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Evaluation Of Adverse Effects Of Antituberculosis In El-Idrissi Hospital, Kenitra, Morocco

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ABSTRACT : *The main obejective of the study is to evaluate the adverse effects of antituberculosis. The present prospective study was conducted from the 2nd of April of year 2012 to the 2nd of April of 2013 with the help of pneumo-phtisiologists in El-idrissi Hospital of Kenitra. It focuses on patients with adverse reactions to treatment with anti-TB.For a period of 12 months, among 515 patients treated against tuberculosis, an occurence of side effects was noticed for 45 cases with an incidence of 8.73%. The sex ratio was 1.36 for males, and the mean average was 37.59 ± 2.72 years.The majority of adverse events was observed in the liver and biliary tract (hepatic cytolysis, cholestasis ...) with a percentage of 27.03%, followed by drug reactions (itching, skin rash ...) with a percentage of 21.62%, and damage to the gastrointestinal system (vomiting, nausea, diarrhea. ...) with a percentage of 16, 22%.The evolution of the patients was positive in 34.8%, however, we observed 4.3% of deaths.The prevalence of adverse reactions to anti-TB remains abnormally high, especially those observed in the liver, in the biliary tract and in the gastrointestinal system.At First, better knowledge of the adverse effects associated with anti-TB, awareness and sensitization of the role of notification of these effects. And second, a closer collaboration between pharmacologists and clinicians concerned with drug control are crucial factors that will contribute in a better quantification and qualification of the adverse effects of anti-TB.*

KEYWORDS : *Drug, Adverse Effects, Anti-TB, Kenitra.*

I. INTRODUCTION

Tuberculosis represents a major public health issue on a global scale. In Africa, this pathology is one of the death-realated deseases [24]. According to WHO, 7 thousand million people are infected or affected by this pathology[1]. It is responsible for 8 million new cases each year, and for 2 million deaths around the world [2]. Tuberculosis, in all its forms, continues to plague the developing countries with 95% of these new cases [3].

In Morocco, the epidemiological data of 2012 report a cumulative total of 27 437 new tuberculosis cases, all forms combined [25]. Tuberculosis is an infectuous desease that became curable with a standardized strategy of treatment based on five major antibiotic drugs: isoniazid (INH), rifampin (RMP), pyrazinamide (PZA), ethambutol (EMB), and aminoglycoside streptomycin/ amikacin). Anti-TB treatment is often tolarated, however, some adverse effects(AE), sometimes serious, could occur. This imposes a temporary or definitive interruption of the treatment in question, which can be life-threatening to the patient. Therefore, it is necessary to take certain precautions and measures before prescribing the treatment, like the prescription of vitamin B6, and making ophthalmological and kidney function tests [26]. A close monitoring is required throughout the period of treatment.Adverse effects related to anti-tubercular agents are extreemly variable, involving different biological systems and requiring a multidisciplinary collaboration as to prevent and treat these effects.

Isoniazid is of an epatic toxicity, it can be responsible of neuropathies. Rifampicin is a strong enzyme inducer that can cause severe immunological reactions in case of a discontuous treatment. Pyrazinamide can sometimes have a dangerous hypertoxicity. Ethambutol can be responsible of a severe ocular toxicity. Finally, and as all aminoglycosides, the administration of streptomycin is potentially linked to renal and auditory toxicities which seemed to be less frequent and less serious compared to those induced by other aminoglycosides.

The objective of the present study is to evaluate adverse effects of antitubercular agents observed in Charif El-idrissi Hospital of Kenitra.

