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Signal Management of Disproportionate Reporting in Moroccan Pharmacovigilance: The Lower Limb Edema Induced by Anti-Tuberculosis Drugs

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Abstract

Objective: To detect and validate new signals in Pharmacovigilance of a combined anti-TB drug ERIP-K4.

Methods: It was a prospective study (October 2012-December 2013), conducted in majority Moroccan TB Diagnosis Centers (MTDC). All TB patients admitted to these MTDC and presented ADRs were eligible for inclusion in the study during this period. Each ADR notified was handled by the WHO accountability method and sent to the international database (Vigibase). The detection of signals was based on 3 statistical methods measuring disproportionality of reporting of combined anti-TB form (ERIP-K4) induced ADRs: the information component (IC), the proportional reporting ratio (PRR), and the reporting odds ratio (ROR).

Results: 927 ADRs were reported during the study. The average age of patients was 40.7 ± 17.5 years with a sex ratio of 0.8. Adverse drug reactions of skin and appendages disorders predominated (24.2%), followed by ADRs of gastrointestinal system disorders (21%) and ADRs of liver and biliary system disorders (14.5%). From 11 signals, a new signal never described in our database: edema of the lower limbs which disproportionate scores (IC, PRR, ROR) were (2.03, 7.5, 7.9).

Conclusion: Edemas of the lower limbs are a potential signal in Pharmacovigilance requiring more investigations to argue well the relation of cause and effect and to find risk factors to manage and avoid these effects.

Keywords: Pharmacovigilance; Anti-tuberculosis drugs; Adverse drug reactions; Signals

Introduction

Tuberculosis (TB) is a major public health worldwide scourge. Clinicians that treat TB patients are familiar with these medications and their adverse reactions (ADRs) [1]. These ADRs are frequent because the treatment is long and patients taking multiple medications simultaneously. This increases the likelihood of adverse reactions, some of which are serious. A recent study showed that two-thirds of patients with resistant form of TB at least once stopped treatment temporarily or permanently following the occurrence of adverse effects [2]. These events may diminish public confidence in a structured health program and affect the adhesion of relevant patient for the success of a program [3,4]. Patients who do not properly adhere to their TB treatment pose a risk to themselves and to others, and the generation of TB resistance is a serious risk because the treatment is complex and exposes many serious ADRs.

In spite of public health programs (PHPs) are supported by the Ministry of health, the risk of occurrence of ADRs are important because all vulnerable population is concerned such as the young, the elderly, pregnant women and malnourished. In addition, health professionals and the public need more information on the potential benefits, the rationality of the use and risks of medications prescribed.

Tuberculosis in Morocco also remains a public health problem, with an average incidence of 83.5 cases per 10^5 inhabitants in 2014. Fortunately, the resistant forms of TB treatment do not exceed 1.3% of all cases [5]. Currently the WHO recommends for all countries to create or develop Pharmacovigilance (PV) in their health programs. Morocco is among the first countries that received Global Fund grants to strengthen the PV in AIDS and TB [5].

Since 2010, in Morocco, there is a combined form called ERIP-K4 on the market containing 4 anti-TB drugs (Ethambutol, Rifampicin, Isoniazid, Pyrazinamide) and whose Pharmacovigilance knowledge is still incomplete in a large Moroccan TB population. That is why our objective of this work was to detect and validate new signals of this combined anti-TB drug ERIP-K4.

Methods

Study design and setting

It was a prospective study (October 2012-December 2013), conducted in majority Moroccan TB Diagnosis Centers (MTDC) who are in charge of treating TB patients. These MTDC exist in all cities and receive about 27000 TB patients per year.

Study population

All TB patients admitted to these MTDC and presented ADRs were eligible for inclusion in the study during this period. TB patients who not presented ADRs were excluded of this study.

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Data collection

A broad national sensitization about TB PV was performed for all practitioners who treat TB patients, and by successive workshops a spontaneous reporting system for adverse effects was validated between the MTDC and the Moroccan Pharmacovigilance Centre (MPVC). Each notified ADR was treated by the WHO accountability method [6], which determines the relationship of cause and effect, all adverse events were sent to the international database (Vigibase) [7]. An electronic registry of adverse events has been established that serves as a tool to send responses to different notifiers and exchange information between the MPVC and them.

Analysis

The detection of signals was based on 3 statistical methods measuring disproportionality of reporting of combined anti-TB form (ERIP-K4) induced ADRs:

1. The information component (IC) [8] available in Uppsala Monitoring Center (UMC) VigiMine software, method of Bayesian Confidence Propagation Neural Network used by UMC for automatic generation of signals:

$$IC=Log_2(\text{Observed ADRs Probability}/\text{Expected ADRs Probability})$$

There is a potential signal when the value of IC is greater than 0. In other words, the probability of the observed ADRs is greater than the likelihood of expected ADRs. (IC_{025}: Information Component within a range of 95% confidence).

2. The proportional reporting ratio (PRR) [9]: statistical method used to detect ADRs in Moroccan PV database. This relative increase in the adverse event reporting for the medicinal product (P) is reflected in Table 1 based on the total number of individual cases contained in a PV database.

