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Pharmacovigilance in tuberculosis: pilot experience of a Reference Center of Rio de Janeiro, Brazil

Farmacovigilância em tuberculose: experiência-piloto de um Centro de Referência do Rio de Janeiro, Brasil

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ABSTRACT

Introduction: Pharmacovigilance is a set of activities that aims to identify, evaluate, understand and prevent possible adverse events (AE) in the use of drugs through the early detection of safety related problems. **Objective:** To describe the experience of the pilot project of Pharmacovigilance in Tuberculosis carried out at the Professor Hélio Fraga Reference Center – ENSP/ Fiocruz, Brazil from July 2013 to February 2014. **Results:** We evaluated 15 reports where the main AE found were: Polyarthralgia (2); Peripheral neuropathy (1); Joint pain (5), one of these with insomnia; arthralgia (2); change in visual acuity (1); diarrhea (3); vomiting, headache, joint pain and nausea (1). The analyzed variables were: Severity, Non-serious, Adopted procedures and Suspicious drugs: Severity = eleven were clinically important and, among them, one was reported as persistent or significant disability. Non-severe = four notifications described. Proceedings adopted = four reports with interruption of the suspected drug; in four the dose was reduced and in seven the dosage was maintained. Suspected medicines = Levofloxacin was the most prescribed drug suspected of causing AE. **Conclusions:** The results showed that some drugs used in the treatment of resistant tuberculosis are more likely to cause AE. There is a need to adopt measures where medicines are the object of permanent attention.

KEYWORDS: Pharmacovigilance; Adverse Events; Notivisa

RESUMO

Introdução: Farmacovigilância é um conjunto de atividades que tem por objetivo identificar, avaliar, compreender e prevenir possíveis eventos adversos (EA) ao uso de medicamentos através da detecção precoce dos problemas de segurança relacionados a esses produtos. **Objetivo:** Descrever a experiência do projeto-piloto de Farmacovigilância em Tuberculose realizado no Centro de Referência Professor Hélio Fraga da Escola Nacional de Saúde Pública (ENSP) da Fundação Oswaldo Cruz (Fiocruz), no período de julho de 2013 a fevereiro de 2014. **Resultados:** Foram avaliadas 15 notificações e os principais EA encontrados foram: poliartralgia (dois); neuropatia periférica (um); dor articular (cinco), sendo um desses com insônia; artralgia (dois); alteração da acuidade visual (um); diarreia (três); vômitos, cefaleias, dor articular e náuseas (um). As variáveis analisadas foram: Gravidade, Não graves, Providências adotadas e Medicamentos suspeitos. Gravidade: 11 eram efeitos clinicamente importantes e, dentre estes, um foi notificado como incapacidade persistente ou significante; Não graves: quatro notificações descritas; Providências adotadas: quatro notificações com interrupção do medicamento suspeito e em quatro houve redução da dose e em sete houve manutenção da dose; Medicamentos suspeitos; o Levofloxacino foi o medicamento mais prescrito aos pacientes e suspeito de causar EA. **Conclusões:** Os resultados mostraram que alguns medicamentos utilizados no tratamento da tuberculose resistente são mais propensos de causarem EA. Existe a necessidade de adotar medidas para que os medicamentos sejam objetos de atenção permanente.

PALAVRAS-CHAVE: Farmacovigilância; Eventos Adversos; Notivisa

INTRODUCTION

The Brazilian Health Surveillance Agency (Anvisa) defines pharmacovigilance as the science and activities to identify, evaluate, understand and prevent adverse effects or any other problems related to medication[1].

Adverse drug reactions (ADRs) are defined by the World Health Organization (WHO) as any harmful or unintended response to a drug as a result of the intake of doses normally used in humans for prophylaxis, diagnosis, treatment of a disease or physiological function change[2].

