that allows assessment of treatment results.

DOTS program had been implemented in Iraq (Baghdad) on the 1st of April 1998 and in Basrah on the 1st of October 1999 as a pilot project and then expanded to cover all primary health care districts in the governorates of Iraq on the 1st of April 2000.

1.7 Targets for TB control[9,10]

* To reduce morbidity, mortality and disease transmission by:

- curing 85% of newly detected, sputum smear-positive TB cases.
- detecting 70% of existing cases of sputum smear-positive TB.
- to achieve, in the long run, a prevalence rate of 1% for a TB infection.

* To prevent the development of drug resistance.

1.8 Drug resistant tuberculosis

Mycobacterium tuberculosis could be resistant to one or more anti TB drugs. The resistance may be primary or acquired. Primary drug resistance develops in patients who had not previously been treated.[2] Tubercle bacilli have well documented capacity to undergo spontaneous

unlinked mutation that confers resistance to various anti-TB medications. These mutations occur at predictable frequencies, usually in the range of 1 in 10^8 replications. This may result in resistance to only one drug and with low probability of spontaneous resistance to two or more drugs by a single microbe.[1] If patients stopped one or more of their medications due to non-adherence, poor medical management of patient treatment and limited drug supplies or due to low drug quality,[17] the unopposed mutants are allowed to proliferate, resulting in treatment failure or relapses associated with acquired drug resistance. When this happens serially, multi-drug resistance is created. Such organisms can be transmitted then to other persons, giving rise to primary drug resistance.[1]

Multi-drug resistant tuberculosis (MDR-TB) is a specific form of drug-resistant TB due to a bacillus resistant to at least isoniazid and rifampicin; the most powerful anti-TB drugs.[18] In a recent "Center for Disease Control And Prevention" (CDC) survey, the prevalence of resistance to one or more drugs in the United States was (14.3%). Resistance to isoniazid was noted most commonly in new cases and in 21.5% of recurrent cases.[1] MDR-TB was noted in 3.5% of strains studied.[1,18]

In a study in Basrah,[19] it has been shown that drug resistance to one or more anti-TB drugs was 20% for new cases; increased to 54.15% and 80%, for relapsed and chronic cases respectively. Multi-drug resistance was estimated to be 17.2% of total isolates form old cases.[19]

Patients with MDR-TB have about 56% chance of recovery as compared to 95% chance for TB patients overall.[20] MDR-TB is more difficult to manage[2] and requires extensive chemotherapy for up to two years, that is also more toxic to patients.[18] For patients with bacilli resistant to isoniazid and rifampicin, a combination of ethambutol, pyrazinamide and

streptomycin may be given for 12-18 months and at least 9 months after sputum culture conversion is effective. For patients with bacilli resistant to all first-line anti-TB drugs, a combination of at least three drugs are chosen from second-line drugs to which the organisms known to be sensitive.[2]

In 1998, WHO and several partners around the world conceived DOTS-plus strategy; a strategy currently under continuous development and testing for the management of MDR-TB. It works as a supplement to the standard DOTS strategy and needs to be addressed in areas where there is high prevalence of MDR-TB. DOTS-plus, builds upon the foundation of DOTS strategy for TB control, but includes additional components, such as the use of second-line anti TB drugs to directly manage MDR-TB cases.[18]

1.9 Recent advances in treatment of MDR-TB

In a recent study on MDR-TB, an enhancement of anti-TB drug activity against MDR-TB by phenothiazines has been reported.[21] Phenothiazines have been shown to inhibit, in-vitro, growth of MDR-TB. They have been considered as a potential adjuvant to the four or more anti-TB drug regimens for the management of newly diagnosed TB patient from areas known to have a high prevalence of MDR-TB.

One of these phenothiazines, chlorpromazine, is concentrated by human macrophages to 10-100 times its concentration in plasma, and has activity against mycobacteria that have been phagocytosed by these cells. Chlorpromazine has been shown to enhance the activity of anti-TB drugs except ethambutol to which M.tuberculosis is susceptible. This might

result in reduction in the dose of some or all of the anti-TB drugs employed without sacrificing the integrity of treatment.

Additional studies[21] evaluating the use of phenothiazines as an adjuvant may eventually allow a reduction in the dosage of these antibiotics and result in decreased frequency of adverse effects.

1.10 Definition of certain terms[9,13]

New case: a patient who has never had treatment for TB or who has taken anti-TB drugs for less than 4 weeks.

Previously treated case: a patient who received anti-TB drugs for more than one month and include:

 # Relapse: a patient who has been declared cured of TB in the past by a physician after one full course of chemotherapy, and has become sputum smear positive.

 # Treatment failure: a patient who, while on treatment, remained or became again smear-positive five months or later after commencing treatment. It is also a patient who was initially smear- negative before starting treatment and became smear-positive after the second month of treatment.

 # Treatment after interruption: a patient who interrupts treatment for two months or more, and returns to the health service with smear-positive sputum (sometimes-negative but still with active TB as judged on clinical and radiological assessment).

 # Chronic case: a patient who remained or became again smear-positive after completing a fully supervised re-treatment regimen.

1.11 Treatment regimens in DOTS strategy[9]

The chemotherapeutic regimens are based on standardized combinations of five essential anti-TB drugs (table 1):

- Isoniazid,
- Rifampicin,
- Pyrazinamide,
- Ethambutol,
- Streptomycin.

Each of the standardized chemotherapeutic regimens consists of 2 phases:

* Initial (intensive) phase, for 2-3 months with 3-5 drugs given daily under direct observation.

* Continuation phase, for 4-6 months with 2-3 drugs also given under direct observation.

Table 1: Essential anti-TB drugs and recommended daily dosage

Drug	Abbreviation	Daily dose
Isoniazid	H	5 (4 – 6) mg/kg
Rifampicin	R	10 (8 – 12) mg/kg
Pyrazinamide	Z	25 (20 – 30) mg/kg
Ethambutol	E	15 (12 – 20) mg/kg
Streptomycin	S	15 (12 – 18) mg/kg

1.12 Treatment categories in DOTS strategy[9,11,13]

Once diagnosis is made, and before beginning treatment, every patient should be classified according to the following criteria into one of four categories:

1. Site of disease (pulmonary or extra-pulmonary).
2. Severity of disease.
3. Bacteriological status (assessed by sputum microscopy).
4. History of anti-TB treatment (newly or previously treated).

Treatment categories are essential for prioritization of TB treatment according to public health risk. Category 1 is the highest priority, while category 4 is the lowest (table 2).

Table 2: Categories of patients for DOTS strategy[9]

Cat.	Type of patient	Duration of treatment		Regimens
1	1.New smear-positive pulmonary TB 2.Seriously ill smear-negative pulmonary TB 3.Seriously ill extra-pulmonary TB	6 months	Initial phase (2 months)	HRPE or HRPS
			Continuation phase (4 months)	HR
2	Sputum smear-positive TB patients (previously treated): 1.Treatment after interruption 2.Treatment failure 3. Relapse after treatment	8 months	Initial phase (3 months)	(2 months HRPES) + (1 month HRPE)
			Continuation phase (5 months)	HRE
3	Less severe form of: 1. New smear-negative pulmonary TB 2. New extra pulmonary TB	6 months	Initial phase (2 months)	HRP
			Continuation phase (4 months)	HR
4	Chronic cases		DOTS not applicable	

H= Isoniazid R= Rifampicin P= Pyrazinamide E= Ethambutol S= Streptomycin.

1.13 Essential anti-TB drugs[2,15]

Five major drugs are considered the first-line agents for the treatment of TB; isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin. The first four, having similar pharmacokinetic characteristics, are given orally, well absorbed, with peak serum level at 2-4 hour and nearly

complete elimination within 24 hours (Table 3 and 4). These agents are recommended on the basis of their bactericidal activity (ability to rapidly reduce the number of viable organisms), their sterilizing activity (ability to kill all bacilli and thus sterilize the affected organ, measured in terms of the ability to prevent relapse), and their low rate of induction of resistance.

During the initial phase (bactericidal phase), the majority of the tubercle bacilli are killed; symptoms resolve, and the patient becomes non-infectious. The continuation phase (sterilizing phase) is required to eliminate semidormant "Persisters" (bacilli that metabolize slowly or intermittently), which need long-term treatment of at least 6 months. Rifampicin and pyrazinamide are the most efficacious drugs in treating persisters. If optimum drug treatment is stopped early, i.e. before 6 months, there is a high relapse rate (about 20%) with organism sensitive to the original combination. Multiple therapy are used to prevent the emergence of drug resistance by suppressing drug resistant mutants that exist in large bacterial populations, and to ensure that poor compliance does not result in monotherapy with consequent drug resistance.

1.14 Treatment regimens in special clinical situations

Most first-line anti-TB drugs can be used in pregnant women except streptomycin which is ototoxic to the fetus.[2,9] It should not be used in pregnancy, where it can be replaced by ethambutol.[9] Rifampicin and pyrazinamide may be given, although rifampicin is teratogenic in animal studies in very high doses in first trimester and increases the risk of neonatal bleeding in third trimester.[23] Data concerning pyrazinamide safety in pregnancy are not available.[1,2]

Pyridoxine, should be added to the drug treatment of TB in all pregnant women taking isoniazid to prevent peripheral neuropathy.[2,9] Although the second-line anti-TB drugs have higher degree of intolerability and toxicity, ciprofloxacin seems to have the best safety profile in the treatment of drug-resistant TB.[24]

All anti-TB drugs are compatible with breast feeding. The baby should receive isoniazid prophylaxis and BCG vaccination,[9] because most of the drugs administered will be present in small quantities in breast milk, though at a concentration too low to provide any therapeutic or prophylactic benefit to the child.[2]

Rifampicin enhances the metabolism of oral contraceptive pills with a risk of decreased protective efficacy against pregnancy. The women should be advised to take a pill containing a higher dose of estrogen (0.05mg), or to use another form of contraception.[2,9]

Patients with hepatic disease pose a special problem because of hepatotoxicity of isoniazid, rifampicin, and pyrazinamide.[2] In patients with chronic liver disease, the recommended regimens are isoniazid, rifampicin and one or two non-hepatoxic drugs such as streptomycin and ethambutol in the initial phase (2months) followed by isoniazid and rifampicin for continuation phase (6months), with a total treatment duration of (8months). The alternative regimen, streptomycin, isoniazid and ethambutol in the initial phase (2months) followed by isoniazid and ethambutol in continuation phase (10months) with total treatment duration of (12months). Patients with liver disease should not receive pyrazinamide.[9] In rare cases, patient may have acute hepatitis unrelated to TB or anti-TB drugs. In some cases it is possible to defer TB treatment until the acute hepatitis has resolved. In others, when it is necessary to

treat TB during acute hepatitis, the combination of streptomycin and ethambutol for (3months) (initial phase) until hepatitis has resolved, then patients receive a continuation phase of (6months) with isoniazid and rifampicin.[9]

Isoniazid, rifampicin and pyrozinamide may be given in the usual doses in case of mild to moderate renal dysfunction because these drugs are eliminated by biliary excretion or metabolized into non-toxic substances. But the doses of isoniazid and pyrazinamide should be reduced for all patients with severe renal impairment. Streptomycin and ethambutol should be avoided or given in reduced doses (if necessary) with close monitoring of renal function, because these drugs are extracted by the kidney.

Chapter Two: Review of literature

2. Monitoring and managing anti-tuberculosis drugs toxicity

Most TB patients complete their treatment without any significant adverse effects of drugs.[9] However, the incidence of adverse reactions varies widely. It ranges from 4% to 67.7%.[25-31] These adverse effects could be minor and can be managed by reassurance and explanation,[32] or, sometimes, may be severe enough to cause modification and/or termination of one of the standard drugs.[1,33,34] A study in Germany in 1996,[34] showed that the final termination of anti-TB drugs because of severe adverse effects occurred in 23% of patients. Hepatotoxicity represented 11% of these adverse effects. Pyrazinamide in the above cited study showed more severe side effects (15%) than both isoniazid (7%) and rifampicin (1.5%). While a study in Iraq (in Al-Anbar Governorate),[35] showed that drug side effects were minimum and patients appeared to tolerate anti-TB drugs well.

