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Management of Drug Toxidermia: Experience of the Pharmacovigilance Service of Oran EHU

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ABSTRACT

Introduction: Cutaneous reactions are among the most frequently observed adverse effects after drug treatment. They are a common problem, almost daily for doctors and represent an important part of drug iatrogenic.

Aims: The objective of this work is to study the cases of cutaneous adverse reactions declared in the pharmacovigilance department of UHE Oran to identify the iatrogenic character of the rash.

Material and method: A prospective study was carried out over a period of 30 months from January 2013 to June 2015. It involved 61 notifications accompanied by reporting forms, from different departments of the EHU of Oran. We carried out an analysis of the declaration forms with estimation of the accountability.

Results and discussion: The results of our study show that the toxidermia account for 58% of the reported side effects. 61 patients were collected, the average age was 45 years, and there were a female predominance with a percentage of 54%. The dermatology department is the most reputable service with a rate of 41%. The most common clinical forms were: maculopapular exanthema (31.8%) and pruritus (22.9%). The most incriminated drugs were antibiotics (42.2%) and cytotoxics (22.7%). Accountability was plausible in 32.1% cases and likely in 27.6% of cases. Serious toxidermias account for 21% of reported cases with Stevens Johnson syndrome occurring in half of the reported cases and the class of antibiotics was the most incriminated in the occurrence of these reactions.

Conclusion: The results of our study have highlighted the importance of surveillance for adverse effects in a hospital setting, as well as the role of pharmacovigilance in the management of patients who have had side effects to the use of drugs.

Keywords: Drug toxicidermies, Pharmacovigilance, Drug accountability.

INTRODUTION

The drug is the essential component of the treatment of many diseases. Being an active product, whose consequences of its action on the body are never exclusively beneficial, it can be at the origin of undesirable effects, more or less severe, intense or frequent, which constitute a problem major public health Skin reactions are among the most common side effects after drug therapy, affecting 0.5% to 4% of hospitalized patients [1-5].

Nearly 90% of cutaneous adverse reactions are mild and clinically manifest as a small maculo-papular rash, accompanied by or not pruritus. However, there are severe forms that are life- threatening [6-10].

These last are fortunately rare. The objective of this work is to evaluate the incidence and frequency of drug toxidermias and to identify the iatrogenic nature of the rash of the reports recorded in the pharmacovigilance department of the UHE of Oran.

MATERIALS AND METHODS

This is a prospective study on the records of patients who developed drug-induced drug-related illness over a 30-month period from January 2013 to June 2015. It included 61 patients who were consultants and hospitalized in the various health services. ORAN EHU for undesirable dermatoses secondary to drug intake.

All cases recorded are reported on a reporting form, which includes patient information, information about the registrant, the drug (s) taken by the patient, and information about the adverse reaction. (Figure 1)

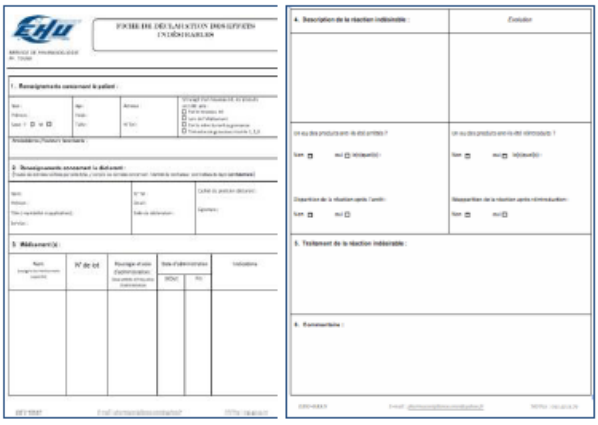

Figure 1: Pharmacovigilance declaration form.

Then the evaluation of the cause-and- effect relationship between the health products and the adverse effect by determining the score of the accountability, which is estimated according to the French method

RESULTS

61 notifications of drug-related toxiderma were recorded, including 22 in 2013, 22 in 2014 and 17 in the first half of 2015. This corresponds to 56.7% of the cases recorded in 2013, 51.1% in 2014 and 77, 2% in the first half of 2015.

The results obtained show that medicated skin disorders affect all ages. The average age of patients is 45.7 years (median 46 years), with a standard deviation of 16.4 years. The most represented age groups are those ranging from 40 to 69 years old with 35 patients (57.3% of cases) (Figure 2).