Brazil ranks 20th among the countries with the highest tuberculosis (TB) burden. In 2015, 69,000 people were diagnosed with TB and 1,077 developed multidrug-resistant tuberculosis, the most severe form of the disease. Also, the 2014 incidence rate, according to the Epidemiological Bulletin of 2016, was 34.2 cases per 100,000 inhabitants. We expect to achieve the goal proposed by the WHO Global Strategy to end TB in 2035 by increasing the coverage of the Family Health Strategy, performing Directly Observed Treatment and gradually improving the indicators[3,4].

Because of the high number of TB cases over the years and the multiple drug use by patients, in 2013, the Brazilian Tuberculosis Control Program (PNCT) and Anvisa came up with a TB pharmacovigilance pilot project that aimed to increase the number of notifications of antituberculosis ADRs and to implement TB-specific pharmacovigilance in Brazil.

Three Reference Centers were chosen to participate in the pilot project. These health facilities are located in the Brazilian cities of Manaus, in the state of Amazonas, Belo Horizonte, in the state of Minas Gerais, and Rio de Janeiro, in the state of Rio de Janeiro. Among them, the Professor Helio Fraga Reference Center (CRPHF), founded in 1984 and located in the Curicica district, in Rio de Janeiro, aims to act on Sanitary Pulmonology, especially TB and other mycobacterioses.

The main objective of this pilot project was to increase the number notifications of adverse reactions to antituberculosis drugs and to implement TB-specific pharmacovigilance in Brazil so that this activity becomes routine in health services.

METHODS

This is a descriptive study performed at the Professor Helio Fraga Reference Center of the Oswaldo Cruz Foundation (Fiocruz) in Rio de Janeiro. Because it is a tertiary reference, CRPHF receives patients with multidrug-resistant tuberculosis (MDRTB), extensively drug-resistant tuberculosis (XDRTB), and other mycobacteriosis.

In July 2013, PNCT professionals, Tuberculosis Control Innovation Project (InCo-TB) consultants and Anvisa technicians performed a training session with the medical staff, nurses, pharmacists and pharmacy technicians of the CRPHF TB Pharmacovigilance Pilot Project[5].

At the time, they showed the Adverse Event Reporting Form (FNEA) for patients on TB drugs prepared according to the variables of the Health Surveillance Notification System (Notivisa) - a computerized system developed by Anvisa to receive incident notifications, adverse events (AE) and technical complaints (TC) - and the Adverse Reactions Reporting Guide for TB. They also presented the Notivisa and taught the workers how to register and notify AE in the system[6].

During the medical appointment, the doctor filled in a hard copy of the FNEA for patients on TB drugs reporting the patient adverse reaction. Later, this form was taken to the pharmacy service so that the adverse reaction could be notified to Notivisa at the appropriate time. Collection of adverse reactions (AR) began in October 2013 and ended in February 2014. Four pharmacy service professionals had access to Notivisa: two technicians with submitting permission (the notification could be submitted directly to the Brazilian Health Surveillance System - SNVS) and two technicians without it (the notification was received by the Notivisa manager of the institution for approval until it was submitted to the SNVS).

From October to December 2013 and, in January and February 2014, 512 and 228 patients took at least one of the six drugs suspected of causing AR, respectively.

The study protocol was analyzed and approved by the Research Ethics Committee of the Sergio Arouca Brazilian School of Public Health - Fiocruz of Rio de Janeiro, on October 5th, 2018, under opinion n. 2.943.979 and CAAE n. 98760818.7.0000.5240.

RESULTS

In the five-month review of this pilot project, 740 patients used at least one of the six drugs suspected of causing AR.

In total, 15 AE were notified during the project, nine from October to December 2013 and six from January to February 2014.

Of these, nine came from female and six from male patients between 18 and 64 years old; seven patients were white, four were brown and four were black. Of the 15 patients who reported AE, one was a smoker, one was diabetic, one had hyperthyroidism, and one had urinary incontinence.