If these adverse reactions went unrecognized, they can lead to increased morbidity and mortality as well as high health care costs and social hazards.[36] Therefore, all TB patients should be kept under clinical monitoring and should be informed about the side effects of therapy during their treatment for early detection of toxicities.[9,28]

The frequency of adverse drug reactions may increase with age;[26] it ranges from 2.3% at age 0-19 years to 8.4% at age 60 years and over. Females had higher reaction rates than males. There is also racial

differences as white patients had higher reaction rates than Asian patients in UK.[26]

According to the WHO classification,[9] side effects of anti-TB drugs were classified into minor and major as shown in Table 5. In general, a patient who develops minor side effects should continue the anti-TB treatment, usually at the same dose but sometimes at a reduced dose. The patient may also receive symptomatic treatment. If a patient develops a major side effect, the treatment or the offending drug should be stopped, and further management depends on the nature of the adverse reaction.

Table 5: Symptoms-based approach to adverse effects of anti-TB drugs.[9]

Side Effects	Drug(s) probably responsible	Management
Minor		Continue anti-TB drugs, check drug doses
Anorexia, nausea, abdominal pain	Rifampicin	Give drugs last thing at night
Joint pains	Pyrazinamide	Aspirin
Burning sensation in the feet	Isoniazid	Pyridoxine 100 mg daily
Orange/red urine	Rifampicin	Reassurance
Major		Stop responsible drug(s)
Itching of skin, skin rash	(Streptomycin)	Stop anti-TB drugs
Deafness (no wax on auroscopy)	Streptomycin	Stop streptomycin, use ethambutol
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin, use ethambutol
Jaundice (other causes excluded)	Most anti-TB drugs (especially isoniazid, pyrazinamide and rifampicin)	Stop anti-TB drugs
Vomiting and confusion (suspect drug-induced acute liver failure)	Most anti-TB drugs	Stop anti-TB drugs, urgent liver function tests and prothombin time
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin

2.1 Gastrointestinal and hepatobiliary adverse effects

Gastrointestinal complaints (such as nausea, vomiting, heartburn and epigastric distress) are relatively common in association with all anti-TB drugs, especially rifampicin.[1,9] It ranged from mild to severe symptoms.[36] However, most patients can be induced to tolerate these drugs by reassurance and explanation or by giving these drugs last thing at night.[1,9] Caution should be taken that patients do not take anti TB drugs directly with meals, antacids and/or H_2-blockers; any of which may substantially reduce the intestinal absorption of some of these agents.[1]

2.2 Hepatic adverse effects

Most anti-TB drugs have been associated with liver toxicity.[2,37] It ranges from minor and asymptomatic elevation of liver enzymes to severe and fatal hepatitis. Isoniazid and pyrazinamide are considered to be major hepatotoxins, whereas rifampicin is relatively less hepatotoxic. Rifampicin, however, is a powerful enzyme inducer which may enhance the hepatotoxicity of isoniazid.[38]

The incidence of anti-TB drug-induced liver injury is high in elderly, after gastrectomy, with hypoalbuminemia, with higher doses of isoniazid (more than 7.5mg/kg), or of pyrazinamide (above 30mg/kg) and with positive hepatitis C virus (HCV) antibody.[25,39] A study in Iraq published in 2002,[40] showed that anti TB-drug-induced hepatotoxicity developed in 20% of patients and occurred in those more than 35 years of age and in malnourished patients, and more in females than males. Another study in Australia in 1997,[41] showed that 26% of patients developed anti-TB drug-induced liver injury which was more frequent in patients over 35 years of age.

Isoniazid-induced hepatitis was reported to be the most frequent major toxic effect.[15] It ranges from asymptomatic elevation of liver enzymes to fulminant hepatic failure resulting in liver transplantation and/or death.[14,15,42] Minor increases in liver transaminases have been found in 10-20% of patients. These increases are usually seen during the first few months of treatment, but can occur at any time. They are usually asymptomatic and return to normal despite continuation of drugs.[2,15,16,40,43]

Progressive liver damage may occur in about 1-2% of patients and liver failure can, rarely develop rapidly during anti TB therapy.[2,15,44,45]
For patients with symptomatic hepatitis and those with marked elevation in transaminases, treatment should be stopped, since continued use of the drugs in these patients can cause a more severe form of liver damage.[1,2,9,16]

The risk of isoniazid-induced hepatitis is idiosyncratic and increases in incidence with age. It occurs rarely under age of 20 years, and in 0.3% for those aged 21-35 years, 1.2% for 35-49 years of age and 2.3% for those aged 50 years and above.[2,16] The risk also increased with daily consumption of alcohol, malnutrition, slow acetylation, and possibly during pregnancy and postpartum period.
Mortality from isoniazid-induced hepatitis has been reported to be 6-12%, but the real risk may be much lower.[2] A study in USA,[46] showed that eleven patients out of more than 11 thousand patients (0.1%) of those starting, and 0.15% of those completing treatment had hepatotoxic reaction to isoniazid during preventive treatment. The rate of hepatotoxicity increased with increasing age and in women. On the other hand, a study in Australia[47] showed a high rate of isoniazid toxicity in

health care workers (41%),when given as prophylaxis, and in 76% of them, toxicity was sufficiently severe to require cessation of treatment.

Rifampicin occasionally causes hepatitis.[16]Concomitant administration of rifampicin increases the risk of isoniazid-associated hepatitis.[2] Moderate and transient rise in serum concentration of bilirubin and transaminases usually occurs at the onset of treatment and it is not an indication for stopping the drugs but dose-related hepatitis may occur which is potentially fatal.[15,38,48]

One major adverse effect of pyrazinamide is hepatitis which may occur in 1-5% of patients, and is particularly associated with high doses.[14,15] At the currently recommended daily dose of 15-30 mg/kg, and a maximum of 2 grams, the frequency of hepatitis is not higher than that for concomitant isoniazid and rifampicin therapy.[2] Hepatotoxicity may range from asymptomatic derangement of liver function tests to severe hepatitis.[40] Moderate rises in serum transaminses are common during the early phase of treatment. However, severe hepatitis is rare,[9]and when occurs, it has poorer prognosis in regimen containing pyrazinamide than without it.[49] Pyrazinamide can also induce granulomatous hepatitis.[50] On the other hand, a study in Japan,[25] showed that the frequency of drug-induced hepatitis among patients treated with pyrazinamide containing regimens was similar to that among patients treated with regimens without pyrazinamide.

Regular monitoring of liver chemistries is indicated for all patients receiving multi-drug therapy.[1] Although biochemical monitoring is not routinely recommended,[2] all TB patients should undergo baseline assessment of liver function tests (especially in high risk patients) and at monthly intervals.[1,38] In addition, patients should be educated about the

signs and symptoms of hepatitis (fatigue, weakness, anorexia, nausea, vomiting, malaise, epigastric pain, and dark-colour urine). They should be instructed to discontinue treatment promptly and consult their physicians when these symptoms occur.[2,15,28,38] Continued use of the drug in these cases can cause more severe form of liver damage.[1,16] When patients develop hepatitis, all potentially hepatotoxic drugs should be withheld until liver chemistries and symptoms normalize and the same regimen can be re-introduced after hepatitis has resolved.[1,9,31] The drugs can be re-introduced one at a time at 3 to 4 day intervals, with monitoring of liver function tests and symptoms to identify the offending agent.[1,9] Patients were re-treated with anti TB drugs by gradually increasing the number and dosage of the drugs to prevent the recurrence of hepatotoxicity.[51] If drug-induced hepatitis has been severe, the pyrazinamide and rifampicin are avoided and the patients are treated with a two-month initial phase of daily streptomycin, isoniazid and ethambutol followed by a 10 month continuation phase of isoniazid and ethambutol.[9]

2.3 Neurotoxic effects of anti-TB drugs.

2.3.1 Peripheral neuropathy is the most common toxic effect associated with isoniazid and rarely with ethambutol therapy.[9,16] Isoniazid-associated peripheral neuropathy has been observed in 2-20% of patients.[2,15] It is a dose-related effect which occurs most often, in patients given dosage greater than 5mg/kg/day, but is infrequently seen with the standard 300 mg/day adult dose.[2,15,16] It is probably related to interference with pyridoxine metabolism.[2] Isoniazid is a structural analogue of pyridoxine and accelerates its renal excretion resulting in pyridoxine deficiency and development of peripheral neuropathy with numbness and tingling sensation of the extremities.[15]

Peripheral neuropathy is readily reversible by pyridoxine administration. Its risk can be reduced to 0.2% with prophylactic administration of 10-50mg of pyridoxine (vitamin B_6) daily, which does not interfere with the therapeutic effect of anti-TB drugs. It is especially required in patients with predisposing conditions, such as slow acetylator status, malnutrition, elderly, and those with liver disease, diabetes, AIDS and uremia.[15,16] A study in Australia[52] showed that peripheral neuropathy due to isoniazid occurred in 1.2% of patients, all of whom were over the age of 40 years.

Ethambutol-associated peripheral neuropathy has been reported in-frequently.[9,15,16]

2.3.2 Optic neuritis is a serious toxic effect associated with ethambutol therapy and rarely with isoniazid therapy.[9,16,53]

Retrobulbar optic neuritis (axial or central) involves the papillomacular bundle of fibers resulting in reduced visual acuity, central scotoma, and red green colour blindness.[2,15] This toxicity is dose-related, and reported in 5% of patients taking a daily dose of 25mg/kg, and in less than 1% of patients taking a daily dose of 15mg/kg.[2,49] Symptoms of ocular toxicity may develop several months after initiation of therapy, but rapid onset optic neuritis has also been reported.[2] Early changes are reversible when administration of the drug is discontinued promptly and recovery may take several weeks to 6 months, or longer.[2,16] Blindness can occur if treatment is not stopped.[2,9] It is, therefore, prudent to note any history of eye disease and to get a baseline and periodic tests of visual acuity and red-green colour vision during ethambutol therapy.[15,16]

Ethambutol should not be given to patients whose vision is much reduced and who may not notice further minor visual deterioration and also should not be given to children below 6 years of age who cannot report visual deterioration.[15]

A study in India,[54] showed that the incidence of subclinical ethambutol-induced toxicity was higher in older patients, in high doses of ethambutol, and longer duration of treatment, while Choi et al in Korea[55] showed that ethambutol can cause optic neuritis at a lower dose (12.3mg/kg).

2.3.3 Ototoxicity is a serious toxic effect associated with streptomycin therapy. It is a dose-related toxicity. The risk increased in the elderly; and in patients with renal impairment. However, it is uncommon with currently recommended doses.[9,15]

Both auditory and vestibular damage may occur with hearing loss, vertigo, and tinnitus which may be permanent.[15,16,56] To decrease the incidence of this toxicity, it is necessary to limit the dose and duration of therapy especially in elderly patients and to conduct, if possible audiometry before and as needed during therapy. Education of patients about symptoms of auditory and vestibular damage (decreased hearing, headache, tinnitus, vertigo and dizziness) and stopping the drug at first development of these symptoms is important in reducing the incidence of this toxicity.[1,2]

On the other hand, Voogt et al[57] showed that streptomycin is very slightly ototoxic and the standard anti-TB drug combination had practically no ototoxic effect.