The PRR is computed as follows: PRR=(A/A+B)/(C/C+D). Signal if The PRR ≥ 2 and the number of individual cases greater or equal to 3.

3. The reporting odds ratio (ROR) [10]: statistical method used to detect ADRs in Moroccan PV database. ROR=AD/CB. Signal if the PRR>1 and the number of individual cases greater or equal to 3.

Results

Descriptive study: general information

The MPVC registered 927 ADRs from 600 TB patients during the study. The average age of patients was 40.7 ± 17.5 years with a sex ratio of 0.8. The ERIP-K4 was prescribed in the intensive phase of treatment (83.7%), followed by Riniazide (Rifampicin, Isoniazid) in maintenance treatment (10.1%). Accountability of cases according to the WHO method showed that 5% had a certain relationship of cause to effect, 25% had a probable relationship, and 70% had a possible relationship. About gravity, 140 of the cases were serious (23%) with 7 deaths (1.3%), 21 cases had a commitment prognosis (3.4%), 4 cases developed sequelae (0.6%), and 107 cases required hospitalization or prolongation of hospitalization (17.5%). The outcome was favorable in 47.2% of cases, 16.2% were healing, 35.2 were unknown, and 1.3% died.

	Event (R)	All other events	Total
Medicinal Product (P)	A	B	A+B
All other medicinal products	C	D	C+D
Total	A+C	B+D	N=A+B+C+D

Table 1: Contingency Table

The general criteria to run the PRR are as follows:
- The value A indicates the number of individual cases with the suspect medicinal product P involving an adverse event R.
- The value B indicates the number of individual cases related to the suspect medicinal product P, involving any other adverse events but R.
- The value C indicates the number of individual cases involving event R in relation to any other medicinal products but P.
- The value D indicates the number of individual cases involving any other adverse events but R and any other medicinal products but P.

Descriptive study: nature of ADRs (Table 2)

Adverse drug reactions of skin and appendages disorders predominated (24.2%) with pruritus as the most predominant symptom, followed by ADRs of gastrointestinal system disorders (21%) with epigastric pain and vomiting as the most predominant symptom and ADRs of liver and biliary system disorders (14.5%) with cytolytic hepatitis as the most predominant symptom.

Signals detection

1. The signal detection was focused on the cases related to combined anti-TB drug form (ERIP-K4) recorded in the international database VigiMine. We found 875 ADRs related to this combination; 268 of them were issued from Morocco (30.6%). 18 international signals have been generated; 11 of them were from Morocco (Table 3).

We were interested to a new signal never described in our database: edema of the lower limbs which Moroccan IC was 2.03.

2. The proportional reporting ratio (PRR) in moroccan PV database was 7.5.

3. We also calculated the reporting odds ratio (ROR) of these edemas in our database, which were 7.9.

Discussion

Among 927 ADRs collected during this period, a new signal has emerged never described in our database: 27 edemas of the lower limbs with the combined form ERIP-K4.

According to the European Medical Agency [11], the term signal in PV causes enormous ambiguity among health professionals. The use of statistical algorithms for the detection of PV signals, devoid of any clinical setting, amplifies this confusion. So it is better to use the term disproportionate reporting ratio instead of the signal. This requires more clinical investigation of the occurrence of the ADR in the patient. In other words the relationship of cause and effect between a drug and an adverse event cannot be established only in the context of the analysis of databases.

This agency stressed that there is currently no officially validated statistical method for the detection of PV signals. Only some considerations on the evaluation of the performance of different methods have been discussed [12,13].

Any potential signal must be validated by a didactic approach to become a true signal. We followed different steps to confirm this signal:

Data collection

We collected 27 edemas of the lower limbs in 12 months from different regions of Morocco following use of the ERIP-K4. The average age of these patients was 39.3 ± 17.3 years with no particular history, the sex ratio was 1.2. The median time to onset of these edemas was 20 days [1-90 days]. Hepatic and renal laboratory tests of patients were normal.

System Organ Class (Disorders)	Number of reports (%)	Predominant ADR
Skin and appendages disorders	145 (24.1)	Pruritus
Gastro-intestinal system disorders	126 (21)	Epigastric pain and vomiting
Liver and biliary system disorders	87 (14.5)	Cytolytic hepatitis
General disorders	86 (14.3)	Lower limb edema
Central and peripheral nervous system	46 (7.6)	Dizziness
Musculo-skeletal system disorders	36 (6)	Multiple arthralgia
Psychiatric disorders	20 (3.3)	Abnormal behaviour
Hearing and vestibular disorders	10 (1.6)	Deafness
Respiratory system disorders	10 (1.6)	Dyspnea
Metabolic disorders	9 (1.5)	Hyperuricemia
Platelet, bleeding and clotting disorders	6 (1)	Thrombocytopenia
Endocrine disorders	6 (1)	Amenorrhea
Vision disorders	5 (0.8)	Eye irritation
Heart rate and rhythm disorders	3 (0.5)	Tachycardia
White cell disorders	2 (0.3)	Neutropenia, eosinophilia,
Red blood cell disorders	1 (0.1)	lymphopenia
Urinary system disorders	1 (0.1)	Anemia
Reproductive disorders	1 (0.1)	Pyelonephritis
TOTAL	**600 (100)**	Galactorrhea

Table 2: Frequency of system organ classes involved in ADRs induced by anti-TB drugs.