The main AE described were: polyarthralgia (two); peripheral neuropathy (one); joint pain (five), one of them with insomnia; arthralgia (two); change in visual acuity (one); diarrhea (three); vomiting, headache, joint pain and nausea (one).

AE notifications were separated by the variables: Severity, Measures Taken, and Suspected Drugs (Chart).

Chart. Adverse reactions reported at Professor Hélio Fraga Reference Center (CRPHF).

Suspected drug(s)	Adverse Event	Severity	Measures taken
Levofloxacin 250 mg Levofloxacin 500 mg	Polyarthralgia	Clinically important effects	Maintenance of the drug dose and painkiller prescription
Ethambutol 400 mg	Peripheral neuropathy	Clinically important effects Persistent or significant disability	Interruption of the drug use
Levofloxacin 500 mg	Joint pain	Clinically important effects	Drug dose decrease
Pyrazinamide 500 mg Levofloxacin 500 mg	Polyarthralgia	Clinically important effects	Drug dose decrease (Levofloxacin) Maintenance of the drug dose (Pyrazinamide)
Levofloxacin 250 mg Levofloxacin 500 mg	Joint pain	Clinically important effects	Maintenance of the drug dose
Levofloxacin 500 mg	Joint pain	Clinically important effects	Maintenance of the drug dose
Levofloxacin 500 mg Levofloxacin 250 mg Pyrazinamide 500 mg Streptomycin 1 g	Vomiting Headache Joint pain Nausea	Non-severe	Maintenance of the drug dose
Levofloxacin 250 mg Levofloxacin 500 mg	Arthralgia	Clinically important effects	Maintenance of the drug dose
Ethambutol 400 mg	Change in visual acuity	Clinically important effects	Interruption of the drug use
Levofloxacin 500 mg	Joint pain	Non-severe	Drug dose decrease
Para-aminosalicylic acid 4 g	Diarrhea	Clinically important effects	Interruption of the drug use
Para-aminosalicylic acid 4 g	Diarrhea	Clinically important effects	Interruption of the drug use
Levofloxacin 500 mg Pyrazinamide 500 mg Terizidone 250 mg	Joint pain Joint pain Insomnia	Non-severe	Maintenance of the drug dose
Levofloxacin 250 mg Levofloxacin 500 mg	Arthralgia	Non-severe	Maintenance of the drug dose
Para-aminosalicylic acid 4 g	Diarrhea	Clinically important effects	Drug dose decrease

Source: Adverse Event Notification Forms (FNEA) of patients on antituberculosis drugs.

- Severity: 11 patients had clinically important effects and one of these was notified as a persistent or significant disability.
- Non-severe: four notifications were described.
- Measures Taken: four patients interrupted the use of the suspected drug; four decreased the dose and seven maintained it, one of which received a painkiller prescription.
- Suspected Drugs: among the antituberculosis and antimicrobial drugs suspected of causing AE, levofloxacin was the most prescribed.

AE were associated with seven antituberculosis and antimicrobial drugs regularly prescribed. Among these, levofloxacin was the most prescribed and the most severe AE was decreased muscle strength and gait change.

DISCUSSION

Although medication used to treat TB effectively fight the disease-causing microorganism, side effects can occur during its use, either by the active ingredient itself or by its metabolites[7]. These side effects may appear mildly and temporarily during treatment and follow-up clinical appointments and may lead patients to consider that it's not important to report them to their caregivers[7].

Among the studies performed outside Brazil, there is this work from October 2012, supported by the Global Fund Organization in Morocco, in Northern Africa, about the efforts to organize a national strategy to implement Pharmacovigilance in the Moroccan Tuberculosis Control Program. In this country, TB is also a public health problem, as its incidence was 83.5 cases per 105 thousand inhabitants in 2011. Cases of resistant TB represent 1.3%[8].

Although it is a study to show an efficient Pharmacovigilance model for sensitive tuberculosis in Morocco, it is important because it reports that the number of AR notifications and the list generated from these notifications after the implementation of the model increased. The most frequently reactions were: increased liver enzymes, cholestasis, jaundice, arthralgia, acne, lower extremity edema, itching, rash and vomiting.

