Frequency and type of Reactions Occurring During Antiberculosis Therapy : An Interview of 87 Patients

Abdullah M Jawad* , Athra M Selman* , Sofik V Vartan*,
Simon V Vartan**, Khais M Ali**

* Department of Pharmacology, College of Medicine, University of Basrah, Iraq.

** Basrah Center for tuberculosis, Basrah, Iraq.

Abstract

Adverse reactions associated with antituberculosis treatment have not yet been published in Basrah. The main aim of this study is not to establish the actual frequency of adverse reactions to individual drugs, but to find out how common that major incidents, like hepatitis, peripheral neuropathy, eye problems, ... etc, may occur during TB treatment. Eighty seven tuberculous patients who completed, at least, their initial 2-month phase of treatment were interviewed during their monthly visits to the TB center in Basrah. They were asked to recall any adverse reaction they have at the time of interview, in addition to what they can recall of their past treatment. If both minor and major adverse reactions known to occur during patients treatment were considered, the overall incidence is, expectedly, high (85.1%). This high incidence may not be related to the drugs only, but also to the disease as well as the nutritional status. Gastrointestinal problems, dizziness and cutaneous manifestations are leading. Features of peripheral neuropathy occurs in 32.1%, problems related to the eye are claimed by 26.4%, and a pricking pain, specifically, at the left submammary region in 14.9% of patients. The incidence of burning sensation and numbness in upper and lower limbs, increases with increasing age, and eye problems and chest pain are more common in those below 20 years of age. Joint manifestations are higher in females, while the incidence of cutaneous adverse effects is higher in males. Features pointing to severe hepatic dysfunction are found to be rare in this study. The strategy of directly observed short course therapy (DOTS), which is now implemented in Basrah, provides a good opportunity to study the adverse effects in relation to individual drugs.

Introduction

Tuberculosis (TB) is one of the major health problems and is emerging again worldwide (1). Treatment of TB is satisfactorily achieved if proper compliance is observed. Defaulting and non-compliance are one of the most common problems in TB management programs (2-4). In one study (4), 19% of the defaulters were found to be due to the side effects. For the reason of defaulting and others (improper case detection and management), the strategy of directly observed therapy (DOTS) is now successfully implemented (5).

The incidence of adverse reactions varies widely (6-11). It ranges from 5.1% (8) to 67.7% (10). These adverse effects could be severe enough to cause modification and/or termination of the standard drugs (7,8,10,11). Similarly, if these reactions are unrecognized, they can lead to increased morbidity and mortality as well as high health care costs and social hazards (12). Proper knowledge of potential adverse reaction is essential for physicians using antituberculosis drugs (13). The present study was, therefore, conducted to assess the incidence and type of reactions associated with the use of antituberculosis drugs in an unselected tuberculous patients during their periodic attendance to the TB centre in Basrah.

Patients and Methods

Eighty seven patients with tuberculosis, pulmonary and extrapulmonary, reporting for their treatment at the TB centre in Basrah governorate, were interviewed during the period of June and July 1999. They were questioned according to a pre-set form which included age, sex, weight, residency, site of infection, details of their treatment, smoking and alcohol habits, preferred diet, and skin colour. Only those patients who completed their initial 2-month treatment were included. They were asked to recall any unwanted effects during

their present and initial phase of drug treatment following a check-list of system-wise signs and symptoms, involving all described side effects of antituberculosis drugs.

Adverse effects were classified into minor and major effects according to a WHO classification (14), where minor adverse effects include (with the probable offending drugs): anorexia, nausea, abdominal pain (rifampicin), joint pain (pyrazinamide), burning sensation of the feet (isoniazid) and orange/red urine (rifampicin). While major adverse effects include; itching of skin and skin rash (thiocetazone, streptomycin), deafness (streptomycin), dizziness (including vertigo and nystagmus) (streptomycin), jaundice (especially INH, pyrazinamide and rifampicin), vomiting and confusion with suspicion of drug-induced acute liver failure (most anti-TB drugs), visual impairment (ethambutol) and shock, purpura and acute renal failure (rifampicin).

