Adverse reactions among patients being treated for multi-drug resistant tuberculosis in Egypt from July 2006 to January 2009

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Abstract

Background: MDR-TB is regarded as a high-priority medical and public health issue, its treatment is frequently associated with prolonged illness and disability. Second-line TB drugs have a greater incidence of adverse reactions, which increases the morbidity as well as cost.

Objective: To assess adverse reactions of second-line TB drugs in patients treated for MDR-TB in Egypt from 1st of July 2006 to 1st of January 2009.

Methods: A retrospective study included 138 patients enrolled into the MDR-TB department at the Abbassia Chest Hospital during the study period. The patient was treated with 5 drugs according to results of the drug susceptibility test as follows: Any drug of the 1st line if not resistant, One of the injectable aminoglycosides (Kanamycin, Amikacin, Capreomycin or Streptomycin), Quinolones (Ofloxacin), Ethionamide, Cycloserine, and PAS. During the course of treatment, the patients were followed up by radiological and laboratory investigation and adverse reactions were determined by clinical and or laboratory criteria. Severity of adverse reactions was graded according to the National Tuberculosis Program.

Results: Majority of cases were cured (88.4%), one patient was lost to follow-up, 4 patients completed treatment and 7 patients died. There was a significant weight gain beginning from the 3rd month of treatment. There were statistically significant elevations of SGPT beginning from the 6th month, there were significant elevations of creatinine beginning from the 3rd month while there

Abbreviations: MDR-TB, multidrug resistant tuberculosis; DST, drug susceptibility test; NTP, National Tuberculosis Program; HIV, human immunodeficiency virus; DM, diabetes mellitus; PN, peripheral neuropathy; TSH, thyroid stimulating hormone; PAS, para- amino salicylic acid; IBS, irritable bowel syndrome.

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Introduction

Tuberculosis (TB) is a medical, social and economic disaster of immense magnitude that occurs all over the world [1]. The emergence of drug-resistant strains of Mycobacterium tuberculosis is a common consequence of inadequate therapeutic practice [2]. Strains of Mycobacterium tuberculosis that are resistant to both isoniazid and rifampicin with or without resistance to other drugs have been termed multidrug-resistant strains. Isoniazid and rifampicin are keystone drugs in the management of TB. While resistance to either isoniazid or rifampicin may be managed with other first-line drugs, multidrug-resistant TB (MDR-TB) demands treatment with second-line drugs that have limited sterilizing capacity, and are less effective and more toxic [3,4]. The treatment of MDR-TB is frequently associated with prolonged illness and disability. Second-line TB drugs have a greater incidence of adverse reactions, which increases the morbidity as well as cost [5]. Generally, these second-line agents must be administered more frequently than first-line agents, making compliance with medications more difficult. Many authorities have advocated that MDR-TB be regarded as a high-priority medical and public health issue and that these patients should be referred upon diagnosis to a specialized center for systematized and aggressive medical therapy [6]. The treatment of MDR-TB is a challenge which should be undertaken by experienced clinicians at centers equipped with reliable laboratory service for mycobacterial culture and in vitro sensitivity testing [1,4,7].

The aim of this study is to assess adverse reactions of second-line TB drugs in patients treated for MDR-TB in Egypt from 1st of July 2006 to 1st of January 2009.

Patients and methods

This was a retrospective study that included 138 patients enrolled into the MDR-TB department at the Abbassia Chest Hospital, Cairo, Egypt, between 1st July 2006 and 1st January 2009.

Patients were included in this study if they had active tuberculosis as evidenced by positive sputum for AFB and/or positive culture for M. tuberculosis in previously treated patients or new cases suspect to be MDR-TB, and had been documented as MDR-TB by the drug susceptibility test for 1st line anti-tuberculosis drugs done in the National Reference Laboratory. There were no exclusion criteria.

All cases were subjected to the following: Medical history with special attention to: whether primary or secondary resistance, special habits of medical importance, co-morbid diseases, clinical examination, initial laboratory investigation: serum potassium on admission then monthly while receiving an injectable agent, liver functions (SGPT), renal functions (Serum creatinine), HIV testing, and pregnancy test (for married women of childbearing age, and repeated if indicated). The patient was treated with 5 drugs according to results of the drug susceptibility test (DST) with dosage as follows: any drug of the 1st line if not resistant, one of the injectable amino-glycosides (kanamycin, amikacin, capreomycin or streptomycin), quinolones (ofloxacine), ethionamide, cycloserine, and Para amino-salicylic acid (PAS).