II. MATERIAL AND METHODS

II.1. study site : This prospective study covers one year period ranging between April 2012 and April 2013. The study was based on a systematic Collection of adverse effect cases of anti-tuberculosis drugs detected within pneumo-phtisiology department at Charif Elidrissi hospital in kenitra, and reported to the Poison Control and pharmacovigilance of Morocco (CAPM) a declaration form elaborated by (CAPM) and filled in by healthcare professional. The information collected regarding the patient, the treated pathology, therapeutic context, medicines and the precise description of side effects, as well as the seriousness and the patient vital prognosis evolution, are assessed according to the pharmacovigilance usual criteria: death, impairment of vital prognosis, hospitalization or extending of the existing hospitalization[27]. For each notification of pharmacovigilance, the causal Relationship between taking medications and adverse effects occurrence is assessed according to the updated French method of accountability. This method combines the chronological criteria, semiological criteria accompanied by a bibliographic score [4].

II.2. statistical method : Statistical analyses were concerned with the calculation of every studied variable frequencies in order to describe the case of TB adverse effects. We used the Chi-square test to detect the link that may exist between the studied variables, and to study the risk factors we calculate the relative risk.

III. RESULTS

III.1. Descriptive study : 515 admissions registered in pneumo-phtisiology department at hospital, 45 patients showed adverse effects of anti-tuberculosis, being an incidence of 8, 73%. Moreover, it should be noted that more than 42 % of the reported cases occur during winter period. Adverse effects appear within an average period of 25, 49 ± 7, 32, and the table 1 shows the main epidemiological characteristics of patients having shown anti-tuberculosis adverse effects medications.

Table 1: Characteristics of patients with anti-tuberculosis adverse affects

Variables	**Numbers**	**%**
Sex		
Males	26	57,8
Females	19	42,2
Total	45	100
Age		
[0-15[	2	4,3
[15-20[	3	6,5
[20-50[	25	54,3
[50-60[	8	17,4
≥ 60	3	7,5
Undetermined	4	8,89
Total	45	100
outcome		
Favourable	16	35,5
Death	2	4,4
Not yet recovered subjects	6	13,3
unknown	21	46,6
Total	45	100
Severity		
Critical	18	40,0
Serious	14	31,1
Banal	11	24,4
Undetermined	2	4,4
Total	45	100
Traitement		
ERIP-K4	38	84,4
RH 300	3	6,6
ERIP-K4 + Ceftriaxon +Ceftazidim	2	4,4
kanamycin+ethambutol+Pyrazinamid+ Vitamin B6	1	2,2
Kanamycine	1	2,2
Total	45	100

The average age of patients was 37, 59 ±2, 72 years old. The sex-ratio was 1, 37 in favour of male sex. Our results show that 57, 7% of patients aged between 20 and 50 years old, 4, 3 of them are children below 15 years.

The progress of the reported cases was positive in 34, 8%, with 4, 3% died due to taking anti-tuberculosis drugs (2 death cases).
According to the criteria of seriousness, 40% of cases were critical, 24, 4% banal and 31, 1% assessed as serious.

ERIP-K4 treatment consists of anti-tuberculosis drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) was prescribed for 87% of patients, isoniazid, rifampicin combination was prescribed in 6.5% of patients, while 4.3% received anti-tuberculosis in combination with beta-lactam antibiotics.

The spread of adverse effects according to the reached system is shown in the figure 1:

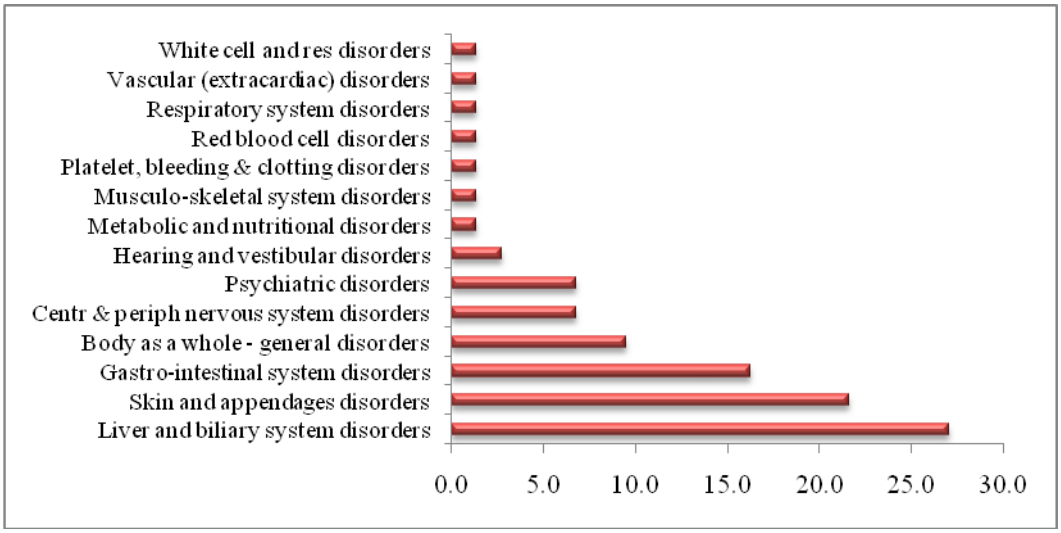

Figure 1: the spread of adverse effects according to the reached organ

These results reveal that the collected adverse effects were observed at the level of pneumo-phtisiology concerning essentially liver and biliary tract particularly cholestatic hepatitis and cytolysis (27.03%).
Toxidermias such as erythematous and vesicular rash was noted in 21.62%, and the gastrointestinal system manifested by haematemesis and vomiting was represented by 16.22% of the cases.The assessment of the causal link between the adverse occurrence and taking of drug according to the French method of accountability is shown in Table 2:

Table 2: Distribution of French accountability scores

		Semiological criteria			
		S1	S2	S3	Σ
Chronological Criteria	C1	C1S1-I1 (11)	C1S2-I2 (22)	C1S3-I4 (3)	36
	C2	C2S1-I2 (8)	C2S2-I3 (6)	C2S3-I5 (3)	17
	C3	C3S1-I4 (1)	C3S2-I5 (0)	C3S3-I6 (1)	2
Σ		20	28	7	55

Chronological Score: C3: Probable chronology, C2: Plausible chronology, C1: Doubtful chronology C0: incompatible Chronology
Semiological Score: S3: Probable semiology, S2: Plausible semioligy and S1: Doubtful semiology
Accountability score: I0: C0 ou S0, I1: C1S1, I2: C1S2/C2S1, I3: C2S2, I4: C1S3/C3S1, I5: C2S3/C3S2, I6: C3S3

According to the results shown above, 54, 5% of couples with drug- effect scored I2, in which accountability is accepted, 20 % scored I1, and thus the effect is doubtful to be the direct consequence of taking medication in question. Nevertheless, the likelihood was aunthenticated in 10,9 % (score I3), 7,27% (score I4), and 5,4% of couples scored I5 where the relation between drug intake and the occurrence of effect is very likely, 1,8% of couples scored I6. Indeed, among the couples with I5 and I6 scores, we mention Isoniazid / Ethambutol / pyrazinamide / rifampin -Hepatitis mixed Isoniazid / Ethambutol / Pyrazinamide / jaundice Rifampin and Isoniazid / Rifampin-cytolysis.

III.1. Analytic study

χ^2 and the relative risk were calculated in order to take out the relations between age bracket and side effect resulting from anti-tuberculosis.