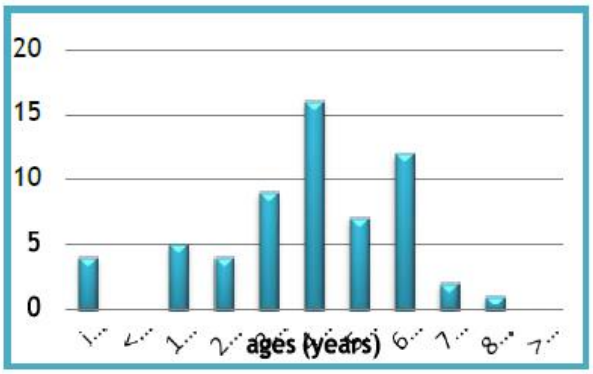

Figure 2: Distribution of cases by age group of patients.

A predominance of females was observed with a sex ratio 87.5% (Figure 3).

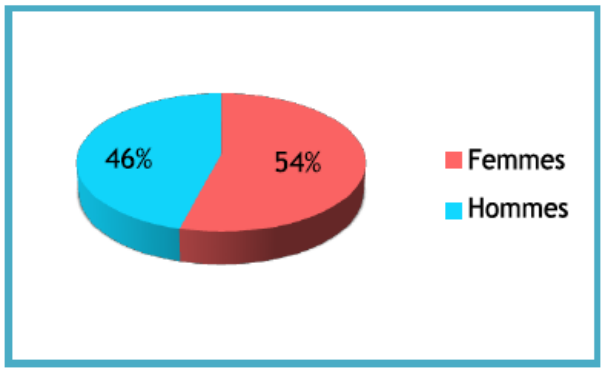

Figure 3: Distribution of cases by sex.

The recorded declarations are made mostly by the dermatology department (41%). Followed by the departments of hematology (21.3%), nephrology and the allograft unit (6.6%) (Figure 4).

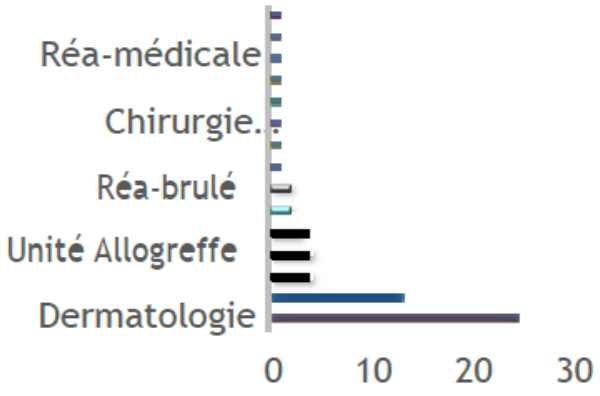

Figure 4: Distribution of reporting service.

Of the 61 drug-related drug-testing cases studied, 84 skin-

related adverse events were identified.

The most common skin manifestation is maculopapular erythema with 19 cases followed by pruritus 14 cases and generalized rash 8 notifications. The medicated skin disorders have a wide variety of clinical manifestations (Table 1).

Table 1: Recorded skin diseases.

Adverse effect	Number of cases
Maculopapular erythema	19
Pruritus	14
Generalized rash	8
Stevens - Johnson Syndrome	8
Erythematous plate	5
Skin rash	5
Diffuse erythema	3
Redness	3
Urticaria	3
Lyell Syndrome	3
Fixed pigmented erythema	2
PEAG	1
DRESS	1
Generalized erythroderma	1
Cutaneous necrosis at the injection site	1
Other skin adverse effects	7

Some skin reactions are grouped under the term "other skin adverse effects" several manifestations that are rare and nonspecific, for example: folliculitis, palpebral edema, oral erosion, squamous plaques, tingling, exacerbation of a skin infection etc.

The most involved drug classes were antibiotics (42.2%), followed by cytotoxics (22.7%), antiepileptic drugs (5.9%), and finally anti-gout drugs and heparin (2.9%) (Table 2).

Table 2: Number of drugs imputed by therapeutic class.

Drug classes	Number of drugs imputed	Percentage
Antibiotics	43	42,2%
Cytotoxics	23	22,7%
Antiepileptic drugs	6	5,9%
Anti-gout drugs	3	2,9%
Heparin	3	2,9%
Others	24	23,76%

According to the obtained results, the responsibility of the generic drugs in the occurrence of the drug reactions is of 53%. This percentage is superior to the original medicine which is of 47% (Figure 5).