Follow up of patients

During the course of treatment, the patients were followed up by radiological and laboratory investigations such as: Sputum smear and culture; monthly until conversion then smear monthly and culture quarterly, Drug susceptibility test (DST) for patients who remains culture positive at the end of the intensive phase or after 8 months of treatment, Chest X-ray every 6 months or when indicated, Serum creatinine, monthly while receiving injectable drugs, serum potassium monthly while receiving injectable drugs, Liver enzymes; periodic monitoring (every 1–3 months), Thyroid stimulating hormone (TSH) every 6 months if receiving ethionamide or PAS and monthly for signs and symptoms of hypothyroidism, Audiometry, visual acuity and psychiatric disorders assessment, Hematological changes and allergic reactions when indicated.

Adverse reactions

Adverse reactions were determined by clinical and/or laboratory criteria as follows: Otoxicity: tinnitus, hearing loss confirmed by audiometry, presence of disequilibrium, Psychiatric disorders: presence of depression, anxiety, nightmares or psychotic symptoms, Gastrointestinal effects: nausea, vomiting, abdominal pain, haematemesis, melena, diarrhea, positive endoscopic findings. Arthralgia, arthritis: pain or swelling in
Adverse reactions among multi-drug resistant tuberculosis patients treated in Egypt

the joints, limitation of movement, Central nervous system (CNS): seizure activity of any type as reported by the patient or witnessed by another individual, Hepatitis: any elevation of serum transaminases in the presence of symptoms or elevation of serum transaminases to five times the normal values without any symptoms, Dermatologic: any skin change characterizing rash or bronzing, Peripheral neuropathy: numbness, weakness, tingling or burning in the extremities, peripheral neuropathy confirmed by electromyography, Nephrotoxicity: rise in the serum creatinine of 0.5 mg/dl from the baseline at any time during treatment, Hypothyroidism: any rise of serum thyroid stimulating hormone (TSH) > 10 mU/L.

Severity of adverse reactions was graded according to National Tuberculosis Program (NTP) as follows:

- Asymptomatic.
- Don’t affect daily activities.
- Limit daily activities.
- Life threatening condition [8]

Specific treatment for every adverse reaction; reduced dosage of suspected drug(s); and removal of drug(s) from the regimen.

Treatment outcome

Treatment outcome was defined according to WHO, 2013 as follows:

- Cured: Treatment completed as recommended by the national policy without evidence of failure, and three or more consecutive cultures taken > 30 days apart are negative after the intensive phase.
- Treatment completed: Treatment completed as recommended by the national policy without evidence of failure, but no record that three or more consecutive cultures taken > 30 days apart are negative after the intensive phase.
- Treatment failed: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of lack of conversion” by the end of the intensive phase, or bacteriological reversion” in the continuation phase after conversion to negative, or evidence of additional acquired resistance to fluoroquinolones, or adverse drug reactions.
- Died: A patient who dies for any reason during the course of treatment.
- Lost to follow-up: A patient whose treatment was interrupted for two consecutive months or more (this category was previously known as “defaulted”).
- Not evaluated: A patient for whom no treatment outcome is assigned (this includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown [9].

Data analysis

The collected data were statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) (V. 22.0) software version 22.0, IBM Corp., USA, 2013. Descriptive statistics were done for quantitative data as minimum, maximum and mean ± SD for quantitative parametric data, median and 1st and 3rd inter-quartile range for quantitative non-parametric data, while it was done for qualitative data as number and percentage. Inferential analyses were done for quantitative variables using the paired t-test in cases of two dependent groups with parametric data and Wilcoxon signed rank test in cases of two dependent groups with non-parametric data. In qualitative data, inferential analyses for independent variables were done using the Chi square test for differences between proportions. P value < 0.05 is considered significant.

Results

The study included 138 patients, the number of enrolled cases in the study according to year of admission were 27 in 2006, 42 in 2007 and 69 in 2008.

Patient characteristics regarding age, sex, special habits of medical importance and comorbid diseases are shown in Table 1.

Demographic, special habits of medical importance (Tobacco smoking – Drug addiction – alcohol consumption) and comorbid diseases of the studied patients. Data are presented either as mean ± SD or frequency (N) and percentage (%).

DM was the most frequent co-morbidity, which affected about one third of cases followed by chronic liver disease then chronic pulmonary disease (COPD) while the majority of cases in the studied group had no co-morbid diseases.

Regarding the type of resistance; 132 patients were secondary resistant “resistance in previously treated cases,” while 6 patients only were primary resistant “resistance in new cases”.