Other neurotoxic effect, which are uncommon with conventional doses of anti-TB drugs,[15,16] include: convulsion, toxic encephalopathy, memory impairment and toxic psychosis, which are associated with isoniazid therapy. These may also respond to pyridoxine administration.[2,15]

2.4 Cutaneous and hypersensitivity reactions to anti-TB drugs.

Allergic reactions that occur with anti-TB drugs are mild and self limiting[49] and can be managed by symptomatic treatment with antihistamines. The anti-TB drugs can be continued with close observation of patients.[9]

If hypersensitivity reactions develops, all anti-TB drugs must be stopped,[3,9,32] and then rechallenged to determine which agent is responsible.[2]

Hypersensitivity reactions are common with streptomycin therapy and can be severe, but they occur rarely with isoniazid, ethambutol and rifampicin.[9,22] These reactions usually but not invariably develop 2-4 weeks after treatment is started.[3] Once the reactions have resolved, anti TB drugs can be re-introduced. Table 6 shows the standard approach to re-introduce anti-TB drugs after a drug reaction occurs.[9]

Drug challenge starts with a small dose of the anti-TB drug least likely to be responsible for the reaction (i.e. isoniazid). The dose is generally increased over 3 days. The procedure is repeated, adding-in one drug at a time. This challenge process does not give rise to drug resistance.[9] Pretreatment with oral antihistamines and methyl-prednisolone before restarting the anti-TB drugs may decrease the recurrence of hypersensitivity reaction.[58] If the drugs responsible for hypersensitivity reactions are pyrazinamide, ethambutol, or streptomycin, anti-TB treatment should be resumed without the offending drug. The offending drug is replaced by another drug, with extension of the treatment regimen. This prolongs the total time of TB treatment but decreases the risk of recurrence of the reaction.[9]

Occasionally, patients develop hypersensitivity to the two most potent anti-TB drugs; isoniazid and rifampicin. In this case, it may be possible to desensitize the patient in order to re-introduce the drug.[9] Desensitization procedures are complex; they should be done in specialized centers, and in HIV negative patients.[9]

Table 6: Re-introduction of anti-TB drugs following allergic drug reaction.[9]

Drugs (in sequence)	Likelihood of causing a reaction	Challenge doses		
		Day 1	Day 2	Day 3
Isoniazid	Least likely	50 mg	300 mg	300 mg
Rifampicin		75 mg	300 mg	Full dose
Pyrazinamide		250 mg	1 gram	Full dose
Ethambutol		100 mg	500 mg	Full dose
Streptomycin	Most likely	125 mg	500 mg	Full dose

2.5 Hyperuricemia and arthralgia

Hyperuricemia is common with pyrazinamide,[2,9,29] and infrequent with ethambutol.[2,22] Pyrazinoic acid inhibits renal tubular secretion of urate resulting in hyperuricemia which is usually asymptomatic, and does not require to stop therapy, and rarely provokes acute gouty arthritis.[2,22]

Arthralgia is relatively frequent with usual daily dosing of pyrazinamide. It is not related to serum uric acid level, and it disappears after pyrazinamide treatment is stopped.[2,9,59].

Arthralgia affects both large and small joints particularly the shoulder[9] and is responsive to simple analgesics and rarely needs to discontinue treatment.[2,9] A study done by Inoue et al[59] on 51 pulmonary TB patients showed that hypercuricemia developed in 86% of patients, arthralgia in 18% of patients and acute gout was observed in only 2% of patients.

2.6 Nephrotoxicity

Renal toxicity is less common adverse effect of anti-TB drugs and can be reduced by limiting dose and duration of therapy especially in elderly patients.[16,22] Streptomycin is less nephrotoxic than other aminoglycoside antibiotics.[9,15] It produces dose-related changes, which are usually reversible and manifested as non-oliguric renal failure.[2] The dose must be reduced by half immediately, if urinary output falls, albuminuria occurs or tubular casts are detected in the urine.[9]

Rifampicin in recommended daily doses occasionally causes nephritis and acute renal failure.[15,16]

Agnihotri et al,[60] Sefer et al,[61] and Kuroda et al[62] reported cases of acute renal failure in association with intermittent doses of rifampicin.

2.7 Other adverse effects

Rifampicin imparts a harmless orange colour to urine, sweat, tears, and contact lenses (soft lenses may be permanently stained).[15,16]

Other adverse reacting are either rare or less significant and include: drug fever, thrombocytopenia, hemolytic anemia, aplastic anemia, leukopenia, eosinophilia, acne, menstrual disturbances, and a systemic lupus erythematosus-like syndrome. Intermittent administration of rifampicin may cause a flu-like syndrome.

Streptomycin may cause impairment of neuromuscular transmission and aggravation of myasthenia gravis, or cause a transient myasthenic syndrome in patients whose neuromuscular transmission is normal.[16]

Liu et al[63] reported a case of chronic pancreatic insufficiency as a sequelae of a hypersensitivity reaction to anti-TB drugs, and Lee et al[64] also reported a rare case of isoniazid induced fever.

The study objectives

Background

Any drug may produce unwanted or unexpected adverse reaction. Detection and recording of these adverse reactions is of vital importance.[3] A study in the United States, reported that 1,547,000 patients were admitted to hospitals in one year because of adverse drug reactions, and 160,000 hospitalized patients died as a result of adverse drug reactions.[65] On the basis of these calculations, adverse reactions are considered as the fourth to sixth leading cause of death after heart disease, cancer, stroke and accidents.[65]

A country which did not yet have an organized system for monitoring adverse drug reactions was considered by one author,[66] as a developing country. All systems for monitoring safety and efficacy of marketed drugs are included under the term of "post-marketing surveillance" (PMS).[66] However, whatever method used to monitor adverse drug reactions, the objectives are similar: to identify drug safety problems, to validate the cases and investigate causality, to establish incidence, to assess the risks in the light of benefits, and to communicate appropriate information to prescribers and patients.[66]

I. General objectives

of patients To study the adverse reactions associated with anti-TB drugs used in treatment involved in the application of DOTS strategy.

III.Specific objectives

To investigate the adverse effects of anti-TB drugs prescribed through the strategy of DOTS with regard to:

1. The type and frequency of these adverse effects and their relationship to onset and duration of treatment.
2. The influence of age, sex, severity of disease, genetic factors (like blood group and Hb type) and coexisting diseases on the type and frequency of these adverse reactions.
3. The effect of anti-TB drugs on different laboratory parameters: serum transaminases (AST and ALT), serum uric acid, blood urea, ESR, Hb and WBC count.
4. Establishment of a data base on the subject of adverse effects after DOTS application for future studies.

Chapter Three: Patients, Materials and Methods

The present work is a prospective follow up study, carried out at the TB center of Basrah governorate during the period from November 2001 to July 2002.

The study protocol was approved by the College Ethical Committee and the General Directorate of Health in Basrah.

3.1 Patients

Patients from centers of the first and second primary health care districts which covers the inner areas of Basrah city were included in this study.

3.1.1 Selection criteria

1. Patients diagnosed for the first time to have TB before being treated.
2. TB patients already under treatment.

These patients were either having extra pulmonary TB and referred to the TB center with proved diagnosis, or pulmonary TB diagnosed at the TB center itself by history taking and physical examination conducted by the center physicians and by chest x-ray and sputum smear microscopy done by medical staff.

3.1.2 Classification of patients

According to the site of infection, severity of disease, bacteriological status, and history of anti-TB treatment, every TB patients falls into one of three categories for treatment in DOTS strategy (Table 2).Each patient

was followed monthly (by the author)for at least three times by referral back to TB center according to:

1. A questionnaire form
2. Clinical examination
3. Laboratory investigations

Patients, after being diagnosed as tuberculous at the TB center,will be referred to TB organizer of each district for registration and follow-up. Patients were, then, referred to the PHC that serves the area where he lives, to receive his treatment under direct supervision. These patients were interviewed, clinically examined and investigated by the author of this thesis (Utoor Talib) herself at the TB center and given monthly appointment to come back again to the TB center for follow-up.

3.2 The questionnaire form

Questionnaire form was filled with the necessary information for all patients included in this study (figure1, page 38).

3.3 Clinical examination

The height and weight of the patients were measured to estimate the nutritional state, which is expressed as body mass index (BMI= Wt/Ht^2 in Kg/m^2).

Patients were, then, examined for general condition, blood pressure, jaundice, anemia, skin scratch marks, rash, ecchymosis and purpura. The abdomen was examined for epigastric tenderness, and liver and spleen enlargement. Blood sample was taken for laboratory investigations.

3.4 Sampling method

Venous blood (8 ml) was collected gently using a 10 ml syringe and divided into 4 tubes as follows:

1. 2 ml transferred to plain tube with 0.5 ml trisodium citrate to perform ESR.
2. 1 ml into a tube with ETDA to estimate total hemoglobin and WBC count.
3. 1 ml into a tube with ETDA, washed thrice by normal saline to be used for hemolysate formation to perform hemoglobin types.
4. 4 ml transferred to plain tube without any anticoagulant and allowed to coagulate at room temperature for 30-45 minutes and serum was separated by centrifugation for 5-10 minutes to estimate liver enzymes, serum uric acid and blood urea.
5. Few drops of blood were used to find out the blood group.

Table 7: Essential anti-TB drugs used in treatment of TB patients (included in this study)

Drug	Strength	Daily dose	Manufactured by
Isoniazid (H)	100 mg tablet	5 mg/kg	SDI
Rifampicin (R)	300 mg capsule	10 mg/kg	SDI or Indofarma (Indonesia)
Isoniazid and Rifampicin in combination	Two forms 1.150 mg + 300 mg capsule 2. 150 mg+ 300m mg tablet	-	Ajanta pharma Limited (India) Labalec-pharma S.A. (Geneva).
Pyrazinamide (P)	500 mg tablet	25 mg/kg	Pharmamed (Amesterdam)
Ethambutol (E)	400 mg tablet	15 mg/kg	Medochemie LTD-cyprus
Streptomycin (S)	1 gram vial	15 mg/kg	NorthChina Pharmaceutical corporation

3.5 Hemolysate formation

One ml of washed packed cells was added to 2 ml of cold distilled water and shaked using vortex mixture for 2 minutes.[68]

3.6 Diagnostic kits

Diagnostic kits were obtained from Randox (U.K), Biomerieux (France) or Biomaghreb, (Ariana). These were used for the determination of the following:

1. GPT "Glutamic pyruvic transaminase" (kit No. 146) (Randox).
2. GOT "Glutamic oxaloacetic transaminase" (kit No. 147) (Randox).
3. Uric acid (kit No. 150) (Biomerieux).
4. Blood urea (kit No. M96) (Biomaghreb).

3.7 Identification of blood groups

This was made by using Seraclone^{R} Anti-A, Anti-B and Anti-D (RH) Blend for (Biotest AG, Dreieich). Manufacturer instructions were followed and the reaction was read macroscopically.

3.8 Measurement of erythrocyte sedimentation rate (ESR)

ESR was measured by Westergren method.[67] The test was performed on venous blood diluted in the proportion of 1 volume of 109 mmol/l (32 g/l) trisodium citrate, added to 4 volumes of blood. The blood sample was mixed thoroughly and then drawn up into Westergren tube (30 cm in length and 2.55mm in diameter) to the 200 mm mark. The tube was placed in vertical position in a special rack and left undisturbed for exactly 60min, at room temperature (18-25 °C) and with out exposure to direct sunlight. The tube was, then, read to the nearest 1mm of the height

of the clear plasma above the upper limit of the column of sedimenting cells.

3.9 Hemoglobin types estimation

Hemoglobin type was tested by cellulose acetate electrophoresis at alkaline pH performed at the Hemoglobinopathies Unit, College of Medicine, University of Basrah. This method can detect the common type of Hb. It is based on differences of their migration within an electric field towards theanode. Tris/EDTA/borate buffer, pH 8.6±0.1 was used which contains: Tris 14.4 g; EDTA 1.5g; boric acid 0.9 g; water to one litre.[67]

3.10Total hemoglobin and white blood cell estimation

Hb and WBC estimations were performed at the Hematological Unit at Basrah General Hospital using MS9 (Hematology cell counter), Mallet schloesing laboratories, France.