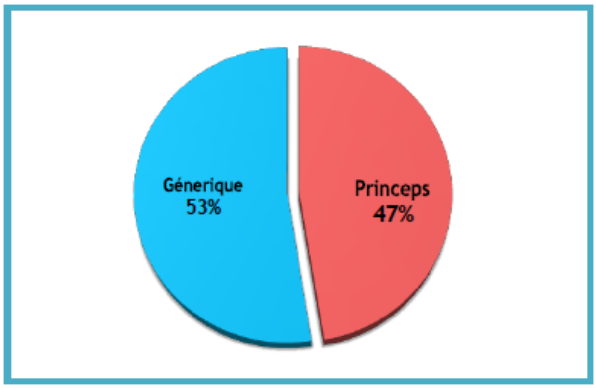

Figure 5: Distribution of imputed princeps / generic drugs.

The estimation of the intrinsic accountability of reported notifications indicated that in ¾ of the cases, the most frequently recorded chronological score is C2. The C3 chronological score is rather low (22.9%). The C0 chronological score is rare with a percentage of 2.9% of cases.

Regarding the semiology it was noticed that the most frequent semiological symptom is the S2 found in 57.4% of the cases.

The combination of the 2 scores leads to a low final intrinsic

accountability score that is estimated in 65.4% at I1 or I2 (Figure 6).

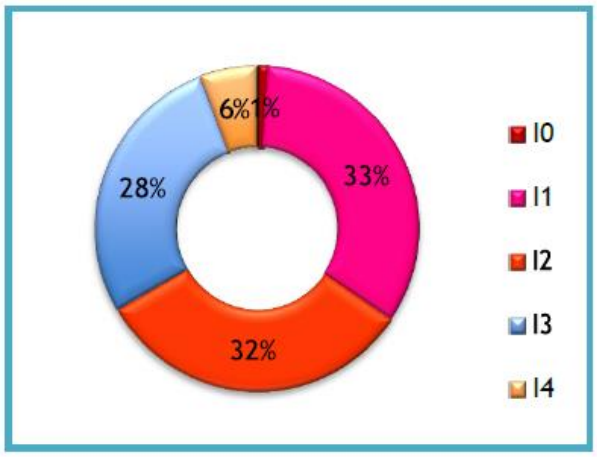

Figure 6: Distribution of the incriminated drugs according to their intrinsic accountability score.

DISCUSSION

The reported cutaneous adverse effects are generally well known and described effects; the majority of the drugs have received a B3 type of accountability (Figure 7).

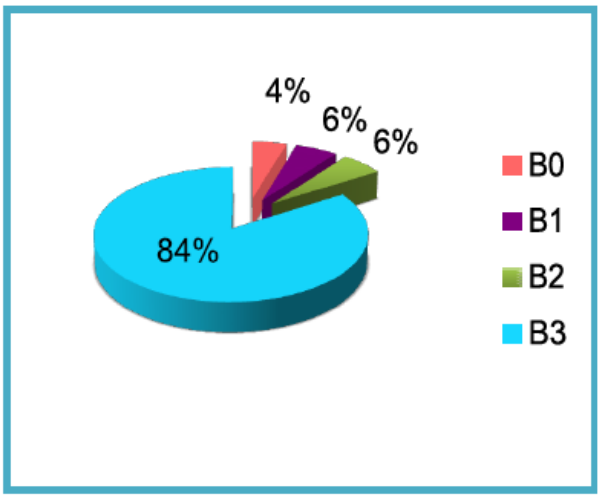

Figure 7: Distribution of incriminated drugs according to their extrinsic accountability score.

The results of this study reveal a female predominance, with a sex ratio of 87.5% comparable to the sex ratio observed in the retrospective study of Thiessard (82, 7%) is mainly explained by a higher consumption of drugs in elderly and female subjects but also by a different or decreased metabolism [2,5]. The study also confirms the existence of a great variability of the cutaneous medicinal effects, whether in terms of clinical manifestations or severity, as well as a great diversity of the drug classes whose implication in the occurrence of skin adverse effect was retained.

The prognosis of the medicated cutaneous attacks is good, the cure usually occurs without sequels. The incriminated drug classes listed in the study are often the same as in most literature studies, although with variations in the respective percentages according to the structure of the studies.