Results

1. Characteristics of patients

Of the 87 patients, 51(59%) were males and 36 (41%) were females. Most female patients were housewives. The age of the 87 patients ranged from 15 to 60 years with a mean of 32.6+16, and their mean weights 52.2+10.7 kg. Six patients were students, three having a university qualification, and twenty one patients were illiterate.

Most of the patients (91%) were having pulmonary tuberculosis, and nearly half (45.5%) were living in the inner areas of the city. No Negro patients was seen. Only 32.9% of the male patients were smokers, and one patient claimed to be a heavy drinker.

Around 72% were receiving INH, rifampicin and ethambutol during their initial phase of treatment, while the rest received, in addition, pyrazinamide and/or streptomycin. Analgesics and tonic drugs were the main type of drugs consumed by the patients (12 and 8 patients respectively) in addition to their antituberculous drugs.

2. Incidence of adverse effects:

The overall incidence of adverse effects associated with antituberculosis drugs in the 87 patients was 85.1%. Symptoms of gastrointestinal upset (anorexia, nausea, heartburn, epigastric pain, change in bowel habit) are predominating (56.3%). This is followed by dizziness (postural) and cutaneous manifestations (popular rash, itching, flushing). Features of peripheral neuropathy (numbness and burning sensation in extremities) claimed by 32.1% of patients.

Twenty three patients (26.4%) suffered eye problems in the form of redness, burning sensation, flashing lights, or reduced visual acuity. Thirteen patients (14.9%) complained of chest pain in the left submammary region. Other adverse effects are shown in table 1.

3. Correlation of individual adverse effects with various patient characteristics

When the characteristics of patients with GIT, joint, cutaneous, visual and other reactions were compared individually with that of the whole group of 87 patients, the following differences were found (table 1):

a. Patients with GIT reactions had significantly lower body weight (40.8±15 and 52.2±10.7kg for patients with GIT reactions and the total number of patients respectively).

ii. Joint adverse effects occurred more in females (female to male ratio is 1.12 compared to 0.71 in the whole group).

iii. Cutaneous reactions were more common in males (male to female ratio is 2.4 compared to 1.42 in the whole group). These reactions occurred more in those patients who received pyrazinamide in addition to other drugs (29.6% compared to 19.3% in the whole group). Cutaneous reactions seem to occur less frequently in patients with fair skin (3.7% and 10.2% in patients with fair skin and in the whole group respectively).

iv. Patients with visual disturbances are characterized by having lower body weights and lower smoking habits; none of them had extrapulmonary TB and higher percentage of patients had fair skins.

v. Dizziness (mostly postural) occurred more in patients with lower body weight and extrapulmonary TB, and in those receiving streptomycin.

4. Incidence of adverse effects in relation to age:

When patients were divided into four age groups (20 years each), the results showed that the following adverse effects were more inclined to occur in the specified age group when compared to the total number of patients: joint reactions in patients over 60 years; eye problems and pricking chest pain below 20 years; and headache in those between 20 and 39 years of age (table 2). The incidence of burning sensation and numbness (n=28) seems to increase the increasing age (28.6% , 27.7% , 41.2% and 44.4% with each 20 years successively).

Table 1: Characteristics of patients with individual adverse reactions.