As regards the 2nd line drugs taken by the patients; all of them share one drug (Ofloxacin) and almost shared Ethionamide (137), Cycloserine (136), PAS (137) but they were different as regard to the injectable aminoglycosides. Kanamycin was the most frequent injectable drug (73), followed by amikacin (42) then Capreomycin (18) and Streptomycin was the least one (5 patients). Also, two drugs

| Table 1 | Demographic and special habits of medical importance in the studied cases. |
|---------|-----------------|----------------|
|         | Mean ± SD       | Range       |
| Age (years) | 37.6 ± 12.3 | 15.0–67.0 |
| Sex | | | % |
| Male | 99 | 71.7 | |
| Female | 39 | 28.3 | |
| Smoking | 38 | 27.5 | |
| Addiction | 4 | 2.9 | |
| Alcohol | 7 | 5.1 | |
| Co-morbidities | N | % | |
| DM | 48 | 34.8 | |
| Chronic liver diseases | 5 | 3.6 | |
| Chronic renal diseases | 1 | 0.7 | |
| Ischemic heart diseases | 2 | 1.4 | |
| Chronic pulmonary diseases | 4 | 2.9 | |
| HIV | 1 | 0.7 | |
| No co-morbidities | 77 | 55.9 | |
from 1st line were received, Ethambutol (25) and pyrazinamide (3 patients only). This is presented in Table 2.

At the end of treatment the majority of cases were cured after a full course of treatment (88.4%), while one patient was lost to follow-up, 4 patients completed treatment and 7 patients died. Results are described in Table 3.

There was a significant weight gain beginning from the 3rd month of treatment as shown in Fig. 1.

Regarding laboratory follow up tests for the drug effects; there were elevations of SGPT beginning from the 3rd month after treatment, but the elevations were statistically significant beginning from the 6th month as illustrated in Fig. 2.

Also there were significant elevations of creatinine beginning from the 3rd month of treatment as presented in Fig. 3, while there were no significant changes in serum potassium levels among the studied cases all through the follow up period as shown in Fig. 4.

As regards the adverse effects of the used drugs; gastrointestinal manifestations were the most frequent adverse reaction, followed by PN, hypokalemia, Ototoxicity, Hypothyroidism, Skin manifestations, Hepatotoxicity then nephrotoxicity. Hyponatremia and dizziness were the least encountered adverse reactions. This is illustrated in Fig. 5.

The severities of adverse reactions according to NTP program (presented in Table 4) were as follows:

1. Does not affect daily activity
2. Limits daily activity
3. Life threatening conditions.

The majority of adverse reactions did not affect daily activity of the patients.

Comparisons between cases with and without adverse reactions were done using the Chi square test as regards smoking being the most special habit of medical importance in the studied group and other special habits (drug addiction and alcohol consumption) were rare. In addition, comparisons were done using the Chi square test between cases with and without adverse reactions as regards DM being the most frequent comorbidity affected about one third of cases while other comorbidities were rare. As a result all patients shared 4 drugs in this study (Ofloxacin, Ethionamide, PAS and Cycloserine), Comparisons were done using the Chi square test between cases with and without adverse reactions as regards the rest of the anti-tuberculosis drugs (Kanamycin, Amikacin, Ethambutol, Capreomycin, Streptomycin, and Pyrazinamide). There was no significant relation between smoking, DM and used antituberculosis drugs with ototoxicity, hypokalemia, hepatotoxicity, hypothyroidism, gastrointestinal manifestation (including IBS), skin manifestation ($p > 0.05$); while there was a significant relation between smoking and peripheral neuropathy ($p = 0.005$).

