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Pharmacovigilance system: primary care physicians' knowledge and attitudes, and reporting rate of adverse effects caused by anti-tuberculosis drugs

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Abstract

A cross-sectional study with a descriptive and an analytical component was conducted to describe and analyze the incidence of anti-tuberculosis adverse drug effects and its reporting rate at Hospital Parmenio Piñero CeSACs [Centros de Salud y Acción Comunitaria (Community Healthcare Centers)] between 2007 and 2014, as well as the knowledge and attitudes of primary care physicians regarding the pharmacovigilance system. The clinical and socio-demographic variables of patients diagnosed with tuberculosis were analyzed based on statistical records and the assessment of medical records. These records were compared with the reports made to the Program of the City of Buenos Aires. Primary care physicians were interviewed. Five hundred and sixty-two cases of tuberculosis were evaluated. Two hundred and forty-two adverse effects were documented in 109 patients (19%). Of these, 39% were hepatic, 36% were gastrointestinal, and 29% were hematological. Adverse effects were mild in 63% of the patients, moderate in 28% and severe in 8%. Treatment had to be discontinued in 7% of the cases. Seven cases (19%) required hospitalization and two patients passed away (0.36%). Being unemployed [OR: 3.26 (1.29-8.25)], being of Bolivian nationality [OR: 2.98 (1.32-3.28)] or having a comorbidity [OR: 3.06 (1.84-5.08)] was associated with a higher risk of exhibiting adverse effects. Twenty-nine percent of the physicians surveyed mentioned they had reported an adverse effect. The adverse effects found were not reported to the Tuberculosis Program. It is essential to handle the information associated with the adverse effects of tuberculostatic drugs more efficiently

Key words: Pharmacovigilance, Adverse drug reaction, Tuberculosis, Healthcare centers.

Introduction

Tuberculosis (TB) is an infectious disease with a predominant etiologic agent known as *Mycobacterium tuberculosis hominis* and it is spread from person to person mainly through the air. It is a major global health problem related to social issues, such as poverty and marginalization, which makes monitoring and eradication difficult[1].

In 2015, 10,600 new cases were reported across the country, which represents a rate of 22.3 cases per 100,000 inhabitants[2], making Argentina a medium-incidence country.

In the year 2015, according to data from the National Health Surveillance System, 1,254 new TB cases were diagnosed at the Autonomous City of Buenos Aires, of which 184 patients (14.7%) were assisted at Hospital P. Piñero.

The Programmatic Area of Hospital P. Piñero is in charge of 11 Community Healthcare Centers (CeSACs), and it is the largest area in the city of Buenos Aires responsible for a population of

300,000 people. There are poor neighborhoods and shantytowns in the area, where the population grew in number and in health issues in recent years.

TB treatment consists of an intensive initial phase and a continuation phase. The initial phase lasts between 2 and 3 months according to the category of the patient. The continuation phase lasts between 4 and 6 months. Well-managed chemotherapy has a significant impact on TB control, achieving high healing rates in patients with this disease. By itself, this measure can achieve an annual decrease of this endemic disease that ranges from 7% to 8%[3, 4].

At present, there are five basic or first-line drugs to treat TB: isoniazid (H), rifampicin (R), pyrazinamide (Z), streptomycin (S), and ethambutol (E)[5]. Even though these drugs are generally well tolerated, patients may have adverse effects. An adverse effect is a disorder that results from the intended use of a drug. It can be due to the toxicity of the drug, the interaction with other drugs and its metabolic effects. They are classified into mild, moderate and severe. The most common ones to tuberculostatics are abnormal liver function, gastrointestinal and skin reactions or hypersensivity reactions.

Adverse reactions or adverse effects to drugs are a common and frequently preventable cause of disease, hospitalization, disability and death. To prevent them and reduce them and to contribute to improve the health of patients, pharmacovigilance systems are implemented.

Pharmacovigilance is the set of methods, analyses and disciplines that enable, during the commercialization phase or widespread use of a drug, to detect adverse reactions and pharmacological or therapeutic effects that were not anticipated in previous product control and evaluation phases.

In Argentina, the Ministerio de Salud y Acción Social (Ministry of Health and Welfare) by means of Ruling N° 706/93 created the National Pharmacovigilance System in the year 1993[6]. Said system is based on the spontaneous, voluntary and confidential reporting of suspected adverse reactions and/or drug quality failures by health professionals when they are used during the post-commercialization phase by a population under natural conditions. Said system systematically collects, documents and evaluates this information aiming to early detect drug adverse reactions and interactions that were unknown until that moment, to detect increases in the frequency of known adverse reactions, to identify risk factors and to spread the information to improve drug prescribing[7].