3.11Liver function tests

3.11.1 GOT (Glutamic-oxaloacetic transaminase) or AST (Aspartate aminotransferase)

Serum AST was done according to an enzymatic method using Randox (Kit No. 147).

Principle

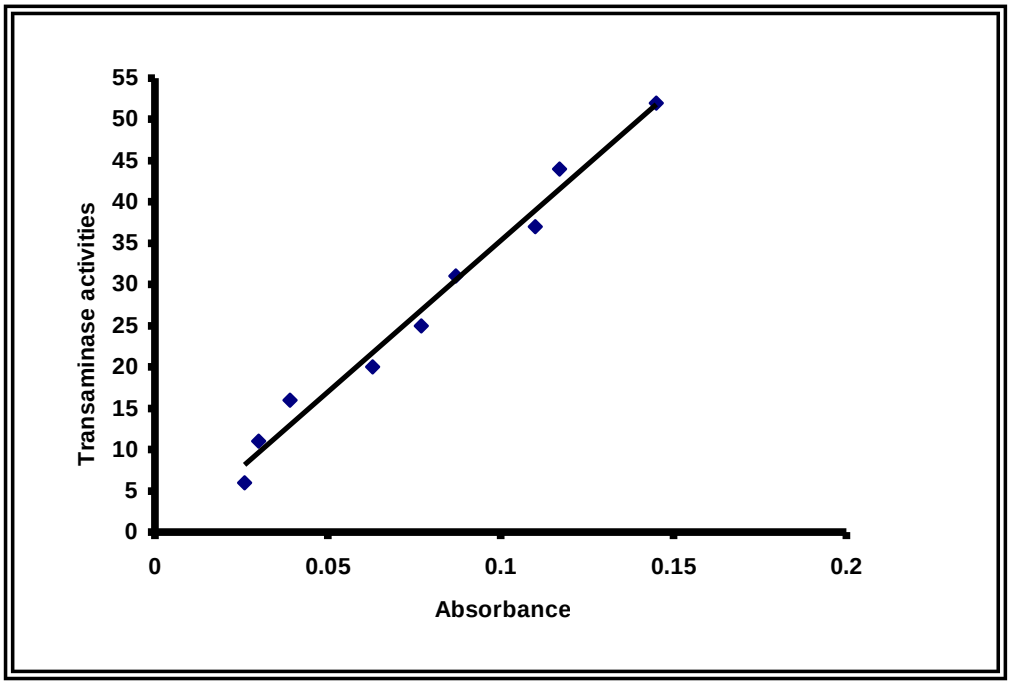
$$\alpha\text{-oxoglutarate} + \text{L-aspartate} \xrightarrow{\text{AST}} \text{L-glutamate} + \text{Oxaloacetate}$$

AST is measured by monitoring the concentration of oxaloacetate hydrazone formed with 2,4 dinitrophenylhydrazine.

Calculation

The GOT activity (U/l) was determined directly from a calibration curve (Figure2)

Figure 2: Standard curve of AST estimation



3.11.2 GPT (Glutamic Pyruvic Transaminase) or ALT (Alanine aminotransferase)

Serum ALT was done according to an enzymatic method using Randox kit No. 146

Principle

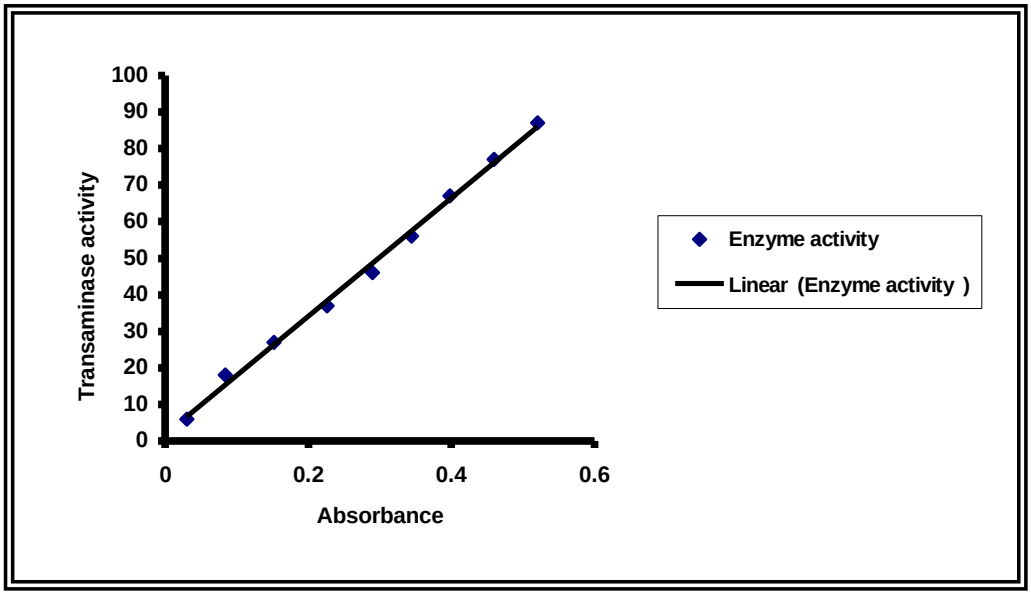
$$\alpha\text{-oxoglutarate} + \text{L-alanine} \xrightarrow{\text{ALT}} \text{L-glutamate} + \text{pyruvate}$$

ALT is measured by monitoring the concentration of pyruvate hydrazone formed with 2, 4-dinitrophenylhydrazine.

Calculation

The ALT activity (U/l) was determined directly from a calibration curve (Figure.3).

Figure 3: Standard curve of ALT estimation



3.12 Blood urea estimation

Serum blood urea was made according to an enzymatic colorimetric method using Biomaghreb kit No. M96.

Principle

Enzymatic determination of urea depends on the following reaction:

$$\text{Urea} + H_2O \xrightarrow{\text{Urease}} Co_2 + 2NH_3$$

Salicylate and hypochlorite in the reagent react with the ammonium ions to form 2,2 dicarboxy-indophenol. The quantity of this green compound is proportional to the urea concentration.

Calculation

$$\text{Urea} = \frac{\text{OD sample}}{\text{OD standard}} \times n$$

mg/dl: n= 50

g/l: n= 0.50

mmol/l: n=8.325

3.13 Uric acid estimation

Serum uric acid was performed according to an enzymatic method using BioMerieux Kit No. 150.

Principle

Uric acid present in the sample, is determined according to the following:

$$\text{Uric acid} + 2H_2O + O_2 \xrightarrow{\text{uricase}} \text{allantion} + CO_2 + H_2O_2$$

$$H_2O_2 + 2H_2O + \text{3.5 dichloro-2-hydroxybenzene sulfonic acid} + \text{4-aminoantipyrine} \xrightarrow{\text{Peroxidase}} \text{Chromogen} + HCl +$$

Procedure

The estimation of uric acid was performed at the Biochemistry Unit at Basrah General Hospital.

Statistical analysis

Statistical analysis was made using SPSS for windows computer package for means, standard deviation and correlation coefficient. Differences between two proportions were tested using standard normal deviation test (SND).

Results were considered significant if $P < 0.05$.

Figure1: the Questionnaire Form

Patient no:		Date:		
Name:	Age:	Sex:	Occupation:	
Education:	Address:		Origin:	
PHC:	Smoking:		Alcohol:	
Skin colour:	Blood group:		Height:	Weight:

Past History:

- Previous diseases: liver, kidney, diabetes, epilepsy, peptic ulcer, gout, others
- Blood diseases: hemoglobinpathies, G6PDD.
- History of TB.

Family History of:

- TB
- Hereditary diseases
- Others

Drug history:

- Previous anti TB drugs (types and duration)
- Other drugs taken at the present time (type, dose, and duration)
- Hypersensitivity reaction to drugs.

Present illness:

- Type of TB
- Category
- Treatment regimen and duration

Adverse effects		Baseline	Time after treatment (months)					
		Before treatment	Visit 1 one month	Visit2 two months	Visit3 three months	Visit4 four months	Visit5 five months	Visit6 six months
Gastrointestinal	Abdominal pain							
	Nausea, vomiting							
	Anorexia							
	Heartburn							
	Diarrhea							
	Constipation							
	Others							
Central nervous system	Headache							
	Ataxia							
	Numbness & tingling sensation							
	Drowsiness							
	Seizures							
	Psychosis							
	Others							
Eye/ Ear	Visual disturbance							
	Loss of color vision							
	Visual loss							
	Tinnitus							
	Hearing loss							
	Others							
Blood	Epistaxis							
	Ecchymosis/purpura							
	Menorrhagia							
	Others							
Skin	Itching							
	Rash							
	Acne							
	Others							
Miscellenous	Joint pain							
	Fever							
	Flu-like illness							
	Discoloration of secretion							
	Others							

Clinical examination

	Baseline	Time after treatment (months)					
	Before treatment	Visit1 one month	Visit2 two months	Visit3 three months	Visit4 four months	Visit5 five months	Visit6 six months
Weight							
General examination							
B.P.							
Abdomen							
Liver							
Spleen							
Others							

Investigations

	Baseline	Time after treatment (months)					
	Before treatment	Visit1 one month	Visit2 two months	Visit3 three months	Visit4 four months	Visit5 five months	Visit6 six months
Blood group							
Hb type							
ESR							
Hb%							
WBC							
ALT							
AST							
S. uric acid							
Blood urea							

NB: Estimation of serum transaminases (AST and ALT), blood urea, ESR and blood group, were performed by the author (Utoor T. Jassim), while, WBC, Hb% and Hb electrophoresis were estimated at the Laboratory of Basrah General Hospital and Hemoglobinopathy Unit.

Chapter Four: results

4.1 Characteristics of patients

The study included 83 TB patients; 61 of them were diagnosed for the first time and 22 patients already under treatment.

Among the 83 patients, there were 48 (57.8%) males and 35 (42.2%) females. Their age ranged from 13 to 68 years with a mean of (32.5±13.6) year (table 9). Most of the patients (68 patients, 82%) were having pulmonary TB. The remaining 15 patients (18%) have extra-pulmonary TB (table 8). Regarding their treatment, 68 patients (82%) were on category 1 treatment, 6 patients (7.2%) on category II and 9 patients (10.8%) were on category III treatment.
Thirteen (15.6%) patients gave a history of diabetes mellitus; one (1.2%) patient had peptic ulcer and one (1.2%) with epilepsy.

Out of the 83 patients, there were 30 patients (36.2%) with low body mass index (BMI), 50 patients (60.2%) with normal BMI, 2 patients (2.4%) with high BMI and only one patient (1.2%) was obese.

4.2 The overall incidence of reported adverse effects to anti-TB drugs

Twenty-one out of 83 (25.3%) patients had reported adverse effects. Eighteen patients reported both major and minor adverse effects according to the WHO classification (table 9), and an additional three patients developed acne (not listed in the WHO classification).

Female patients reporting adverse effects were double the number of males (14 vs 7 for females and males respectively, table 10). On average, patients with adverse effects are about 10 years older than those without.

In addition, patients with adverse effects are characterized by the followings (table 10): a relatively more extra-pulmonary type of TB (33.3% vs 13 % for the groups

with and without adverse effects respectively); more associated diseases particularly diabetes (33.3% vs 1.6%); higher percentage of raised AST level. 47.6% vs 26%); but lower incidence of raised serum uric acid level (14.3% vs 34%) and low BMI (19% vs 42%).

No abnormal Hb was detected in the group with adverse effects while 4 patients (3 HbAS and 1 HbSF) were found in the group without adverse effects.

