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Risk Factors Linked to the Occurrence of Neurological Signs Following Poisoning by Cosmetic Products in Morocco (1981-2011)

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Abstract

Objectives: The objective of this study is to determine the risk factors associated with the onset of neurological disorders during poisoning by cosmetic products. **Methods:** This is a retrospective study of all cases of poisoning by industrial cosmetic products reported to the Poison and pharmacovigilance center of Morocco over a period of 30 years from

January 1981 to the end of December 2011. **Results:** During the study period, 431 cases were reported with a sex ratio (F/M=1.66). Hair products and skin products are the most incriminated with 48% and 32.5% respectively. Clinical signs are described in 51% of cases with a clear predominance of gastrointestinal system disorders (39% of cases), followed by nervous system signs (17.8% of cases). Oral administration was the most common route with 84% of cases. Logistic regression analysis allows us to qualify poisoning by skin lightening creams as the only predictive factor strongly associated with the occurrence of neurological signs (p = 0.011). **Conclusions:** The establishment of very precise regulations with clarity concerning the law governing cosmetic products will certainly ensure better orientation of care in the event of a declaration of poisoning.

Keywords: Retrospective study; Cosmetic; poisoning; lightening creams; neurological signs; Poison and pharmacovigilance center of Morocco

Introduction

Intended to provide well-being and aesthetics, cosmetic products are widely used by both women and men, and at all ages. Cosmetics placed on the market must not harm human health when applied under normal conditions. However, many substances in cosmetics have become a source of concern for consumers because they may cause allergic reactions. Moreover, some substances described as highly toxic, whose use is restricted to certain cosmetic products, can cause serious or even fatal poisoning in the event of acute poisoning by mouth or inhalation following a handling error.

In the United States, no fewer than 5,144 consumer complaints concerning cosmetic products were recorded between 2004 and 2016. Among these ranges, baby products, skin cleansers, hair dyes and other hair care products were the subject of the greatest number of complaints following their "serious effects" on health (Kwa et al., 2017).

In Morocco, the absence of a specific legal framework that regulates cosmetic products has allowed the proliferation of a very profitable informal market (smuggling, counterfeiting.). Counterfeit products manufactured in Morocco or imported from Asia are sold at symbolic prices and may contain compounds that are banned or controversial internationally such as parabens, hydroquinone, formaldehyde, ether glycol, aluminum, paraphenylenediamine, pesticides, corticosteroids. The absence of data on the composition of these products makes treatment in the event of poisoning very hazardous.

The objective of this work is to determine the risk factors related to the appearance of neurological signs following poisoning by cosmetic products.

Methods

This is a retrospective study of all cases of poisoning by cosmetic products (from which mineral and plant products were excluded) reported to the Poison and pharmacovigilance center of Morocco over a period of 30 years from January 1981 to the end of December 2011. This concerns 431 cases.

All the data from the poisoning declaration forms, received from the health structures of the different Moroccan regions to the toxicovigilance unit on a regular basis, and from the medical files filled out following the telephone responses. The data was thus entered into a single database and then submitted for processing.

The statistical analysis was done using the Epi Info software version 3.2.2. It was based on analytical descriptive statistics which consisted of;

- -Identify the frequencies of the parameters studied,
- Study the relationship between two categorical qualitative variables using the Chi-square test ($\chi 2$),
- a logistic regression analysis to predict the effect of several explanatory variables on the emergence of the dependent variable.