Discussion

This retrospective study was to assess the adverse reactions among 138 patients treated for MDR-TB in the period from 1st of July 2006 till 1st of January 2009 at MDR-TB department in the Abbassia Chest Hospital. Results of this study verified that the number of MDR-TB patients increased annually which was 27 in 2006, 42 in 2007 and reached 69 in 2008 which
means that drug resistant tuberculosis is a rapidly increasing health problem in Egypt, which agrees with Prasad who stated that multi drug resistant tuberculosis (MDR-TB) is a growing hazard to human health worldwide [10]. In our study, the mean age was 37.6 years as in agreement with another previous Egyptian study [11]. This age represents the period of physical, mental, and occupational stress. The results also coincide with those found in Russia, South Africa and Iran [12–14]. As regards sex distribution, there was male predominance (99 cases) representing (71.7%) which agrees with some studies [11–14] but disagrees with others who stated that the females were more because they were more likely to be young with HIV positive [13]. In 2013; the male: female ratio of notified cases across all age groups was 1.6 globally [15]. This has been explained both by socio-cultural factors, thus run a greater risk of exposure to contagious cases [16], and by immunological differences between men and women that make males more susceptible than females to some infections [17]. As regards special habits, the most frequent special habit in this study was tobacco smoking that represented 27.5% of cases (38 patients), followed by Alcohol intake that comes second in 7 cases and represents 5.1% of the studied group and lastly drug addiction by 4 patients which represents 2.9% only. Many results of earlier studies are in agreement [11–19]. Thus smoking has been found to be associated with both risk of relapse of TB and TB mortality, moreover Passive smoking also increases the risk of TB [20]. The incidence of overall co-morbidity represents 54.1% (61 cases) and the most common co-morbidity was diabetes mellitus [34.8% of the studied patients (48 cases)], followed by liver disease; represented by 3.6% of patients (5 cases) and lastly chronic pulmonary disease