Table 9: Classification of TB patients according to their age and type of TB

Age groups		Pulmonary TB smear +ve		Pulmonary TB smear –ve		Extra pulmonary TB		Total
		Male	Female	Male	Female	Male	Female	
1	0-19	4	6	1	1	2	-	14
2	20-29	20	5	2	-	3	1	31
3	30-39	3	4	2	1	-	2	12
4	40-49	3	3	1	-	-	4	11
5	50-59	4	4	-	1	2	-	11
6	60^{+}over	-	2	1	-	-	1	4
Total		34	24	7	3	7	8	83

4.2.1 Gastrointestinal adverse effects

Seven patients (8.4%) developed gastrointestinal adverse effects (Table: 9). Most of these patients developed mild nausea, epigastric pain and some times vomiting and become better with explanation and reassurance. One patient developed severe nausea, epigastric pain and vomiting (female, 40 year old, Cat III) at the 4th day of starting treatment and become better after changing pyrazinamide to streptomycin.

4.2.2 Cutaneous adverse effects

Seven patients (8.4%) reported itching and skin rash; five of them had itching without rash and became better on anti-histamines and topical corticosteriod therapy. The two patients who developed skin rash; one was 40 year old

diabetic male with pulmonary TB (Cat 1) diagnosed 2 months after starting treatment as photo-dermatitis that remained to the end of follow-up period in spite of symptomatic treatment. The other was 20-year-old female with extra-pulmonary TB (Cat 1); she had generalized erythema one month after starting treatment and became better when streptomycin was stopped.

4.2.3 others adverse effects

These include joint pain (n=3, 3.6%), acne (n=3, 3.6%) and impaired hearing [n=1, 1.2%, a female patient, 13 year old, with pulmonary TB and (Cat 1) became better after 3rd month of treatment]. It is remarkable to note that no case of clinical jaundice was encountered despite raised serum liver enzymes and no case suggestive of peripheral neuropathy (burning sensation, numbness and parasthesia) was found. However, it

should be mentioned that most patients received pyridoxine (vit. B_6) routinely with their anti-TB treatment.

Table 11: Adverse effects of anti-TB drugs based on WHO classification

Adverse effects		1st month	2nd month	3rd month	4th month	5th month	6th month	Total no. of patients	
								No.	%
Minor	Anorexia, nausea abdominal pain	3	4	-	-	-	-	7	8.4%
	Joint pains	-	1	2	-	-	-	3	3.6%
	Burning sensation in the feet	-	-	-	-	-	-	-	-
	Orange/red urine	All patients							
Major	Itching, skin rash	-	6	1	-	-	-	7	8.4%
	Deafness (Impaired hearing)	-	1	-	-	-	-	1	1.2%
	Jaundice	-	-	-	-	-	-	-	-
	Total no. of patients	-	-	-	-	-	-	18	21.6%

*Data are presented as the number of patients at the time of their report of the adverse effect.

Table 12: Comparison of patients with and without adverse effects

Parameters		Patients with no adverse effect		Patients with adverse effect	
Total no. of patients 83		62	74.7%	21	25.3%
Male	N=48	41	66%	7	33.3%
Female	N=35	21	34%	14	**66.7%****
Mean of age		30 ± 12.8 yr.		39.5 ± 14.4 yr.	
TB type	Pulmonary	54	87%	14	66.7%
	Extra pul.	8	13%	7	**33.3%***
Category	1	49	79%	19	90%
	2	6	9.7%	-	-
	3	7	11.3%	2	10%
Blood group	A	16	25.8%	5	23.8%
	B	14	22.6%	6	28.6%
	AB	6	9.7%	1	4.8%
	O	26	41.9%	9	42.8%
	Rh+	53	85.5%	17	81%
	Rh-	9	14.5%	4	19%
Hb electrophoresis	A	58	93.6%	21	100%
	AS	3	4.8%	-	-
	SF	1	1.6%	-	-
Associated diseases	Diabetes	6	9.7%	7	**33%****
	Peptic ulcer	-	-	1	4.8%
	Epilepsy	1	1.6%	-	-
AST level	Normal	46	74%	11	52.4%
	Raised	16	26%	10	**47.6%***
Uric acid level	Normal	41	66%	18	85.7%
	Raised	21	34%	3	**14.3%***
BMI (nutritional state)	Low	26	42%	4	19%
	Normal	35	56.4%	15	71.4%
	High	1	1.6%	1	4.8%
	Obese	-	-	1	4.8%

Significant difference with respect to patients with no adverse effects: *P< 0.05, **P < 0.01

4.3 Laboratory changes after anti-TB treatment

4.3.1 Changes in liver enzymes AST and ALT

I. AST changes

There was a general trend towards an increase in serum AST levels starting from the first month after treatment (table 11). The main increase occurred around the second month (figure 4). There were 26 patients with AST levels above the upper limit of 12 U/L; 24 had baseline AST values and 2 without these values.

Table 11: Change in AST enzyme levels over 6 month follow-up period

Parameter	Before treatment	Months after treatment					
		1st	2nd	3rd	4th	5th	6th
Male	5.9±1.7	8.9±4.85	8.9±4.8	8.8±4.27	10.1±5.45	9.3±3.6	9±2.3
Female	6.2±2	9.2±2.46	9.2±2.4	13.1±6.21	11.5±5.6	9.1±2.4	7.7±2.0
Total	6.03±1.87	9.06±4.19	9.06±4.1	10.77±5.6	10.77±5.4	9.19±2.9	8.2±2.1

* Data are presented as mean ± S.D of AST enzyme level in U/L

أ. Characteristics of patients with raised serum AST level

Out of the 83 patients, 26(31.3%) patients exhibited raised serum AST level (over 12 U/L) over the six-month observation period.

Out of 61 patients who had their baseline serum AST level measured before the start of their treatment, 24 (40%) patients exhibited raised serum AST level over the six-month observation period. When this group of patients was compared with the 37 patients with normal liver enzyme (table 12) in terms of age, sex, BMI, TB type, blood group, Hb type, uric

acid level and associated diseases and adverse effects, the two groups were comparable with each other except that the group with raised AST levels had more female to male ratio (1.18 compared to 0.37 in the group of normal AST levels), more extra-pulmonary TB (33.3% vs 13.5%), more incidence of other adverse effects (37.3% vs 13.5%) and fewer patients with low BMI.

ii.Onset of rise of AST level

Although the onset of rise in serum AST level had occurred at any time during the follow-up period, the highest number of patients appeared to be at the second month after starting the treatment (n= 10, 38.5%) (table 13).

iii. Cumulative number of patients at each measurement point

Again, the highest number of patients showing increased serum AST level is at the second month after the start of treatment. The number starts to decrease after the initial phase of treatment to become only one patient at the sixth month (table 14).

iv. Relationship with age

When the patients with raised serum AST level were divided arbitrarily into those below and above 35 year, a statistically significant difference in the number of patients having raised AST levels was found (43% vs 23.5% for those above and below 35 years of age respectively, $P<0.05$, table15).

Figure 4: Changes in AST enzyme level over 6 month follow-up period

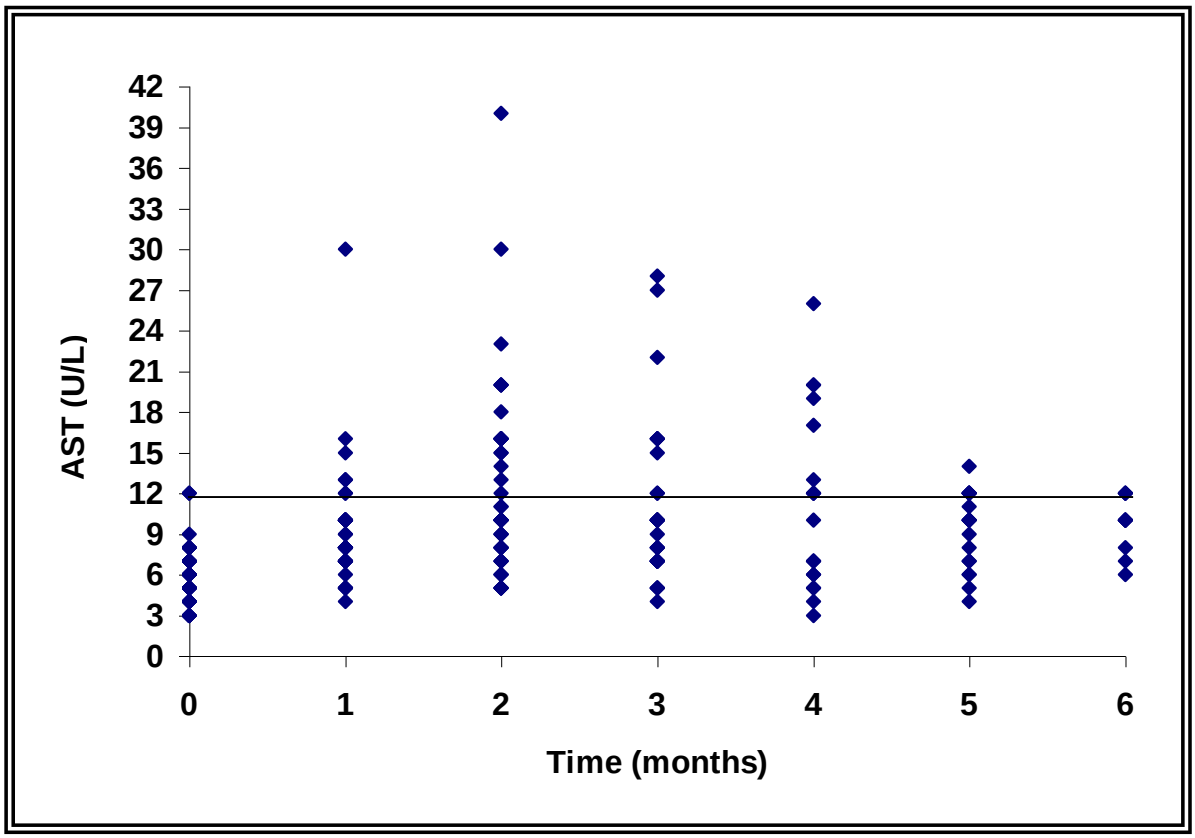


Table 12: Characteristics of patients with normal and raised AST enzyme level

Parameters		Patients with normal AST		Patients with raised AST	
		No.	%	No.	%
Total no. of patients 61		37	60%	24	40%
Male	38	27	73%	11	45.8%
Female	23	10	27%	13	**54.2%***
Mean of age		29.5 ± 12.16 yr.		35.8 ± 13.3 yr.	
TB types	Pulmonary	32	86.5%	16	66.7%
	Extra pul.	5	13.5%	8	**33.3%***
Category	1	33	89%	18	75%
	2	1	2.7%	2	8.3%
	3	3	8.1%	4	16.7%
Blood group	A	5	13.5%	6	25%
	B	11	29%	6	25%
	AB	4	10.8%	2	8.3%
	O	17	45.9%	10	41.7%
	Rh+	31	83.8%	20	83.3%
	Rh-	6	16.2%	4	16.7%
Hb electrophoresis	A	34	92%	23	95.8%
	AS	2	5.4%	1	4.2%
	SF	1	2.7%	-	-
Associated diseases	Diabetes	5	13.5%	4	16.7%
	Peptic ulcer	-	-	1	4.2%
Uric acid level	Normal	21	56.8%	17	70.8%
	Raised	16	43.2%	7	29.2%
Associated other adverse effects		5	13.5%	9	**37.5%***
BMI (nutritional state)	Low	18	48.6%	5	**20.8%****
	Normal	18	48.6%	18	**75%***
	High	1	2.7%	-	-
	Obese	-	-	1	4.2%

Significant difference with respect to patients with normal AST enzyme level: * P< 0.05, **P<0.01

Table 13: The onset of AST level elevation*

	1st month	2nd month	3rd month	4th month	5th month	6th month
Male n=12	3	5	1	1	2	-
Female n=14	2	5	2	5	-	-
Total n=26	5	10	3	6	2	-
% of the 26 pts.	19.2	38.5	11.5	23.1	7.7	-

Data are presented as the number of patients at the onset of AST elevation

* A total of 26 patients; 24 of them were having baseline AST readings before starting treatment

Table 14: Patients with raised AST levels at various times

	1st month	2nd month	3rd month	4th month	5th month	6th month
Male	3	8	3	2	3	-
Female	2	7	8	7	1	1
Total	5	15	11	9	4	1

Table 15: Effect of age (divided arbitrarily into above and below 35 yr) on AST and uric acid level

Parameters	Patients under 35 yr of age	Patients 35 yr of age and above
Total no. of patient	51(61.4%)	32 (38.6%)
Mean of age	23 ± 5yr	47.2 ± 9.2yr
Male	35 (68.6%)	13 (40.6%)
Female	16 (31.4%)	19 (59.4%)
Raised AST level (>12 U/L)	12 (23.5%)	**14 (43%)***
Raised uric acid level (> 7mg/dl in male and > 6mg/dl in female)	17 (33.3%)	9 (28.8%)

*Significant difference with respect to patients under 35 yr. of age: P<0.05

B. ALT changes

There was a general trend towards an increase in serum ALT levels starting from the first month after treatment (table 16). Out of the 83 patients, only six patients exhibited serum ALT level above the normal range (12 U/L) over the six month observation period. Although increases in ALT levels had been detected from the first to fifth month after commencing anti-TB treatment, the main increase occurred around the second month (figure 5).