The drugs are ranked in descending order antibiotics (42.2%), followed by cytotoxic (22.7%), antiepileptic drugs (5.9%), and finally antigens and heparin (2.9%). In the Fiszenson-Albala study (4), the drug classes involved are primarily antibiotics (55.9%), 21% of which are due to amoxicillin, followed by sulphonylurea (12%) and chemotherapy molecules (10.5%).

It turns out from the results, as confirmed in the literature, that antibiotics are the drug class most likely to cause cutaneous side effects, but these are not the best-selling and most prescribed drugs. Thus, in the Algerian market, it is the drugs of the cardiovascular system that are the best- sellers (in quantities), followed by drugs from the digestive tract, metabolism and after antibiotics.

However, this overrepresentation of antibiotics and especially the class of cephalosporin which represents 44% in the study population may be explained by overconsumption of this class because of the increased prevalence of nosocomial infections and also because of the high number statements from the hematology department where patients are prone to infections (majorities are in a state of aplasia).

More than 79% of the reported toxidermias are benign compared to 90% described in the literature. According to Fiszenson [4], the most common types of toxicology are erythematous rashes (or maculopapular exanthemata) (40 to 60%) and urticaria (0 to 30% of notifications). However, in this study, maculopapular erythema was the first case of drug induced drug (31.1%) followed by pruritus with a percentage of 22.9%.

In the present study, the main recruitment services were the dermatology department (41%) considering the dermal expression of the affection and the hematology department (23%) given the use of cytotoxic molecules known by their adverse effects. cutaneous followed by the nephrology department and bone marrow allograft unit with a percentage

of 6.5%, this high proportion of reporting is due to our close collaboration with the nephrology department and the allograft unit in the context of therapeutic follow-up of renal transplant patients and allografted bone marrow. Fiszenson found a high incidence in the medical services and especially in the dermatology department (15%), resuscitation (10%) and gastrology (6%) [4]. The causality of drug toxicity was evaluated according to pharmacovigilance algorithms, the imputability was doubtful and plausible in 33.2% and 32.1% respectively, likely in 27.6% of cases, the drug liability was confirmed in 5.7% of the statements and the cause of the drug in the occurrence of a toxidermy was excluded in a single case. The novelty of drug-toxidermy pairs was as follows: 83.9% were well known, 5.7% not well known, 5.7% not described and 4.6% never described before. To know that our results are close to Thiessard results [5].

According to the results the responsibility of the generic drugs in the occurrence of the drug reactions is of 53% this percentage is higher than the original medicine which is of 47% that can be explained by the consumption of the generic drugs which did not stop increasing at to the detriment of princeps, from 21% in 2004 to 30% in 2010 [11-13]. The responsibility for generic drugs in the occurrence of the toxidermies must be still greater than 53% because at the beginning of the work in the pharmacovigilance unit the declaration of the drugs imputed in the reaction is done almost exclusively with the name of the originator and, in very rarely, the generic used is mentioned. This is due to many causes, in particular the doctor's ignorance of the need to declare the exact commercial name of the molecule and not the usual originator they are accustomed to each time, which led us to insist, mentioned the exact name of the drug and move to the patient's bed to check that. The issue of generics can nevertheless be important in dermato allergology where a reaction to the active ingredient is often the most common, but the role of excipients sometimes essential [3].

CONCLUSION

The prevalence of drug-related illnesses continues to increase with the advent of new molecules and in parallel with the increase in drug consumption and the aging of the population.

They are nowadays a frequent, almost daily problem for doctors and represent an important part of the iatrogenic medications, responsible for mortality, morbidity and poorly evaluated costs. Their diagnosis and management are difficult.

This difficulty is related to several factors; the variability of clinical manifestations, the complexity of physiopathological mechanisms that are far from being fully understood the limitation and lack of standardization of *in vivo* and *in vitro* diagnostic procedures.

In addition, the responsibility of the drugs in the occurrence of a toxidermia is not easy to establish because the pharmacovigilance algorithms are insufficient to be able to identify with certainty the drug(s) responsible for a toxidermia.

A better awareness of doctors, the very existence and the interest of the declaration of observations of cutaneous adverse drug reactions is necessary, not only for their patient, but also in a more general context for pharmacovigilance, in order to improve knowledge of cutaneous adverse effects and to revise some therapeutic recommendations.

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