In order to assess and manage the risks arising from the use of drugs, an efficient cooperation between the different individuals involved throughout the process is required. The lack of content in undergraduate programs regarding surveillance systems to detect health-related incidents, the lack of awareness among staff members and authorities at health facilities, and the lack of resources to implement these systems are some of the obstacles that hinder the generation of the quality information required to generate and assess the impact of health policies associated with pharmacovigilance. Training of health staff members on drug safety, means of notification, and the association between clinical experience, research and health policy are elements that work together towards an efficient operation of the pharmacovigilance systems[8].

With the purpose of cooperating to strengthen the pharmacovigilance system and to generate evidence on its current operation, the frequency of adverse effects to tuberculostatic drugs for the period 2007-2014 were analyzed, including the reporting rate, the association with the sociodemographic characteristics of patients, and the knowledge, attitudes and experience of physicians regarding pharmacovigilance.

Materials and Methods

We conducted a cross-sectional study based on the cases documented by the CeSACs' Statistical Systems; patients with a TB diagnosis who started treatment between January 2007 and December 2014 were screened. An assessment of the clinical variables, the medical history and the sociodemographic information in the medical records of the patients diagnosed with tuberculosis and treated at the CeSACs of the area was performed. The adverse effects found were classified into types and severity.

Physicians from the CeSACs were interviewed on their knowledge and usage of the pharmacovigilance system.

The inclusion criteria implemented were: patients treated for tuberculosis between 2007 and

2014 and a physician who, at the moment of the study, provided medical assistance at the CeSACs from the Programmatic Area of Hospital P. Piñero. The exclusion criteria were: patients with adverse effects to other drugs, documented in their medical records; patients who abandoned treatment; physicians who did not provide medical assistance; physicians who did not want to fill out the survey or physicians who took part in the Tuberculosis Program and at the same level simultaneously.

With the data from the medical records, we performed univariate and bivariate analyses of the endpoints of interest. For the univariate analysis we used the chi-square test and T-tests.

For the association analyses between the proposed variables and the absence or existence of adverse effects, we used logistic regression models for the dichotomous results. The variables with $p > 0.05$ were included in the univariate analysis.

All the information was entered in a database designed for this investigation. We used SQL Server and STATA 11 statistical package (statistical software package created in 1985 and owned by "Statacorp", College Station, TX, USA) for the analysis.

Results

Eighty-one percent (562/694) of the medical records of patients diagnosed with TB were assessed in the period under study. These included 272 (48.4%) females and 290 (51.6%) males between the ages of 0 and 74 (mean: 19.2, SD: 13.8). The average age of those who had adverse effects was 21.1 years (SD: 14.6) and for those who did not have adverse effects it was 18.3 (SD:13.6). The employment status (only analyzed in patients over the age of 18) corresponding to 88 cases (32%) was informally employed, and 28 patients (10%) were unemployed; conversely, only 3 cases (1%) were documented as employed and 1 (0.4%) as a pensioner. In the rest of the cases (150, 55% of the patients over the age of 18), the employment status was not specified. In terms of the drugs used for the treatment, Isoniazid was used in 549 cases (98%), Rifampicin in 547 cases (97%), Pyrazinamide in 529 cases (94%) and Ethambutol in 350 cases (62%).

Two hundred and forty-two adverse effects were documented in 109 patients (19%). Of these, 42 (39%) had hepatic adverse effects, 39 had gastrointestinal adverse effects (36%), 32 had hematological adverse effects (29%) and 14 had dermatological adverse effects (13%), whereas 3 cases had ophthalmological adverse effects (3%) and there was 1 case of neurotoxicity, 1 case of ototoxicity, and another case of rheumatologic adverse effects (1% respectively). In 69 patients (63%), the adverse effects were classified as mild, in 31 patients (28%) as moderate and in 9 cases (8%) as severe. The cases documented as severe exhibited a combination of hepatic, gastrointestinal and dermatological adverse effects.

The average age of the patients who were affected was 24.6 years. (See Table 1). Out of all the patients included, 83 (15%) had comorbidities. Of these, 23 (28%) were conditions associated with the consumption of substances (multiple substance use, alcohol, crack, marihuana), 8 patients (10%) had obesity and diabetes respectively, 7 cases (8%) had hepatopathy and another 7 hypothyroidism, 5 cases (6%) were HIV+ and another 5 had Chagas disease, 4 patients (5%) had asthma, 3 (4%) had hypertension and another 3 had anemia, 2 (2%) had pneumonia and another 2 had renal failure.