Type	Total	GIT	Joint	Dizziness	Cutaneous	Visual
Number	87	49	36	32	27	23
Age (y)	32.6 ±16	36.5 ±15.3	36 ±15.6	31.7 ±14.4	31.3 ±15	24.9 ±13.8
Weight (kg)	52.2 ±10.7	40.8 ±15	50.5 ±9	39.6 ±15.1	41.4 ±16.5	31.6 ±16.8
Sex: Male	50%	57.1%	47.2%	59.4%	70.4%	56.5%
Female	41%	42.9%	52.8%	40.6%	29.6%	43.5%
Smoking	32.9%	28.6%	25%	25%	29.6%	21.7%
Site of TB: pulmonary	91%	87.8%	94.4%	84.4%	92.6%	100%
Skin colour Fair:	10.2%	8.2%	13.9%	12.5%	3.7%	17.4%
Drugs:						
H/R/E	70.5%	69.4%	75%	62.5%	55.6%	65.2%
H/R/E/S	1.1%	2.04%	0	6.25%	0	4.3%
H/R/E/Z	19.3%	20.4%	16.7%	21.9%	29.6%	13%
Others	10.3%	8.2%	8.4%	3.1%	14.8%	13%13%

H = INH (300 mg/day), R=Rifampicin (450-600mg/day),
E = Ethambutol (15mg/kg/day), S=Streptomycin (15mg/kg/day),
Z = Pyrazinamide (1.5-2g/day).
Percentages are to be compared horizontally in relation to the total.

Table 2: Incidence and type of adverse reactions associated with antituberculosis drugs in relation to age.

Type of reaction	Number of pts (n=87)	0-19 (n=14)	20-39 (n=47)	40-59 (n=17)	Over 60 (n=9)
GIT	49	7 (50%)	29 (61.7%)	10 (58.8%)	3 (33.3%)
Dizziness	32	4 (28.6%)	18 (38.3%)	7 (41.2%)	3 (33.3%)
Burning sensation & numbness	28	4 (28.6%)	13 (27.7%)	7 (41.2%)	4 (44.4%)
Cutaneous	27	3 (21.4%)	17 (36.2%)	5 (29.4%)	2 (22.2%)
Eye	23	8 (57.1%)	12 (25.5%)	2 (11.8%)	1 (11.1%)
Joint	22	1 (7.1%)	14 (29.8%)	5 (29.4%)	2 (22.2%)
Drowsiness	16	3 (21.4%)	10 (21.3%)	2 (11.8%)	1 (11.1%)
Headache	15	1 (7.1%)	12 (25.5%)	1 (5.9%)	1 (11.1%)

Miscellaneous adverse effects include: flu-like symptoms (5 patients), menstrual disturbances (6 out of 36 females), muscle cramps, epistaxis, polyuria, tinnitus (2 patients each), loin pain, retention of urine, backache, bad taste in the mouth (one patient each).

Discussion

The high percentage of adverse reactions found in this study might reflect the interaction of several factors that include the disease itself, its severity, and the nutritional status, in addition to drugs. Treatment of the interviewed patients is not regular for reasons related to the patients and their compliance, and also related to irregularities in the supply of these drugs. Such irregular protocols not only promote secondary drug resistance, but also disturb the benefits of TB control (12,15).

After this study is completed, the strategy of directly observed short course therapy (DOTS) was implemented in Basrah with encouraging results. This strategy provides a good opportunity to establish a causal relationship between these adverse effects and antituberculosis drugs.

Studies of kazakov et al. (9) and Batian et al. (10) have reported high incidence of adverse effects (66.2% and 67.7% respectively). Both toxic and allergic components are thought responsible for the adverse effects to anti-TB drugs (7,9). The 67.7% rate was reduced to 17.5% by administration of immunomodulating agents e.g. T-activin and levamisole (10). Therefore, improving the nutritional status in our patients might contribute in lowering the incidence of adverse effects to these drugs.

Risk factors in developing these adverse effects include age of the patient, where the frequency has been shown to increase with increasing age (e.g. from 2.3% at below 19 years of age to 8.4% in those over 60 years (8,16). In our sample of patients, this is true for joint and peripheral neuropathic manifestations, while eye problems are more common in those below 20 years of age. Similarly, the above cited study (8) also showed females to have significantly higher reactions than males. In the present study, females tend to

have higher incidence of joint manifestations but lower cutaneous reactions. The lower cutaneous reactions could be related to males being exposed, because of their jobs to sunlight more than females.