Table 3: Relation between age range and the side effect reached systems

Age range	WHO ART	χ^2	P	RR	Y	IC	
[0-15[	Liver and biliary tracts	0.06	≤ 0.90	1.24	0.15	16.72	37.56
[0-15[	Nervous System	3.24	≤ 0.05*	5.58	0.77	1.11	13.17
[0-15[	Psychiatric	3.24	≤ 0.05*	5.58	0.77	1.11	13.17
[15-20[	Nervous System	8.76	≤ 0.01*	8.67	0.86	1.11	13.17
[15-20[	Gastro-intestinal System	2.4	≤ 0.20	2.89	0.61	7.19	24.23
[15-20[	Psychiatric	1.34	≤ 0.30	3.25	0.58	1.11	13.17
[20-50[	Gastro-intestinal System	0	≤ 0.90	1.03	0.02	7.19	24.23
[20-50[	Respiratory apparatus	3.92	≤ 0.05*	3.55	0.64	10.63	29.37
[20-50[	Liver and biliary tracts	0.28	≤ 0.90	0.81	-0.14	16.72	37.56
[20-50[	General	0.24	≤ 0.90	1.48	0.21	2.97	17.03
[20-50[	Gastro-intestinal System	0	≤ 0.90	1.03	0.02	7.19	24.23
[20-50[	Psychiatric	0.02	≤ 0.90	0.89	-0.06	1.11	13.17
[20-50[	Système musculo-skeletal	0.6	≤ 0.90	-	1	-1.35	4.21
[20-50[	Red blood cells troubles	0.6	≤ 0.90	-	1	-1.35	4.21
[20-50[	Platelets , blood coagulation,	0.6	≤ 0.90	-	1	-1.35	4.21
[20-50[	Cardiovascular system	0.6	≤ 0.90	-	1	-1.35	4.21
[20-50[	Metabolism and nutrition	0.6	≤ 0.90	-	1	-1.35	4.21
[20-50[	Respiratory apparatus	0.6	≤ 0.90	-	1	-1.35	4.21
[50-65[	Liver and biliary tracts	4.62	≤ 0.05*	2.33	0.57	16.72	37.56
[50-65[	General	0.36	≤ 0.50	1.6	0.26	2.97	17.03
[50-65[	Gastro-intestinal System	0.03	≤ 0.90	0.89	-0.07	7.19	24.23
[50-65[	Auditory -vestibular system	8.24	≤ 0.01*	infinite	1	-1.04	6.76
[50-65[	Red-White blood cells disorders	18.99	≤ 0.001*	infinite	1	-1.6	4.98
>65	Nervous System	11.75	≤ 0.001*	11	0.91	1.11	13.17
>65	Skin and appendages	2.39	≤ 0.20	2.75	0.64	10.63	29.37

χ2: chi-square, RR: Relative Risk, Y: Yule coefficient, 95% CI: confidence interval of 95% and p: level of significance (p> 0.05: no significant link, 0.01 <p ≤ 0.05: significant linkage (5%), 0.001 <p≤0,01: very significant link (1%), p≤0,001: Highly significant linkage) Odds: Odds Ratio * highly significant difference

These results show that age ranges were included in a significant, or very significant, highly significant manner in the appearance of side effects resulted from anti-tuberculosis. Also, the link of range age [0-15[is significantly linked with nervous system and psychiatric system; the same link exists between range age [20-50[and respiratory apparatus and between range age [50-65[and liver and biliary tracts.It is worth noting that there was a significant link between the ages [15-20[and the Nervous system, and the ages [50-65[and the auditory and vestibular system. Moreover, we were able to highlight a highly significant link between the age group [50-65[and Red-White blood cells disorders, and between the age of 65 or above and the Nervous system.

Likewise, it should be noted that the nervous system remains the most affected organ in patients aged below 15 and above 65 years.

III. DISCUSSION

We note that there is a considerable distinction demonstrated in axe 2; at the bottom of the axe, patients having developed serious side effects are particularly of female sex, and almost all age ranges were affected. At the top of the axis, it is observed that patients aged above 65 years have presented normal side effects with an unknown evolution.

If anti-tuberculosis treatment is generally well tolerated by patients, sometimes major adverse effects, however, can appear and impose a temporary or permanent stop of the drug in question and be life threatening.