In 37 cases (7%), treatment had to be discontinued due to an adverse effect, after which 18 of these cases (49%) successfully completed the treatment, 16 abandoned the treatment (43%) and in 3 cases (8%) none of these outcomes could be assessed.

For the bivariate analysis, we selected the variables with $p < 0.05$ in the univariate analysis. Being informally employed for the total population of the sample [OR: 2.10 (1.25-3.53)], or having another type of job for the total population of the sample [OR: 0.17 (0.21- 0.96)], being unemployed for individuals over the age of 18 [3.26 (1.29- 8.25)], being informally employed for individuals over the age of 18 [3.05 (1.60- 5.90)], being of Bolivian nationality [OR: 2.98 (1.32- 3.28)] and having a comorbidity [OR: 3.06 (1.84- 5.08)] were statistically associated with a higher risk of exhibiting adverse effects. On the other hand, there were no reports of adverse effects associated with the use of tuberculostatic drugs neither at Hospital Piñero nor in the Tuberculosis Program of the City of Buenos Aires during the period under study.

With regard to the main specialties surveyed, 37% (28) were general practitioners, 32% (24) were pediatricians and 21% (16) were gynecologists. Eighty-two percent (28) reported having assisted

TABLE 1. Characteristics of the sample classified by the presence or absence of adverse effects, Programmatic Area of Hospital P. Piñero. 2007-2014

Variable	Total = 562	Exhibited AEs	Did not exhibit AEs	p value
Mean age (years) (SD)	19.2 (13.8)	21.1 (14.6)	18.3 (13.6)	0.71
Gender (N, %)				0.07
Males	290 (52%)	48 (44%)	242 (53.4%)	
Females	272 (48%)	61 (56%)	211 (46.6%)	
Education level > 18y (N, %)				0.06
Never attended	4 (1.5%)	2 (3.57%)	2 (0.9%)	
Complete elementary school	30 (11%)	8 (14.3%)	22 (10.1%)	
Incomplete elementary school	12 (4.4%)	4 (7.1%)	8 (3.7%)	
Complete high school	30 (11%)	10 (17.9%)	20 (9.2%)	
Incomplete high school	27 (9.9%)	8 (14.3%)	19 (8.8%)	
Complete or incomplete university studies	5 (1.84%)	4 (1.84%)	0%	
Non-specified	165 (60.4%)	24 (42.9%)	141 (65%)	
Total employment status				0.002
Employed	3 (0.6%)	0 (0%)	3 (0.7%)	
Unemployed	29 (5.1%)	9 (8.3%)	20 (4.4%)	
Informally employed	91 (16.2%)	29 (26.6%)	62 (13.7%)	
Retired/pensioner	1 (0.2%)	0 (0%)	1 (0.2%)	
Others	97 (17.3%)	9 (8.3%)	88 (19.4%)	
Non-specified	341 (60.7%)	62 (56.9%)	279 (61.6%)	
Nationality (N, %)				0.02
Argentina	312 (56%)	50 (45.9%)	262 (57.8%)	
Bolivia	165 (29%)	47 (43.1%)	118 (26.1%)	
Paraguay	6 (1%)	2 (1.8%)	4 (0.9%)	
Peru	8 (1%)	1 (0.9%)	7 (1.6%)	
Uruguay	1 (0%)	0 (0%)	1 (0.2%)	
Others	1 (0%)	0 (0%)	1 (0.2%)	
Non-specified	69 (12%)	9 (8.2%)	60 (13.3%)	
Comorbidity (N, %)				
Yes	83 (15%)	31 (28.4%)	52 (11.5%)	0.00
No	479 (85%)	78 (71.6%)	401 (88.5%)	
Treatment (N, %)				0.28
4 drugs	341 (60.7%)	71(65.1%)	270 (59.6%)	
Other	221 (39.3%)	38 (34.9%)	183 (40.4%)	
Deceased (N, %)				0.053
Yes	2 (0.4%)	1 (0.92%)	1 (0.22%)	
No	541 (96.2%)	108 (99%)	433 (95.6%)	
S/D	19 (3.4%)	0 (0%)	19 (4.1%)	

Source: own research based on data extracted from medical records

a patient with adverse effects caused by anti-TB drugs, hepatotoxicity and gastric intolerance being the most common ones identified. However, 41% considered that adverse effects to said drugs were uncommon (with an incidence between 0.1 and 1%. Rifampicin and isoniazid were the 2 most toxic tuberculostatic drugs identified. Fifty percent of the physicians did not make a report when they identified a potential adverse effect to the drugs.