In a study in Germany (7), the more severe adverse effects included hepatoxicity which occurred in 11% of the 519 patients studied. Pyrazinamide followed by INH showed the most severe adverse effects. This is much higher than the occurrence of hepatotoxic reactions following INH preventive therapy in the united states (11 patients out of more than 11000 patients) (16). In our study, the effect of anti-TB drugs on liver functions cannot be evaluated properly.

Two patients reported having jaundice previously. However, symptoms of hepatitis: the progressive onset of anorexia, nausea and vomiting might be classified as gastrointestinal manifestations. On the other hand, pyrazinamide was associated in the present study with high cutaneous adverse effects.

Race could be a risk factor in the development of adverse effects. A study in UK (8) showed that white patients had higher reaction rates than Pakistani and Indian patients.

The present work, although could not establish a causal relationship of adverse effects and various anti-TB adverse effects, it represents the first published report on this subject in Basrah in order to be followed in the future. It is useful to suggest, though difficult to implement at the present time, that every patient before receiving anti-TB drugs should have his serum level of aspartate aminotransferase and serum bilirubin, serum uric acid, and renal function measured. This is in addition to complete blood picture and eye examination

(opthalmoscopy, finger perimetry and colour discrimination) (14). DOTS strategy can be utilised to follow up the adverse effects according to a well-prepared form to be filled during patient visits to receive his drugs.

References:

1. Darbyshire JH. Tuberculosis: Old reasons for a new increase. BMJ 1995; 310 (6985): 954.
2. Wong CK. Compliance with tuberculosis treatment in Hualien aborigines. J Formos Med Assoc 1995; 94 Suppl, 1:534-8.
3. Racine-Perreaud E, Zellweger DP. Preventive antituberculosis chemotherapy in 250 patients of the antituberculosis outpatient clinic Lausanne. Schweiz Med Wochenschr 1994, 124 (17): 705-11.
4. Masuyama H, Shimada H, Kinoshita T et al. A study of ambulatory treatment for pulmonary tuberculosis in foreigners residing in Japan. Kekkaku 1993, 68(4): 301-2.
5. Caminero JA, Pavon JM, Rodriguez-de-Castro F et al. Evaluation of a directly observed six month-fully intermittent treatment regimen for tuberculosis in patients suspected of poor compliance. Thorax 1996; 51(11): 1130-3.
6. Decocq G, Compagnon M, Andrejak M et al. Adverse effects related to the use of antitubercular drugs in psychiatric centres. Therapie 1996; 51(5): 543-9.
7. Schaberg T, Rebban K, Lode H. Risk factors for side effects of isoniazid, rifampin and pyrazinamide in patients hospitalised for pulmonary tuberculosis. Eur Respir J 1996; 9(10): 2026-30.
8. Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. Tuber Lung Dis 1996; 77(1): 37-42.

9. Kazakov KS, Kalankhodzhaev AA, Kozarez MI, et al. Frequency and character of side effects of antitubercular drugs. Probl Tuberk. 1991; 12:28-31.

10. Batian AN, Abramorskaia AK, Batian ON. Prevention of side effects of specific chemotherapy in patients with pulmonary tuberculosis. Prbl Tuberk 199.

11. Migliori GB, Spanevello A, Ambrosetti M, Neri M. Surveillance of tuberculosis treatment prescription in Italy. The Varese TB study group. Monaldi Arch Chest Dis 1998; 53 (1): 37-42.

12. Ali J. Hepatotoxic effects of tuberculosis therapy. A practical approach to a tricky management problem. Postgrad Med 1996; 99(5): 217-20.

13. Patel AM, Mckeon J. Avoidance and management of adverse reactions to antituberculosis drugs. Drug Safety 1995; 12(1): 21-25.

14. WHO. Treatment of tuberculosis: guidelines for national programmes. Second edition 1997.

15. Nunn P, Felten M. Surveillance of resistance to antituberculosis drugs in developing countries. Tuber Lung Dis 1994; 5(3): 163.

16. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy. A 7 year survey from a public health tuberculosis clinic. JAMA Middle East 1999; 281: 1014-18.

ملخص :

ان التفاعلات الضارة المصاحبة للمعالجة المضادة للتدرن في البصرة لم تنشر لحد الآن. فالهدف الرئيس من الدراسة الحالية هو ليس حدوث هذه التفاعلات الضارة للادوية كل على حدة ، ولكن لتحديد الى أي مدى تكون الحوادث المهمة مثل التهاب الكبد واعتلال الاعصاب المحيطية ومشكلات العين شائعة الحدوث خلال معالجة التدرن.

فتمت مقابلة ٨٧ مريضاً مصاباً بالتدرن والذين اكملوا على الاقل مدة الشهرين الاولين من العلاج ، وذلك خلال زياراتهم الشهرية لمركز التدرن في البصرة ، وطلب ومنهم استعادة أي تفاعل ضار قد حدث لهم عند المقابلة بالاضافة الى ما يمكنهم من استعادة ما حدث اثناء معالجتهم السابقة .

وعند الأخذ بالتفاعلات الضارة الكبرى والصغرى المعروف حدوثها اثناء معالجة المريض ، فان نسبة الحدوث الكلية كانت عالية كما هو متوقع (١ر٨٥%) الا ان هذه النسبة العالية قد لا تتعلق بالادوية فقط بل يمكن ان تكون بسبب المرض او الحالة التغذوية أيضاً .

وجاءت مشكلات المعدة والامعاء والدوّام والمظاهر الجلدية في المقدمة ، وحدثت ملامح اعتلال الاعصاب المحيطية في (١ر٣٢%) ، ومشكلات العين في (٤ر٢٦%) ، وألم واخز في منطقة تحت الثدي الايسر في (٩ر١٤%) من المرضى . ويزداد حدوث الاحساس بالحرقة والخدر في الاطراف العليا والسفلى بازدياد العمر ، وكانت مشكلات العين وألم الصدر اكثر حدوثاً عند مَن اعمارهم دون (٢٠) سنة . أما المظاهر المفصلية فكانت اكثر في الاناث والآثار الضارة الجلدية اكثر في الذكور ، ووجد ان الملامح التي تشير الى خلل وظيفي شديد في الكبد نادرة في هذه الدراسة .

إن ستراتيجية المعالجة قصيرة الامد تحت الاشراف المباشر والتي بدأ تطبيقها في البصرة ستوفر فرصة جيدة لدراسة التأثيرات الضارة الخاصة بكل دواء من أدوية التدرن على حدة.

جمهورية العراق

MINISTRY OF HIGHER EDUCATION
& SCIENTIFIC RESEARCH
UNIVERSITY OF TIKRIT
COLLEGE OF MEDICINE
DEAN'S OFFICE

P O BOX 45 TIKRIT, IRAQ
FAX: + 964 – 21 – 825 293

وزارة التعليم العالي والبحث العلمي
جامعة تكريت
عمادة كلية الطب

Ref.:
Date: /

العدد: ٧ / ٥٦ / ٣٣٤٧
التاريخ: ٧ / ١٠ / ٢٠٠١

جامعة تكريت
عمادة كلية الطب
الصادرة
العدد/
٧ / ١٠ / ٢٠٠١

الى/ الدكتور عبد الله محمد جواد وحماد

م/ بحث

تحية طيبة:

نود أعلامكم بقبول البحث الموسوم

((Frequency and type of adverse reactions occuring after the use of antituberculosis drugs))

للنشر في المجلة الطبية لجامعة تكريت وسوف يظهر في المجلد السابع لسنة ٢٠٠١

مع التقدير

الأستاذ الدكتور
عبد النبي محمد علي السامرائي
رئيس التحرير
٢٠٠١/١٠/ ٧

نسخة منه الى
الصادرة