Nature of Signal	International IC_{025}	Moroccan IC_{025}
Hepatitis*	3.69	0.12
Increase hepatic enzymes	2.85	2.79
Jaundice	2.68	1.25
Cholestatic hepatitis*	2.16	1
Acne	1.54	0.67
Arthralgia	1.54	2.54
Vomiting	1.33	0.76
Pruritus	1.14	1.78
Abdominal pain	0.60	0.33
Periperal neuropathy*	0.41	0.18
Peripheral edema	0.2	2,03

*Critical signal

Table 3: Moroccan signals with anti-TB combined form.

Relationship of cause to effect

Suspect drug ERIP-K4: ERIP-K4 is a combined anti-tuberculosis drug marketed in Morocco since 2010, containing four anti-tuberculosis drugs: Ethambutol (J04AK02): 300 mg; Rifampicin (J04AB02): 150 mg; Isoniazid (J04AC01): 75 mg and Pyrazinamide (J04AK01): 400 mg.

Summary of product characteristics and literature [14,15] specify that only Rifampicin used daily or intermittently rarely gives edema probably by immunoallergic mechanism.

Apart the active ingredients contained in the ERIP-K4, we studied drug's excipients which are: Cornstarch, Pregelatinized corn starch, Crospovidone, Povidone, Sodium lauryl sulfate, Magnesium stearate, Opadry.

We found that sodium lauryl sulfate (C12H25SO4Na) is an excipient with known effect because it may cause fluid retention and can explain this edema of lower limbs.

Study of accountability: accountability according to the French method: [16]

- Intrinsic accountability was doubtful because no pharmacological mechanism in the genesis of these edemas is known and nondrug etiologies have not been eliminated by other diagnostic tests well defined.

- Extrinsic accountability (B1): Effect not described according to the definitions of B2 or B3

Qualitative assessment: analysis of individual case safety reports (ICSRs)

The majority of these edemas occurred after taking the ERIP-K4 in the intensive phase, and declined after the transition to the maintenance phase with RINIAZIDE. It strengthens the relationship of cause and effect between the ERIP-K4 and this ADR.

- The Moroccan PV database doesn't recorded similar cases except these 27 edemas.

- The international PV database contained in addition to the Moroccan cases, 3 other cases: 2 cases in Thailand and one case in Togo.

- The FDA database mentioned 35 peripheral edemas with Rifampicin (0.53%), 22 with Isoniazid (0.28%), 12 with Pyrazinamide (0.34%) and specifies that PRR of edemas increases with combined forms of anti-TB drugs [17].

Quantitative assessment: scores of disproportionate reporting ratios

- The PRR of edema in Moroccan PV database was 7.5 (there are 7.5 times more edema of the lower limbs with ERIP-K4 than with other drugs in our database).

- The ROR of edema in Moroccan database was 7.9 (there are 7.9 times more edema of the lower limbs with ERIP-K4 than with other drugs in our database).

- The Moroccan IC of edema in the international database was 10 times higher than the international IC (2.03/0.2).

Information

We informed all Moroccan TB health practitioners from this potential signal and to sensitize their patients to declare any effect particularly fluid retention. Each case of edema must be investigated correctly to eliminate other causes of edema and sent to the National PV Center.

Validation by Technical Comity of Pharmacovigilance

The Technical Comity of PV has been assembled on July 2013 and decided some recommendations:

- Importance to examine patients with edemas because do not appear if there are not important.

- Diagnose these edemas and eliminate differential diagnosis.

- Achieve a minimum of investigations: electrocardiogram, albumin, coagulability tests (INR, factor V, prothrombin), liver enzymes, liver ultrasound, proteinuria, urine sediment, creatinine, serum protein, serum albumin, renal ultrasound, protidemia.

- Measures to be occurred if significant edema:

- Sodium and water restriction
- Increase sodium excretion: Diuretics
- Monitoring: weight, natriuresis of day

- Information of TB patients about this effect

- Active monitoring of these edemas

- Monitoring of changes in signals' scores (PRR, ROR, IC_{025})

- Achieve a pharmaco-epidemiological study to determine the risk factors for these edemas

- The comity concluded that this side effect may be due to:

- Medication: ERIP-K4 particularly Rifampicin by immunoallergic mechanism
- Excipient: sodium lauryl sulfate?
- Patients: genetic predisposition, malnutrition.

Conclusion

Edemas of the lower limbs are a potential signal in Pharmacovigilance requiring more clinical, biological and pharmaco-epidemiological investigations to argue well the relation of cause and effect, and to find risk factors to manage and avoid these effects.

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