Sixty-one percent (46) of the physicians knew about the pharmacovigilance system; however, in spite of knowing about it, only 8% (6) stated they had received any kind of training about it. With reference to the means of notification, 21% (16) said they knew them, but when they were asked to list them, most of them (38%) did not recall any. As to the knowledge about the form used to report adverse effects, only 37% (28) said they knew about it, but just 29% (22) stated they had ever used it.

Regarding the characteristics of the reports, 18% (14) considered them voluntary, whereas 82% (62) considered them compulsory and only 39% (30) considered them confidential. Thirty-two percent (24) thought patients could make reports, whereas 13% (10) considered only physicians could make the reports. With regard to the severity of the adverse effects that should be reported, 13% (10) will only report severe adverse effects and 16% (12) would only do it if the adverse effect was confirmed as such and not in potential cases.

Discussion

The assessment of medical records showed a similar distribution between males and females and an average age corresponding to young adults. It should be noted that more than half of the patients, 300 in total, were under the age of 18 at the beginning of the treatment. The bivariate analysis showed an association between adverse effects and variables such as "nationality", "employment status", "comorbidity" and CeSAC where the treatment was performed. It should be noted that the Bolivian nationality was statistically associated with having adverse effects to antituberculosis drugs. This association poses some questions: Is genetics involved in this association (e.g. slow acetylators) or are the living conditions of this subgroup (such as food, housing, hygiene) more unfavorable than the rest? The fact that in our sample many Argentine patients had Bolivian parents may rather mean that more unfavorable living conditions in the first generation of immigrants can lead to a higher rate and severity of adverse effects. A study conducted in Argentina with patients from Hospital Muñiz showed that the ethnicity of patients may be considered a risk factor in the development of isoniazid-induced hepatotoxicity[9]. A more detailed assessment of these factors that included other effects and other drugs may contribute to answer this question. On the other hand, having a comorbidity was also statistically associated with having adverse effects, which prompts a future specific analysis of each comorbidity and its association with a particular profile of adverse effects.

Seventy-five percent of the patients completed the treatment and only 17% of the cases abandoned it, whereas the other 8% is comprised of cases in which none of these outcomes could be assessed, whether it was because the patient was referred to continue the treatment at another healthcare center or because his/her record was incomplete[10] (Cáceres, 2008). This success rate, over 75%, exceeds national and international standards in the fight against TB, and it enables to assume that the level of quality of the social services provided by local healthcare centers was very high, given the great difficulties there usually are to maintain adherence to the treatment during the extended periods of time it requires. Nonetheless, it should also be noted that after suffering from a moderate or severe adverse effect, which requires the discontinuation of treatment, less than half of the cases (48%) managed to complete it based on the records; therefore, we can deduce that, should there be adverse effects, they would significantly deteriorate adherence to the treatment and the likelihood of completing it. This suggests that the efficient management, as well as proper information, of adverse effects to tuberculostatic drugs, such as the information that a robust pharmacovigilance system can provide, is essential for the outcome of both treatment and disease. On the other hand, during the study period there were no reports of adverse effects associated with the use of tuberculostatic drugs neither at Hospital Piñero nor in the Tuberculosis Program from the Government of the City of Buenos Aires. Taking into consideration that in the retrospective analysis we found 109 patients with adverse effects, and that 22 physicians assured they had made reports, the shortage of cases may be due to a mixture of a lack of notifications on the part of the local healthcare centers and an absence of assessment on the part of the main program. This should include the training of professionals to observe the various flowcharts recommended, and ongoing evaluations of the documentation and notification processes. Since this is a cross-sectional study, the directionality between the association of nationality or type of employment and the presence of adverse effects cannot be established, nor can the causality in these associations be assessed, which constitutes a limitation of the study.

The development of this protocol showed that a high number (82%) of physicians who assisted patients with TB documented an adverse effect associated with tuberculostatic drugs at least once. However, only 29% stated having used a formal means of notification: the notification sheet or form for drug adverse effects. Regardless of this, there is no record of said reports in the Tuberculosis Program from the Autonomous City of Buenos Aires.

It should be noted that very few of the physicians who completed the survey stated they had been trained on the subject; this fact is confirmed by the number of wrong answers given in the short test evaluating basic notions that was included in the survey. This is a key issue to review in future studies

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