Results

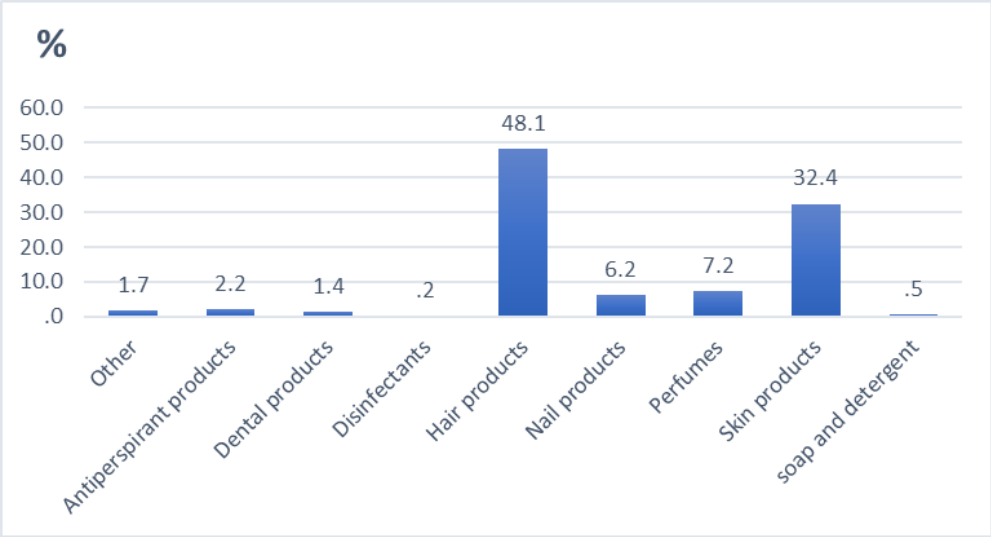

Figure 1: Distribution of cases according to the cosmetic products involved

The cosmetic products involved in these exposures are very varied, they have been broken down according to their use (figure 1). Hair and skin products are involved in 335 cases with 200 and 135 cases respectively. They are followed by perfumes and nail products with 30 and 26 cases respectively.

The sex ratio is in favor of females (F/M=1.66), whose route of exposure is oral in 88% of cases (table 1).

Table 1: Distribution of cases according to route of administration and sex of poisoned persons

Variables studied	**number of cases (%)**
Route of intoxication:	
Oral	363(84)
Cutaneous	27(6,3)
inhalation	15(3,5)
Ocular	5(1)
Rectal	1(0,2)
Unspecified	20(5)
Total	431
Sex:	
Female	260(60,3)
Male	157(36,4)
Unspecified	14(3,3)
Total	431

Clinical signs are described in 51% of cases for which the symptomatology is known (210/410 cases), with a clear predominance of gastrointestinal system disorders (39% of cases), followed by nervous system signs (17.8% of cases) (table 2).

Table 2: Distribution of cases according to clinical symptoms

Variables studied	**Number of cases (%)**
Symptomatology	410((51)
Clinical signs	210 (49)
➢ Gastrointestinal system disorders	159(37)
➢ Nervous system disorder	73(17)
➢ Cardiovascular system disorder	18(4)
➢ Respiratory system disorder	12(3)
➢ Skin disorder	11(2,5)
➢ Eye disorder	5(1)
➢ Alteration of general condition	16(3,7)
➢ Muscle disorder	1(0,2)
➢ Drowsiness	8(2)
➢ Other	1(0,2)
unspecified	21(5)
Total cases	431

To identify the variables that most effectively predict the probability of the occurrence of neurological signs following poisoning by cosmetic products, we performed a logistic regression analysis of the variables retained during the univariate analyses. The explanatory variables initially integrated into the initial model were sex, age group, type of cosmetic product incriminated and route of administration (Table 3).

Among these variables likely to be retained, sex, age group of the poisoned and route of poisoning are excluded from the initial model because they are not associated with the dependent variable, p>0.05. The multivariate analysis allows us to qualify poisoning by skin lightening creams as the predictive factor strongly associated with neurological disorders (RR = 4, adjusted OR = 5.07, p = 0.011).

Table 3: Analysis of factors related to the appearance of neurological signs reported in our study series

Associated factors	**Number of cases**	**Neurological signs**		**Univariate analysis**				**Logistic regression**		
		Number of cases	**%**	**Chi-square**	**RR**	**CI 95%**	**p-value**	**adjusted OR**	**CI 95%**	**p-value**
Sex	**397**	**71**	**18**	**0,447**			**N.S**			
Female	249	47	18,9					-		
Male	148	24	16,21							
Age group	402			**2,54**						
< 1 years (newborn, infant)	16	2	12,5				**N.S**	-		
1-4 years (baby walker)	126	19	15							
5-14 years (child)	35	6	17,14							
15 - 19 years (adolescent)	69	13	18,84							
≥20 (adult)	156	34	21,79							
Class of cosmetic products incriminated	**401**	**71**	**17,7**	**23,88**			**<0,001**			**<0,001**
Skin products:	**131**									
Lightening creams	**98**	**33**	**34**		**3,7**	**[2,21 - 5,18]**		**5,07**	**[1,44 – 17,87]**	**0,011**
Other	33	3	9		1	[0,6 - 1,4]		1		
Hair products	194									
Hair dyes	96	15	15,46		1,7	[1,02 - 2,38]		1,83	[0,49– 6,77]	**N.S**
Other	97	10	10,31		1,14	[0,68 - 1,6]		1,15	[0,29– 4,46]	**N.S**
Other class of cosmetic products	76	10	13,16		1,46	[0,87- 2,04]		1,51	[0,39– 5,9]	**N.S**
Route of intoxication	390	73	18	**1,465**			**N.S**			
Cutaneous	27	8	29,62					-		
Oral	347	62	17,95							
Other	16	3	18,75							