### Table 4 Overall severities of adverse reactions among the studied cases.

<table>
<thead>
<tr>
<th>Severity</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>5</td>
<td>3.6</td>
</tr>
<tr>
<td>Does not affect daily activity</td>
<td>120</td>
<td>87.0</td>
</tr>
<tr>
<td>Limits daily activity</td>
<td>10</td>
<td>7.2</td>
</tr>
<tr>
<td>Life threatening conditions</td>
<td>3</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Severity grade of adverse reactions are represented as frequency (N) and percentage (%).
(COPD); represented by 2.9% of patients (4 cases). This was contrary to other studies that reported that the most common comorbidity in their study was HIV positive followed by Diabetes and chronic hepatic and renal disease [18]. This may be due to the higher prevalence of HIV in the United Kingdom than in Egypt. In agreement with these results, Sobhy et al. reported that the frequency of diabetes mellitus was 15% of the studied patients (17 cases) compared to other co-morbidities in MDR-TB patients [11]. Lower percentage of diabetes mellitus was reported by Furin et al. who found comorbid conditions at MDR-TB diagnosis included diabetes (1.7%); HIV (1.7%) and alcoholism (3.3%) [21]. Another study indicated that poorly controlled diabetes confers a 2.9-fold increase in the risk of developing pulmonary tuberculosis; the risk associated with well-controlled diabetes was minimal [22]. The mechanism by which diabetes may be related in part to altered cytokine expression [23]. The study provided data that “Resistance in previously treated cases”, previously known as acquired or secondary resistance, was 95.7% (132 patients) and “resistance in new cases”, previously known as initial or primary resistance, was 4.3% (6 patients only). This might be due to genetic factors and/or factors related to inadherence to chemotherapy or inappropriate regimens. These results coincided with those reported by Elmahallawy and his coworkers [24]. In the present study, cured patients were 122 cases (88.4%), dead patients were 11 cases (8%), Lost to follow-up was only one case (0.7%) and treatment completed were 4 cases (2.9%). These results do not match with those of Isaakidis et al. who reported that (19.4%) were successfully treated, 20.9% died, and defaulted was 13.4% [25]. This difference might be due to that Isaakidis et al. study enrolled 67 patients only. On the other hand, the results matched with other studies [12,18,24]. As regards occurrence of adverse reactions, this study shows that the overall prevalence of adverse reactions is 96.4 which is much more than that of earlier studies [12,26]. The heterogeneity in the prevalence of adverse events across various studies might be related to several possible factors such as: differences in definitions of adverse events terminologies, patient-reported (subjective) or clinician-validated (objective), [27]. There was insignificant difference between males and females according to the frequency of drug complications. The most common adverse reaction in this study is gastrointestinal manifestations representing 58.7%, followed by peripheral polyneuritis 51.4%, hypokalemia 25.4%, IBS 23.9%, Otoxicity 18.8%, Hypothyroidism 9.4%, Skin manifestations 12.3%, 8.7%, Depression 3.6% and nephrotoxicity 2.9%, coinciding with some of the studies [11,24,28,29]. On the other hand these results do not coincide with those of Jacobs and Ross who reported that adverse events in descending order of frequency were hearing loss and vestibular disturbance; peripheral neuropathy; gastrointestinal disturbances, arthralgia [13]. Comparison between cases with and without gastrointestinal manifestation as regards smoking, DM and used anti-tuberculosis drugs showed that there was no significant difference. Regarding Hepatotoxicity, as adverse reaction, it represented 8.7% of the studied group (12 patients) that started to appear in the fifth month after starting treatment. Higher percentage (16.8%) had been reported by Shin et al. [12]. It is presumed that it is a side effect of prothionamide, PAS, pyrazinamide and quinolones, and the whole treatment was suspended till the recovery and resolution of symptoms. An alarming finding of our study was the highly frequent occurrence of peripheral neuropathy exceeding half the patients enrolled in the study (71 patients) representing 51.4% that started to appear early in the 3rd month requiring awareness and the timely attention of the physician because Baghaei et al. founded a highly significant association between neurologic side effects and mortality [14]. Besides it had significant relation with smoking. During monitoring laboratory investigation for electrolyte abnormalities, 25.4 had hypokalemia (serum potassium less than 3.5 mEq/L). Low serum potassium level started to be detected ranging from the 2nd month to the 5th month with average at the 3rd month of starting treatment which is likely multifactorial. This was due to association with a number of chronic diseases, such as tuberculosis, malnutrition, alcoholism, and diabetes mellitus. In addition, diarrhea and vomiting caused by antituberculous agents can contribute to GI electrolyte loss found with GI manifestations that were the most common adverse reactions. there was no significant difference between cases with and without hypokalemia as regards prescribed anti-tuberculosis drugs as this may be because the patients received another drugs rather than aminoglycosides that can cause hypokalemia, that does not affect daily activities [(31/35), 88.6%] and one patient only suffered from severe hypokalemia and was treated by potassium supplementation only. Ototoxicity, as an adverse reaction to MDR-TB treatment, in our study represented 18.8% in the studied group (26 cases). In comparison between cases with and without ototoxicity as regards smoking, DM and used anti-tuberculosis drugs, we found that there was no significant difference. Also, there was no significant relation between ototoxicity and used antituberculosis drugs. These results do not coincide with those of Kennedy et al. who found that eight patients (61.5%) developed ototoxicity from long-term aminoglycoside use [30], which matched with other studies [12,31]. In this study, nephrotoxicity frequency was 2.9% (4 patients) due to amino glycosides and started to appear in the 4th month after starting treatment. 3 patients experienced mild adverse reactions that did not need stoppage of any drug. Higher results were reported by Shin et al. (9.8%) [12]. Lower results were founded by Nathanson et al. (1.2%) [32]. Psychiatric disorders were minimal (defined as presence of depression, anxiety, nightmares or psychotic symptoms) and were also observed in 5 patients (3.6%) in the form of depression. One patient only suffered from moderate to severe depression and we initiated antidepressant and anti-psychotic therapy. Similar results were observed by Sagwa et al. (3.5%) [26]. Higher results had been reported by Nathanson et al. (3.4%) [32], and were similar to other studies [12,13]. Psychiatric disorders may be explained partly due to loss of confidence in the health services, effectiveness of treatment, long duration of the course and may be a direct effect of the received drugs. Psychosis has been reported as a side effect of CS and fluoroquinolones, and depression, while it has been associated with other drugs in the MDR-TB treatment regimen, and is primarily associated with CS [33]. Concerning hypothyroidism it developed in 13 cases representing 9.4% of studied patients. It appeared in average after 6 months of starting treatment and 8 patients of 13 required only prescription of thyroxin. Our results coincided with Furin et al. (10%) and a more recent and larger study, Bloss et al. (8%) [21,34]. As regards the mean interval from the initiation of therapy to the occurrence of an adverse effect among the studied cases, were during the first 7 months
after initiating treatment course. These results do not coincide with those who reported a shorter duration, early occurrence of adverse effects may be due to the extended exposure to aminoglycosides and capreomycin during or prior to MDR-TB treatment [35]. On the other hand, these results are in agreement with another, who reported that most adverse reactions occurred during the first 8 months of treatment [12].

In conclusion, the most common type of resistance was acquired resistance because of lack of adherence to treatment or inappropriate treatment. There was a relation between both tobacco smoking and drug addiction, and MDR TB. The most common co-morbidities associated with MDR TB were diabetes and chronic liver disease, Mild-to-Moderate adverse events are common during MDR-TB treatment. The most common side effect of anti TB drugs was GIT manifestations and the least complication was dizziness. Adverse reactions did not negatively impact treatment outcome among individuals who were adherent to treatment. To limit the resistance, anti-tuberculosis medication especially INH and rifampicin, they should not be prescribed for diseases other than tuberculosis and restricted in the private health sector. Continuous medical education should be given for medical and paramedical personnel and Health education for general populations.

**Conflict of interest**

There is no conflict of interest.

**References**