These six patients also had raised serum AST level; four of the six patients were females. The correlation between AST and ALT levels is positive and statistically significant (figure 6, r=0.912, P<0.0001).

Figure 5: Changes in ALT enzyme level over 6 month follow-up period

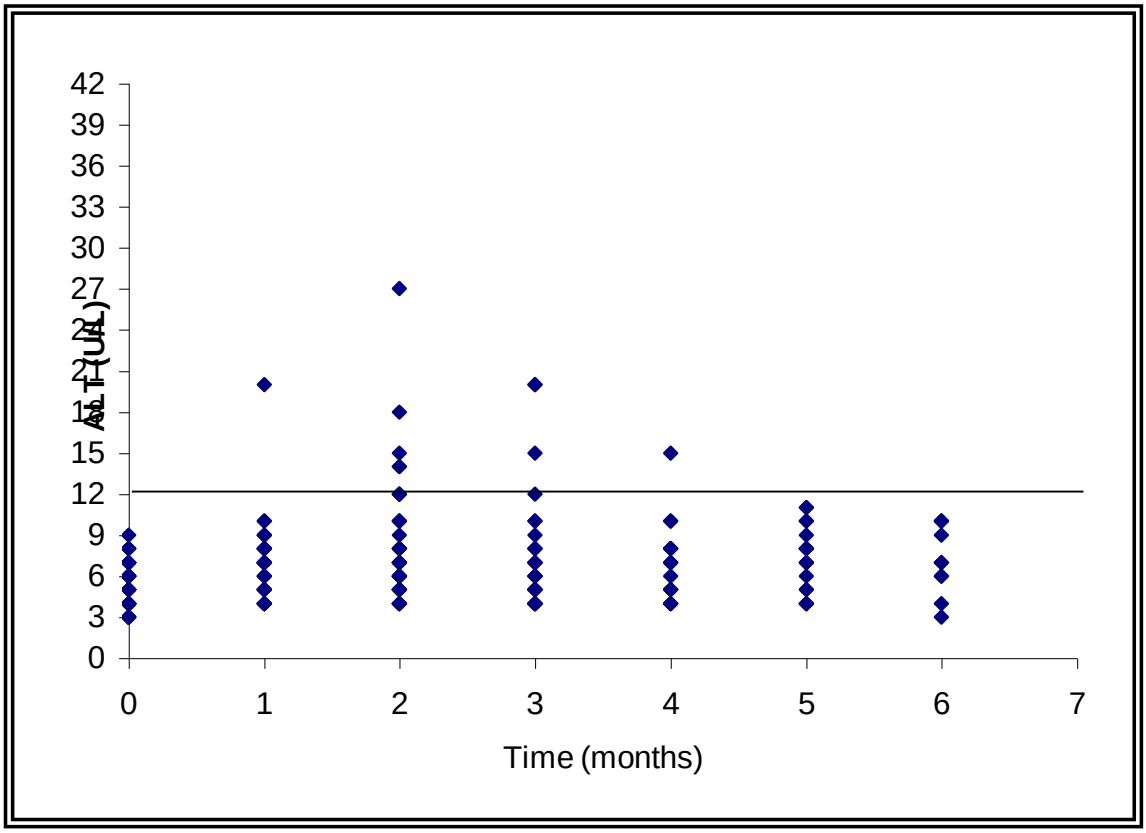
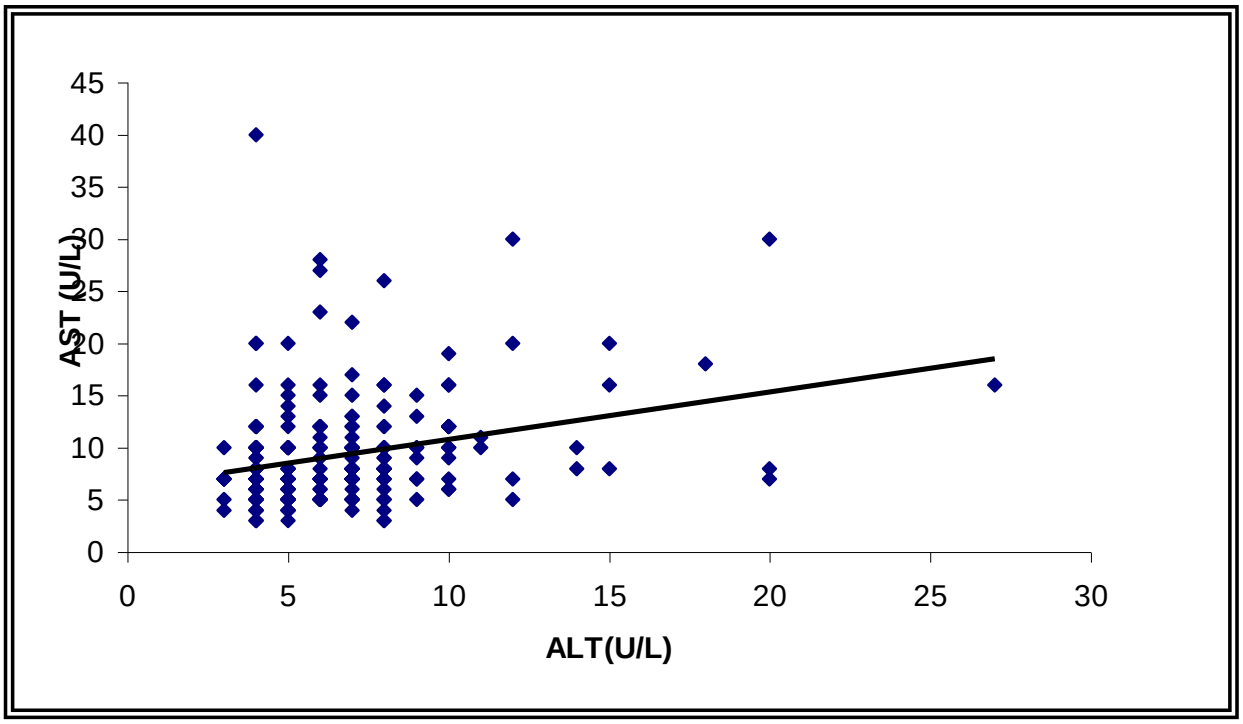


Table 16: Changes in ALT enzyme level over 6 month follow-up period

Parameter	Before treatment	Months after treatment					
		1st	2nd	3rd	4th	5th	6th
Male	5.13±1.6	6.79±3.03	7.16±3.15	6.4±3.38	6.8±3.37	6.76±3.03	6.6±2.5
Female	5.04±1.36	6.78±1.84	8.8±5.15	9±4.01	7.64±3.17	6.83±2.4	5.72±1.95
Total	5.09±1.51	6.79±2.67	7.95±4.27	7.57±3.86	7.19±3.26	6.8±2.65	6.15±2.2

* Data are presented as mean ± S.D of ALT enzyme level in U/L

Figure 6: Correlation between ALT and AST



4.3.2 Changes in serum uric acid level

Serum uric acid, also, tends to increase starting from the first month after treatment (table17). However, there were 26 patients exhibiting serum uric acid level higher than 7mg/dl for males and 6 mg/dl for females.

Table 17: Changes in serum uric acid levels over 6 month follow-up period

Parameter	Before treatment	Months after treatment					
		1st	2nd	3rd	4th	5th	6th
Male	3.57±0.85	6.24±2.29	6.76±2.0	5.09±1.95	5.43±1.47	4.8±1.9	4.4±6.84
Female	3.45±0.64	4.91±1.3	5.48±1.87	4.1±1.04	3.58±0.95	3.88±1.5	4.0±0.94
Total	3.52±0.78	5.76±2.07	6.19±2.05	4.69±1.67	4.6±1.56	4.31±1.73	4.24±0.89

*Data are presented as mean ± S.D of uric acid level in mg/dl.

i. Characteristics of patients with raised serum uric acid level

Out of the 83 patients, 26 (31.3%) showed raised serum uric acid level during the follow up period. 23 out of 61 patients (37.7%) who had their baseline uric acid level measured before the start of their treatment, exhibited raised serum uric acid level. When this group of patients was compared with the 38 patients with normal uric acid level (table 18) in terms of age, sex, BMI, TB type, blood group, Hb type, AST level, and associated diseases and adverse effects, the two groups were comparable with each other except that the group with raised serum uric acid level had significantly more category 3 patients (26% vs 2.7%) and blood group A and AB, and less patients with raised AST level and associated adverse effects and less patients with group B (table 18). The three cases of Hb AS are in the raised uric acid group.

ii. Onset of rise in serum uric acid level and cumulative number of patients with raised uric acid levels

The onset of rise in serum uric acid and the cumulative number of patient are mainly restricted to the first two months of treatment (initial phase) (figure 7 and 8, table 19and 20). After the second month, only 3 patients out of 26 patients continued to have raised uric acid levels. Two patients only had their onset of rise in uric acid level in the third and fourth month of treatment.

iii.Relationship with age

When age of the patients with raised uric acid level was divided into those below and above 35 years, no statistically significant difference was found between the two groups (28% and 33.3% for above and below 35 years respectively, table 15)

Figure 7: Changes in Uric acid level in male patients over 6 months follow up period

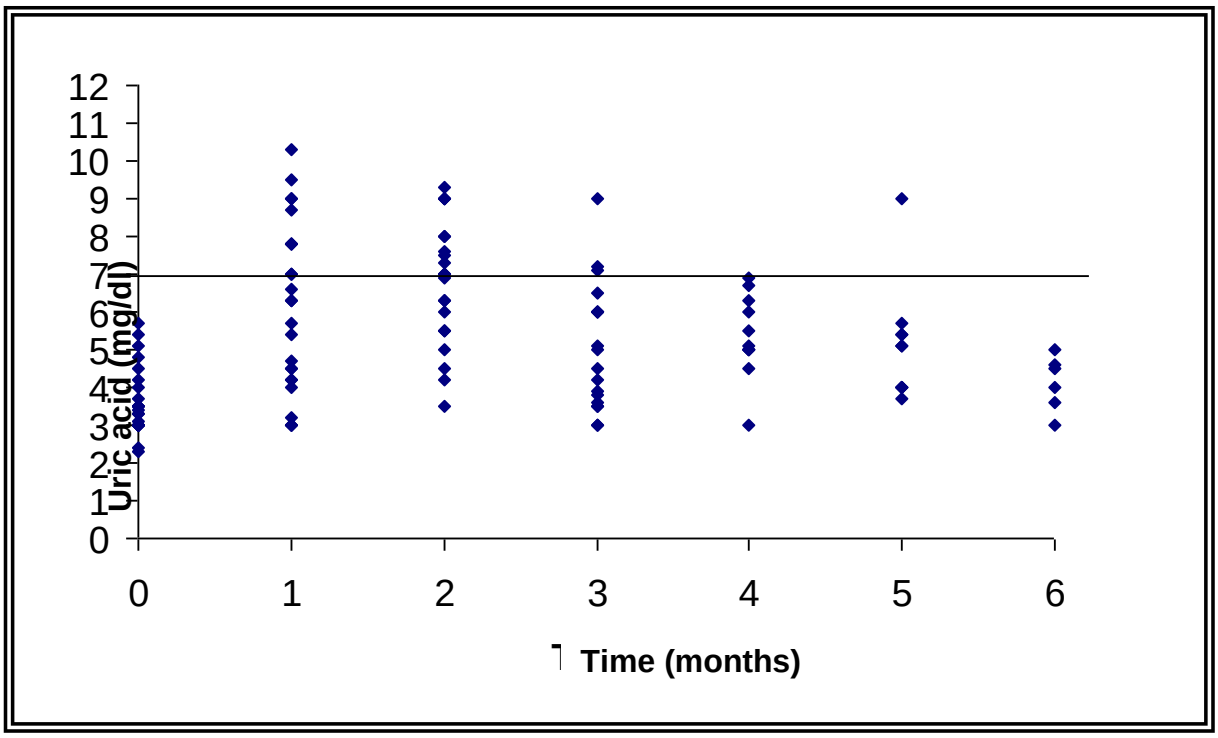


Figure 8: Changes in Uric acid level in female patients over 6 months follow up period