The example in Morocco emphasizes the need for a Public Health Program that focuses on efficient drug management and pharmacovigilance, thus avoiding deaths[8].

In the city of Buenos Aires, Argentina, a study performed between 2007 and 2014 at the Parmenio Piñero Hospital for sensitive TB aimed to describe and analyze the frequency of adverse effects of antituberculosis drugs[9].

Of 562 TB cases, 109 (19%) had AR, with a total of 242 AE: 39% were hepatic, 36% gastrointestinal and in 7% of the cases the treatment had to be interrupted.

Another question raised regarded the lack of content about surveillance systems in academic education, in addition to the scarcity of resources to implement them. Although professionals know the Pharmacovigilance system (61%), few of them received training (8%) and only 29% used it to notify AE. The researchers considered that it raised difficulties to generate good information, which is important to evaluate Pharmacovigilance health policies[9].

In this study, although it is for special TB cases and the number of notifications during the five months period was small considering the monthly average of patients (165), our data provided important subsidies for TB Pharmacovigilance evaluation.

Of all the patients treated with the suspected drugs for special TB (740), from October 2013 to February 2014, 15 of them had drug-related AE. Regarding severity, 73% had clinically important effects and 27% had non-severe effects. Regarding the measures taken, in 27% of the cases the drug treatment was interrupted, in 27% the drug dose decreased and in 46% the drug dose was maintained due to the side effects.

Among the nine women and six men who had AE related to TB drugs, 46% were white, 27% brown, and 27% black.

Of the AE described, 33% had joint pain, 20% had diarrhea and 13% had polyarthralgia.

This result highlights the need to consolidate this AE notification practice and the involvement of the multidisciplinary team. Because of the simultaneous use of multiple drugs during treatment, that lasts from eighteen to twenty-four months in special cases and, eventually, the need for hospitalization, it is necessary to control, monitor and supervise the AE caused by TB drugs.

A recent study in Brazil on Pharmacovigilance as a risk management tool reinforces that drug surveillance helps identify the risks associated with drug use, so it is an extremely important tool for managing the risks associated with medications and, thus, increasing patient safety[10].

On December 10, 2018, in order to contribute to drug safety evaluation, Anvisa launched VigiMed, a system to notify AE of drugs and vaccines. VigiMed is an adapted version of the system used by WHO and the notifications registered in Brazil are sent to the worldwide system that is managed by this organization. Among VigiMed advantages, there is the fact that it provides more modern features to evaluate notifications by Pharmacovigilance, rescinds the requirement for a prior registration, and facilitates the dissemination and generation of information that can be useful for decision making[11,12].

Thus, AE records of vaccines and drugs will have to be performed by this system and no longer by Notivisa. Notivisa will still be used to register and process incident, TC, and AE notifications associated with the use of other products and services under health surveillance. In addition to Brazil, 120 countries use the same procedure[11].

Therefore, to monitor the use and AR notifications of TB drugs, we need to improve the quality of the management of the services where drugs are the object of permanent attention, avoiding prescription, dispensing and administration errors and irrational use, thus helping to prevent or decrease AE.

CONCLUSIONS

Pharmacovigilance is a widespread topic but, in reality, many places still have to put it into practice. Through the online platform for receiving notifications, Notivisa made a significant contribution as a tool for registering notifications related to health surveillance products. Furthermore, on December 10, 2018, in order to contribute to drug safety evaluation, Anvisa launched VigiMed, a system to notify AE of drugs and vaccines. However, even with this pilot project, Brazilian culture still needs to change a lot toward encouraging health professionals to include this practice in the routines of the institutions where they work. Even though the topic of AR is frequent, we found that knowing about the efficacy of a drug is not enough, we must elucidate the consequences of its use and the side effects that may occur[12].

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.