Discussion

At the end of this study, the number of industrial cosmetic products reported to the poison and pharmacovigilance center of Morocco remains very low compared to international data (Nolf, 2001) (Guyodo,2003). This low number of cases shows an under-reporting of cases of poisoning in

general and particularly of cases of poisoning by cosmetic products considered safe by patients and even by health professionals. Certainly, a wide range of cosmetic products were implicated in our study series, however, hair and skin products represent almost all of the products incriminated with 80% of cases. These results diverge from those of the literature (Nolf, 2001) which showed a predominance of cases of poisoning by perfumes and bath products. Furthermore, in Italy, and in an epidemiological study of cases of poisoning reported by the Milan poison control center (Ruggiero et al., 2012), hygiene products were incriminated in 30% of cases followed by perfumes and hair products in 13% of cases. The clinical signs remain dominated by digestive disorders (abdominal pain, diarrhea, nausea and vomiting) throughout the world given the route of ingestion of intoxicating products. High consumption and easy accessibility to cosmetic products by women explains its predominance recorded in our study series.

Multivariate analysis allowed us to qualify skin lightening products as the only incriminated product highly linked to the occurrence of neurological disorders (adjusted odds ratio = 5.07, $p = 0.011$). In our study series, nearly 98% of skin whitening products are represented by a contraband X cream devoid of any labeling whose hydroquinone is singled out. This component has remained for many years a reference in terms of depigmenting agents. It can reduce the epidermal melanin content by competitive inhibition of tyrosinase. In addition, it induces mitochondrial alterations and degradation of melanosomes in melanocytes.

Since January 2001, a European directive has banned the use of hydroquinone in depigmenting cosmetics. Only its use in hair dyes remains authorized, at a maximum concentration of 0.3%. The European decision was motivated by the carcinogenic potential of hydroquinone, which is a benzene derivative (Oualid, 2011) (AFSSAPS, 2011). In Morocco, the use of hydroquinone as a whitening molecule had been banned since 2006 because of its undesirable effects, namely skin irritation, contact allergies, depigmentation and acne of varying severity (DMP, 2006). However, lightening products with high doses of hydroquinone are still present and freely circulated. Once absorbed by the body, hydroquinone is widely distributed in tissues and is metabolized in the liver and gastrointestinal tract into 1,4-benzoquinone and other oxidized compounds including 1,2,4-benzentriol. These oxidized derivatives bind to various biological compounds such as proteins and DNA, act on cellular metabolism and contribute to toxicity (Bonnard et al., 2006). Oral LD50 values in several animal species range from 300 to 1300 mg/kg body weight. In cats, however, LD50 values range from 42 to 86 mg/kg body weight. Acute exposure to high doses of hydroquinone causes severe central nervous system (CNS)

effects including hyperexcitability, tremors, convulsions, coma, and death. At sublethal doses, these effects are reversible. The dermal LD50 value has been estimated to be >3800 mg/kg in rodents (Searchlight Pharma Inc, 2022).

In Fact, a study was able to demonstrate the inhibitory effect of hydroquinone on the acetylcholinesterase enzyme (Scozzafava et al ., 2015). This could explain the appearance of certain symptoms specific to acute hydroquinone poisoning, in particular neurological signs.

Acute exposure to cholinesterase inhibitors may cause cholinergic crisis characterized by severe nausea, vomiting, bradycardia, hypotension, collapse, and convulsions. Progressive muscle weakness may result in death if the respiratory muscles are involved. Indeed, the inhibitory action of hydroquinone may cause an accumulation of acetylcholine in the motor nerves, thus causing excessive stimulation of nicotinic expression at the neuromuscular junction, often accompanied by symptoms such as muscle weakness, fatigue, and paralysis. When there is excessive stimulation of nicotinic expression in the sympathetic system, secondary to an accumulation of acetylcholine in the autonomic ganglia, symptoms such as tachycardia and hypertension are frequently presented. Overstimulation of nicotinic receptors in the central nervous system often results in anxiety, headaches, convulsions, respiratory depression, tremors, general weakness, and potentially coma. When acetylcholine accumulates at muscarinic receptors, symptoms of visual disturbances, bradycardia, hypotension, and salivation may occur (Quinone (T3D4578), nd).

Conclusion

To deal with all this, we demand a resolution that recommends the establishment of very precise regulations with clarity regarding the law governing cosmetic products. Furthermore, we considered it relevant to have better coordination and collaboration between the poison and pharmacovigilance center of Morocco and the authorities responsible for border surveillance in order to intensify security measures and the fight against the infiltration of counterfeit cosmetic products. Also, raising awareness among the population, especially women, about the dangers of these products and education on the risks of domestic accidents among children and on the storage conditions of industrial products at home remain essential to reduce the rate of poisoning by cosmetic products.

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