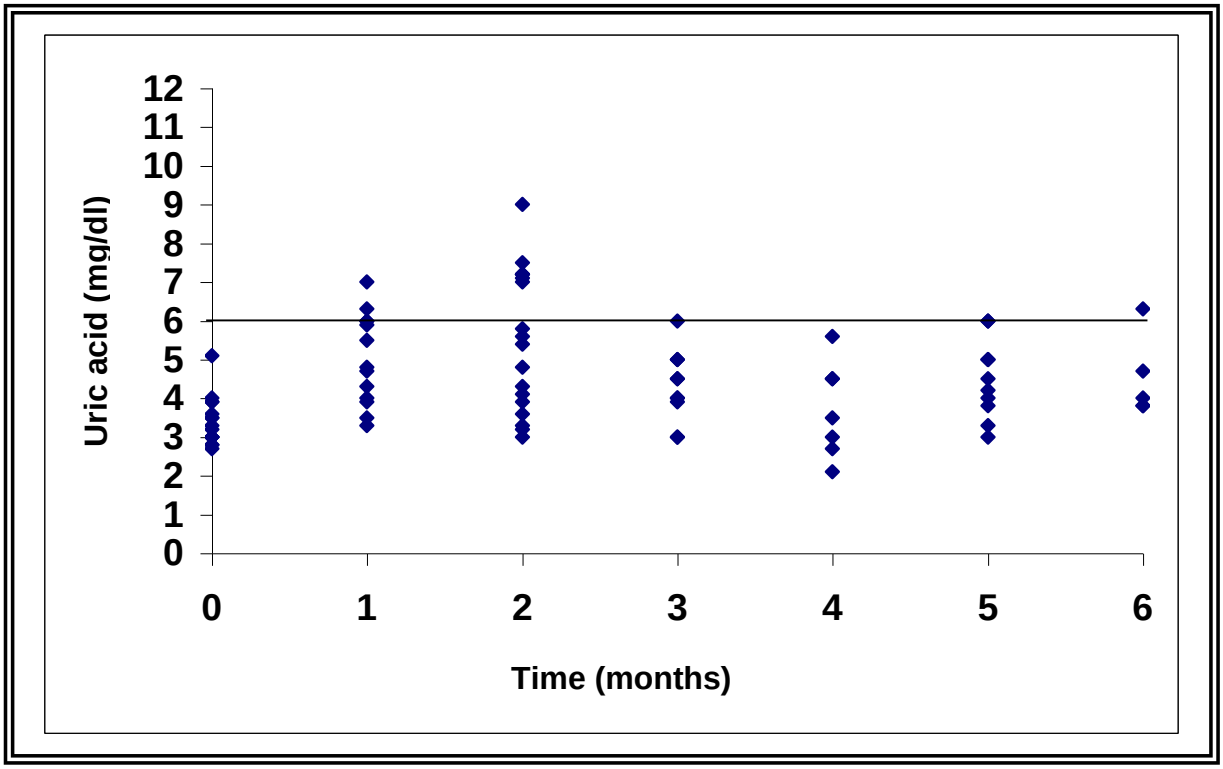


Table 18: Characteristics of patients with normal and raised serum uric acid levels

Parameters		Patients with normal uric acid level		Patients with raised uric acid level	
		No.	%	No.	%
Total no. of patients 61		38	62.3%	23	37.7%
Male	38	22	57.9%	16	69.6%
Female	23	16	42.1%	7	30.4%
Mean of age		32 ± 15.4 yr.		30.6 ± 9.12 yr.	
TB types	Pulmonary	28	73.7%	20	87%
	Extra pul.	10	26.3%	3	3%
Category	1	35	92%	16	69.6%
	2	2	5.3%	1	4.4%
	3	1	2.7%	6	**26%****
Blood group	A	3	7.9%	8	**34.8%****
	B	15	39.4%	2	**8.7%****
	AB	1	2.7%	5	**21.7%****

	O	19	50%	8	34.8%
	Rh+	31	81.6%	20	87%
	Rh-	7	18.4%	3	13%
Hb electrophoresis	A	37	97.3%	20	87%
	AS	-	-	3	13%
	SF	1	2.7%	-	-
Associated diseases	Diabetes	7	18.4%	2	8.7%
	Peptic ulcer	1	2.7%	-	-
AST level	Normal	20	52.6%	17	74%
	Raised	18	47.4%	6	**26%***
Associated other adverse effects		12	31.6%	3	**13%***
BMI (nutritional state)	Low	12	31.6%	11	47.8%
	Normal	24	63%	12	52.2%
	High	1	2.7%	-	-
	Obese	1	2.7%	-	-

Significant difference with respect to patients with normal uric acid level: * P<0.05, **P<0.01

Table 19: The onset of rise of serum uric acid level*

	1st month	2nd month	3rd month	4th month	5th month	6th month
Male n=18	9	7	1	1	-	-
Female n=8	4	4	-	-	-	-
Total n=26	13	11	1	1	-	-
% of the 26 pts.	50%	42.4%	3.8%	3.8%	-	-

Data are presented as the number of patients at the onset of uric acid elevation.

* A total of 26 patients; 23 of them were having their baseline uric acid levels measured before starting treatment.

Table 20: Cumulative number of patients with raised uric acid level over 6 month period

	1st month	2nd month	3rd month	4th month	5th month	6th month
Male	9	16	3	3	-	-
Female	4	6	-	-	-	-
Total	13	22	3	3	-	-

4.3.3 Changes in ESR, Hb, WBC count and blood urea

a. ESR

Initial ESR values in the 61 patients were high (67.5 ± 27.7 mm/h). These values started to decrease as treatment progressed. Where, at the 6th month, it is reduced by 74% (table 21).

Table21: Changes in ESR level over the 6 month follow-up period

Parameter	Before treatment	Months after treatment					
		1st	2nd	3rd	4th	5th	6th
Male	66.6±27.7	42.2±34.5	34.3±26.8	22±19.7	22.5±27.8	18.38±14.2	16.8±8.7
Female	66.8±28.2	44±17.5	37.8±20.1	25±14.8	24.9±16	20.7±13.4	18.54±7.3
Total	67.45±27.69	42.5±29.8	36±23.7	23.4±17.5	23.6±22.7	19.6±13.8	17.8±8
% reduction	-	37%	46.6%	65.3%	66%	71%	74%

*Data are presented as mean ± S.D of ESR in mm/hr.

b. Hemoglobin

Initial hemoglobin values in the 61 patients were low (10.9 ± 1.4g/dl). These values started to increase as treatment progressed to become 12.09 ± 1.37 g/dl at the 6th month after treatment (table 22).

Table22: Changes in hemoglobin level over the 6 month follow-up period

Parameter	Before treatment	Months after treatment					
		1st	2nd	3rd	4th	5th	6th
Male	11.36±1.2	12.1±1.09	12.3±1.06	12.6±0.92	12.9±0.91	12.9±1.29	12.8±1.22
Female	10.1±1.3	10.9±1.17	11.58±1.04	11.47±1.38	11.6±1.38	11.57±1.48	11.45±1.17
Total	10.9±1.4	11.7±1.24	12.01±101	12.1±102	12.3±1.31	12.1±1.54	12.09±1.37
% Increase		7.3%	10%	11%	12.8%	11%	11%

*Data are presented as mean ± S.D of hemoglobin level in g/dl.

c. WBC count

There were no significant changes in WBC counts over the six-month period of treatment (table 23).

Table23: Changes in WBC count over the 6 month follow-up period

Parameter	Before treatment	Months after treatment					
		1st	2nd	3rd	4th	5th	6th
Male	5.5±1.74	6.34±2.0	5.9±1.6	6.0±1.7	5.8±1.5	5.96±1.46	5.5±1.18
Female	5.1±1.73	5.38±1.0	5.3±0.93	5.4±1.5	5.3±1.5	5.49±1.34	5.3±1.03
Total	5.37±1.73	5.04±1.82	5.6±1.35	5.75±1.6	5.62±1.54	5.6±1.39	5.42±1.08

*Data are presented as mean ± S.D of WBC count in 1000/mm^3.

d. Blood urea

The mean blood urea level ranged from 20.9 to 30 mg/dl over six-month observation period that is within normal range of 15-40 mg/dl (table 24).

Table24: Changes in blood urea level over the 6 month follow-up period

Parameter	Before treatment	Months after treatment					
		1st	2nd	3rd	4th	5th	6th
Male	27.5±8.1	24±5.27	21±2.5	28.4±9.7	24±3.8	26.4±4.7	29.6±3.2
Female	26±8.5	19.7±5.28	20.8±4.1	24.8±8.2	29±9	24.9±6.3	30.3±4.32
Total	27±8.03	22.5±5.54	20.9±3.37	26.9±9.1	25.8±6.22	25.6±5.52	30±3.6

*Data are presented as mean ± S.D of blood urea in mg/dL.

4.4 Response to anti-TB treatment

Indicators of response to anti-TB drugs, apart from clinical and radiological improvement include sputum smear conversion, reduction in ESR, and rise in hemoglobin and BMI values.

1. Sputum smear conversion

Fifty six out of the fifty eight patients with sputum smear positive pulmonary TB became sputum smear negative after the first two to three months of treatment (initial phase). Two patients were still sputum smear positive until the fifth month and were considered as treatment failure.

2. Changes in ESR, Hb, and BMI

As cited above, the high initial ESR values of the 61 patients (67.5 ± 27.7 mm/hr) started to decrease progressively by 37%, 46.6%, 65.3%, 65%, 71% and 74% over the 6 months of treatment as compared to initial values (table 21).

The low hemoglobin values before treatment started to increase, again gradually to reach a value about 11% higher than the initial (from 10.9 ± 1.4 to 12.09 ± 1.37 mg/dl, (table 22).

There is a trend towards an increase in BMI; however, the increase is not significant. BMI increased by 12.28% around the 5th month after treatment (table 25).

3. Alteration or cessation of drugs because of adverse effects

A change of drugs because of adverse effects was made in one patient only (a female, 40 yr, Cat 3). Pyrazinamide was changed to streptomycin after severe nausea and vomiting. While in another patient (a female, 20 yr, Cat1), streptomycin was stopped in the second month of treatment because of skin rash.