Indeed, Isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin constitute the most important drugs in the pharmacopoeia of tuberculosis (TB) patients. Knowing the inherent side effects of these drugs is important for the best prescription of anti tuberculosis. The present study demonstrates that the incidence of anti-tuberculosis drug side effects at ELIDRISSI hospital is 8, 73%. This percentage is markedly lower than that found by Mishin et al, [5] where side effects were found in 16, 9% of patients. We notice a male predominance in our studied sample, which is congruent with the results published by M. Loukil 2011 [6]. Moreover, another study conducted by Yee et al [7] and Shakya et al [8] ascertained that the female sex is a risk factor for the occurrence of anti-tuberculosis drug side effects. Thus, women are considered to be more exposed to side effect risk due to their small size and light weight.Concerning the range age parameter, those between 20 and 50 represent the patients more susceptible to side effects with 54, 3 %. The average age was 37, 59 ±2, 72 years.

These results which are comparable to those found by Anupa et al [9] correspond to a period of maximal social activity favorable for the risk of TB infection transmission.Finally, we noted in the present study that the side effects observed within pneumo-phtisiology department are mainly concerned with hepatic adverse reactions(27,03%), followed by toxicodermatitis (21,62%), and Gastro-intestinal System (16,22%), which is consistent with a number of studies[14-25-26-27].It is worth noting that anti-tuberculosis medications might be quite offten responsible for side effects, and are extremely variable. They involve different biological systems and prompt muti-disciplinary collaboration in order to signal and cure these effects [10].

Hepatic side effects : Hepatic impairment exists in different forms. They can be cytolytic (9,6 % of cases). This form of hepatotoxity is observed in 10 to 20 % of patients under the effect of isoniazid only, but with very high percentage when associated with rifampicin[10]. Hepatic impairment can be cholestatic (4, 1% of cases) and can be attributed to rifampicin in association with hepatotoxic medicaments in which isoniazid [11], or under forms of fluminants (2,73% of cases); these are mortal hepatitis according to the literature. They were reported in the case of latent tuberculosis infections treatment in association with rifampicin-pyrazinamid a [12]. Finally, the mixed hepatic impairment (1,4% of cases) appear in since the first term treatment and regress at the end of therapy. It remains exceptionally fatal [13]. Many factors are predisposed to TB hepatic toxicity such as age, sex, pregnancy, mal-nutrition and hypoalbuminemia or patients having multifocal tuberculosis or alcoholic or viral sub-adjacent liver disease [14]. The high rate of transaminases before the beginning of therapy is also considered to be a risk factor [15]. The existence of chronic liver disease increase the risk of drug induced toxicity occurrence in patients. In fact, these patients carrying hepatitis B or C constitute a susceptible environment to get infected with such disease [16]. Hepatotoxicity risk is also frequent in HIV positive subjects compared to HIV negative ones [17].

Cutaneous side effects : Many cutaneous symptoms were signaled because of taking TB drugs. Among the toxicodetermatitis observed in our study, it is worth to mention erythema and vesicular rash which are known reactions and which regress at the termination of therapy. They are linked to taking isoniazid and pyrazinamid[10-11].

Gastric side effect : It appears in more than 16 % of cases in the form vomiting, hematemesis and abdominal pain. Based on literature, these effects are mainly linked to taking rifampicin and pyrazinamid [18-19-20].

V. CONCLUSION

TB drugs side effects are variable, frequent and sometimes, potentially, serious.

The occurrence of side effects prompting the role of anti-tuberculosis poses the problem of determining accountability vis-à-vis the observed adverse effects (hepatic, cutaneous and digestive impairment …) during treatment of tuberculosis. This depends on several parameters inherent in the adverse effects themselves and the administered drug; thus, we highlight the importance of the patient close observation which begins with the respect of medication dosage, along with knowing their side effects. Finally, taking measures aimed at educating the patient to make him involved in his treatment, and eventually his healing, contribute to preventing incidents of adverse effects resulting from TB drugs.

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