Table 25: Changes in BMI over 6 month follow-up period

Parameter	Before treatment	Months after treatment					
		1st	2nd	3rd	4th	5th	6th
Male	18.92±3.72	19.12±3.23	20.4±31	19.85±3.88	20.05±4.25	20.84±4.87	20.92±4.72
Female	19.64±2.9	20.92±5.09	21.5±3.47	22.1±2.24	21.7±3.74	22.31±3.55	22.0±2.14
Total	19.22±3.4	19.58±3.8	20.9±3.32	20.7±4.14	20.7±4.0	21.58±4.2	21.34±3.85
% Increase	-	1.87%	8.74%	7.7%	7.7%	12.28%	11.03%

*Data are presented as mean ± S.D of BMI (kg/m^2).

Chapter Five:

Discussion

The term adverse effects cover all the types of unwanted effects. These could occur through exaggeration of the same pharmacological effect that is responsible for the therapeutic effect of the drug (toxic effect, dose related) or through actions other than that which produces the therapeutic effect (side effect, dose related or not dose-related). Other adverse effects include long-term and delayed effects.[3]

Careful monitoring of adverse effects will help to minimize their impact, and could contribute to the reduction of morbidity and mortality of serious and re-emerging diseases like TB.

The incidence of adverse effects of anti-TB drugs differs widely between countries.[25-31] In the present study, the incidence is relatively low (25.3%, most of them are minor). Serious adverse affects such as severe hepatic damage and peripheral neuropathy had not been encountered. And in no case, termination of treatment as a whole was found necessary because of adverse effects. This is in agreement with a study in Al-Anbar governorate (Iraq),[35] which showed that our patients tolerate anti-TB drugs well.

Racial differences could be one factor contributing to variation in the incidence of adverse drug reactions. Asian patients living in UK showed lower rate of adverse reactions compared to white patients.[26] Pyrazinamide is considered to be an important hepatotoxic agent in Western countries,[15,16] however, it has not been found to be associated with drug induced hepatitis in Japan.[25] The lack of symptoms and signs pointing to peripheral neuropathy may reflect the protection offered by

the routine use of pyridoxine (vit. B_6) prophylaxis for most of our patients rather than a real absence of this adverse effect. In addition the dose of isoniazid may be a factor. Peripheral neuropathy was reported to be infrequent with the standard dose of 300mg/day.[2,15,16] This dose is not exceeded in the present study. Risk factors such as slow acetylation[15,16] have not been well define in our community.

When the group of patients who developed adverse effects over the 6-month follow-up period (n=21) were compared with those who did not show any adverse effect (n=62) certain differences has emerged (table10). Patients with adverse effects are older in age, the majority are females, having higher incidence of extra pulmonary TB, diabetes mellitus and raised hepatic AST enzyme. On the other hand, they had lower incidence of low BMI and of raised uric acid. The presence of abnormal hemoglobin (n=4) seems to be associated with lower incidence of adverse effects. These findings are difficult to explain; small size of the studied patients might be one factor. Several studies, also, reported increasing of adverse effects with increasing age of patients and in females more than males.[2,16,26] This is confirmed in the present study. The proportion of females among those having adverse effects is 66.7% compared to 34% in those without adverse effects. Average age is higher by 9.5 years in the group with adverse effects. It is important to note that none of our patients developed jaundice clinically during the follow-up period. However, transaminases were raised asymptomatically in a good percentage of patients (40%). Bilirubin in those with very high enzyme levels was found to be within normal range. This increase occurred usually within the first 2-3 months after treatment to return, in most patients to normal level during the maintenance phase. This trend is in

agreement with other studies.[16,40,43] One factor that could contribute to this trend is the use of pyrazinamide which is known to be hepatotoxic.

In a study in Baghdad,[40] anti-TB induced hepatotoxicity was found in 20% of patients and in agreement with the present work, bilirubin levels was within normal range.

The groups of patients with raised serum AST enzyme are characterized by being older in age with more females. There were 43% of patients with age more than 35 years had raised AST compared to 23.5% of those below 35 year of age.

If hepatocellular injury is taken as an increase in the AST more than twice the upper normal limit,[40] then hepatocellular injury in this study is estimated to occur in 4 patients (15.4% of those with raised AST, n=24; and 4.8% of the total 83 patients). However, for drugs like isoniazid, rifampicin and pyrazinamide to be stopped, serum transaminases should be markedly elevated (more than 3-5 times the upper normal limit).[1,2] None of our patients reached these levels except one with AST level of 40 U/L who was without symptoms suggestive of hepatitis and with normal bilirubin level. Malnutrition is known as a risk factor for hepatotoxicity.[2] However, as an indicator of nutritional status, BMI, is expected to be lower in the group of patients with raised AST. The reverse was found in the present study that is difficult to explain.

ALT showed a trend similar to AST, but only 6 patients exceeded the normal values; out of them only one patients had more than double the normal level.

The raised AST and ALT occurred mainly in the first three months that corresponds to the use of the three hepatotoxic drugs (isoniazid,

rifampicin, and pyrazinamide). Pyrazinamide seems to be important in this regard since AST levels started to decrease after the initial phase of treatment despite containing use of isoniazid and rifampicin.

Uric acid in this study increased above normal limit in 31.3% of the 83 patients. This increase occurred mainly in first and second months after treatment, where pyrazinamide is used. Although this percentage is significant, but it is less than that reported by Inone et al[59] (86% of the 51 patients with pulmonary TB).

Arthralgia is rare in our patients with raised serum uric acid. This lack of relationship is also reported by others.[2,9,59] Patients with hyperuricemia, in this study, appear to be associated with less severe form of TB (Cat III), and with blood group A and AB compared to those with normal levels. The association between different diseases or symptoms and certain blood groups has been widely reported. For example, patients of blood group A are more prone to chronic dermatophyte infection,[68] and those with group O are associated with increased risk of peptic ulcer.[69] The sample size is small in the present study, future studies are required to establish a relationship between ABO and drug side effects.

Allergic reactions to anti-TB drugs are usually mild and self-limiting.[49] Redal et al.[70] had reported 3 cases of rash after the first dose of anti-TB drugs. Pyrazinamide appears to be responsible. Two patients who developed skin rash had been encountered in our study. The first patient diagnosed as photodermatitis and remained to the end of follow up period in spite of symptomatic treatment. The second case has generalized skin rash, which disappeared after discontinuation of streptomycin.

Acne vulgaris was reported to be frequent after anti-TB treatment in Nigeria (20.6%).[71] Three cases were recorded in the present study (two males and one female). Rifampicin was, also, reported to cause hypersensitivity and cutaneous reaction.[72] Anti-TB drugs were arranged from least likely to most likely drugs to cause allergic drug reaction as: isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin respectively.[9]

In the present study, cutaneous (itching and skin rash in addition to acne) adverse effects occurred in 12% of patients receiving anti-TB drugs.

DOTS strategy can be considered an important opportunity to eliminate as much as possible, the lack of patient compliance as a cause of low incidence of adverse effects. With this strategy implemented at the present time in Basrah, our patients seem to tolerate well anti-TB drugs with minimal incidence of serious toxicities.

Up to our knowledge, no study on the type and incidence of adverse reactions of anti-TB drugs after the application of DOTS has been published except a recent article from Nigeria published in 2002[73]. In this article the authors concluded that DOTS is effective and characterized by low and minor side effects.

Conclusions

1. The overall incidence of adverse effects of anti-TB drugs over a 6 months period is 25.3%.
2. Most of these adverse effects are minor (gastric upset and itching), and occur more in female patients and in older age group.
3. The absence of serious toxicities as hepatic damage and visual disturbances indicates that our patients tolerate anti-TB drugs well.

4. Features of peripheral neuropathy have not been observed, probably because of the protective effect of pyridoxine (vit. B_6) prescribed routinely to most of the patients.
5. Both serum hepatic transaminases (AST and ALT) and uric acid increased during the initial phase. These increases became less during the continuation phase, which might incriminate pyrazinamide as a significant cause of these changes.
6. Four patients only had their serum AST level exceeded more than double the upper normal limit that was not associated with raised bilirubin levels.
7. All, except two, patients responded to treatment as judged clinically, radiologically, sputum smear conversion, gradual reduction of ESR and rise of Hb and BMI; all indicate that anti-TB drugs might have been available enough to produce effects and adverse effects.

Recommendations

1. Monitoring of adverse effects of anti-TB drugs is recommend to become an integral part of DOTS strategy for early detection of toxicities and to continuously scrutinize the quality of drugs used.

2. The effect of other risk factors e.g. the genetic variation in acetylation of isoniazid (slow and fast acetylators) is required to be investigated.

3. Measurement of other enzymes that could not be followed in this study for various difficulties e.g. alkaline phosphatase (to indicate obstructive damage) may be required in the future.

4. The small sample size (83 patients) may not be enough to detect less frequent adverse effects. Thus, extension of such monitoring studies to cover large samples is necessary.

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الملخص

ان مناطرة التأثيرات الضارة مهمة في انقاص المراضة ومعدل الوفيات التي تسببها الأدوية. وتوفر المعالجة القصيرة تحت الاشراف المباشر للتدرن فرصة جيدة لدراسة التأثيرات الضارة المضادة للتدرن.

تمت متابعة 83 مريضاً مصاباً بالتدرن (شخص 61 منهم لأول مرة و22 كانوا بمراحل مختلفة من معالجتهم) وفق قائمة تدقيق للتأثيرات الضارة, كما تم قياس انظيمات الكبد (ترانسأميناز AST,ALT), وحمض اليوريك من مصل الدم ويوريا الدم والهيموغلوبين, وعدد كريات الدم البيضاء, وفصائل الدم والرحلان الكهربائي للهيموغلوبين وفحوصات اخرى.

وكانت نسبة الحدوث الاجمالية للتأثيرات الضارة (وكما صرح بها المرض) وعلى مدى ستة أشهر 25,3 % معظمها بسيطة (اضطرابات المعدة والحكة). وكان ثلثا هؤلاء المرضى من الاناث بمعدل عمري اكبر من الذين ليس لديهم تأثيرات ضارة, وهناك زيادة في مستوى الـ AST اعلى من الحد الاعلى للقيم الطبيعية (12 وحدة/ لتر) في 40% في اولئك الذين تم قياس هذا الانظيم لهم قبل المعالجة (وعددهم 61), وكان لاربعة منهم اكثر من ضعف الحد الاعلى للقيم الطبيعية. هذه الزيادات حدثت بصورة رئيسية خلال المرحلة المكثفة ثم اخذت بالنقصان خلال المرحلة المتممة للمعالجة. كما ان حدوثها كان اكثر في الاناث وفي الاكبر عمراً من 35 سنة. اما انظيم ALT فقد ازداد في ستة مرضى فقط.

من بين الواحد وستين مريضاً ممن كان لهم قياسات قبل المعالجة, ازداد حمض اليوريك في 37,7 % منهم. وانحصرت هذه الزيادات في المرحلة المكثفة حيث استعمال البارزينمايد.

لم يحدث اليرقان عند اي من مرضانا, وكذلك اعتلال العصب المحيطي (علماً ان المرضى وصف لهم بايردوكسين للوقاية).

ان جميع المرضى عدا اثنين منهم استجابوا بشكل مرض للادوية المضادة للتدرن وكما قيم ذلك سريرياً وشعاعياً وبتحول مسحة البلغم وتراجع معدل ترسب الكريات الحمر مع الزيادة الحادثة في نسب كتلة الجسم.

ونستنتج من ذلك ان المرضى الذين تمت متابعتهم في هذه الدراسة يتحملون الادوية المضادة للتدرن بشكل جيد.

ولم يعثر على اية حالة لسمية الكبد الشديدة او لاعتلال الاعصاب المحيطية.

دراسة نوع ومعدل حدوث التأثيرات الضارة للأدوية المضادة للتدرن من خلال تطبيق إستراتيجية المعالجة القصيرة الأمد تحت الإشراف المباشر في البصرة

رسالة مقدمة إلى
كلية الطب – جامعة البصرة
كجزء من متطلبات نيل درجة الماجستير
في علم الأدوية السريري

من قبل

الطبيبة عطور طالب جاسم
بكالوريوس طب وجراحة عامة

1423هـ 2002 م