Food and Chemical Toxicology 64 (2014) 81–85

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Side effects of cade oil in Morocco: An analysis of reports in the Moroccan herbal products database from 2004 to 2012

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ARTICLE INFO

Article history:
Received 13 May 2013
Accepted 11 November 2013
Available online 20 November 2013

Keywords:
Cade oil
Juniperus oxycedrus
Cupressaceae
Phenols
Side effects

ABSTRACT

Cade oil is a dark, faintly aromatic oil which is distilled from the branches and wood of *Juniperus oxycedrus*. Although this oil is known to have toxic effects related to its content of phenols, cade oil continues to be used in folk medicine. Because of this use, a determination of the safety and possible side effects of cade oil is required. The safety of cade oil is discussed based on the experience of the Moroccan pharmacovigilance herbal products database, and supported by literature. The data on the adverse effects of cade oil suggests that it could have life-threatening effects which can occur following topical exposure, ingestion or inhalation. Phenol's adverse effects involve a wide variety of organ systems such as the gastrointestinal system, central and peripheral nervous systems, cardiovascular, liver and biliary systems, the urinary tract, skin and appendages, respiratory system. Platelet function, bleeding and clotting, vision, metabolism, and white cell and reticuloendothelial system function are also affected.

1. Introduction

The concerns regarding the safety of herbal products (HP) have been raised because the use of these products continues to expand rapidly across the world, particularly in countries where folk medicine is popular. This is the case not only in Chinese, Indian, and African societies; the documented use of HP in Western societies is also substantial (Skalli et al., 2007; Fisher and Ward, 1994; Barnes et al., 1999).

There are often debates regarding HM safety, efficacy and quality. This is particularly the case with cade oil (CO), which is widely used in Morocco and in many other countries (Koruk et al., 2005).

Cade oil is obtained from the distillation of the branches and wood of *Juniperus oxycedrus*. The oil is dark and aromatic with a strong smoky smell, and is used in some cosmetics and in popular treatments and drugs. It is also used as incense.

In Morocco, the pharmacovigilance of Herbal Medicines Unit belonging to the Moroccan Pharmacovigilance Center developed an herbal products database that collates reports of adverse events in patients receiving HP, from which we have identified signals in relation to the use of CO. We have used this information to aid in the determination of whether taking CO is safe, or what the possible side effects might be.

Currently, there is not enough information to know if taking CO is safe, or what the possible side effects might be. Also there is not enough scientific information to determine an appropriate use in terms of the range of doses and subpopulations of people that should avoid its use. Natural products are not necessarily safe, and dosages can be important. To follow relevant directions on product labels and to consult a pharmacist or physician, or other healthcare professional, before using this oil remains essential; however, when information is lacking, cases of adverse events reported to the pharmacovigilance center are the only official source of information. Such is the case with CO.

This article describes the Moroccan Pharmacovigilance Center experience in terms of CO adverse effects, and investigates the safety of this oil in humans, along with data from the scientific literature.

2. Methods

The Moroccan pharmacovigilance of HP database was analyzed in a retrospective manner from January 1, 2004 (date of implementation of a computerized database of HP adverse events) to December 31, 2012.

This database includes case reports submitted through the spontaneous reporting system and intensive monitoring programmes (studies and surveys conducted by our Center). Under the spontaneous reporting system, adverse event reports are collected nationwide. The database contains patient demographics, where available, adverse effects associated with HP, and details on seriousness, causality and outcome. Descriptive statistics were used for data analyses.

3. Results

From a total of 1251 reports of side events in the Moroccan database, associated with HP, thirty cases (2.4%) of adverse effects

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http://dx.doi.org/10.1016/j.fct.2013.11.009

to CO were reported. All the cases were obtained from the spontaneous reporting system.

The age range of patients was 1 week to 74 years (mean 11.9 ± 19.4 years). Fifty percent of patients were aged 1–74 years, 37% aged 1–6 months and 13% aged 1–3 weeks with 17 infants (aged 0–1 year), 4 children (2–11 years), 2 adolescents (12–18 years) and 7 adults (18 and above). Female gender was represented in 60% of patients (sex ratio 0.6).

Among the cases, CO was used for a number of folk medicine indications: bronchitis (4 cases), against "evil eye" which is a look that is believed by Moroccans to be able to cause injury or bad luck for the person (mainly babies) (4 cases), abdominal pain (3 cases), scalp treatment (3 cases for hair loss and seborrheic dermatitis), calming children and making them sleep (2 cases), psychiatric disorder (1 case), cancer (1 case), fever (1 case), cephalgia (1 case), angina (1 case), weight decrease (1 case), common cold (2 cases), hypotonia (1 case), and diarrhea (1 case). In four cases, there was an unspecified use or the indication data was missing.

Reported cases were mainly due to topical application (60% of cases), oral ingestion (36.7% of cases) or nasal application where CO was applied to the internal structure of the nose and also topically (3.3% of cases), as shown in Table 1. The dose used was relatively clear in 6 patients only (20%) and the period of use varied from one time to 21 days (Table 1).

Table 2 summarizes the adverse effects reported in patients by WHO system organ class, outcome, and causality assessment in patients. All system organ classes were represented: gastro-intestinal system disorders, psychiatric disorders, central and peripheral nervous system disorders, cardiovascular disorders, liver and biliary system disorders, urinary system disorders with acute renal failure, skin and appendages disorders, respiratory system disorders, platelet, bleeding and clotting disorders, vision disorders, metabolic and nutritional disorders, and white cell and reticuloendothelial system disorders. Renal disorders represent the most common adverse effect associated with the use of CO. After hospitalization with supportive and symptomatic treatment, twenty three (76.7%) patients improved and were discharged. The outcome was unknown for four (13.3%) patients (Table 2). Three deaths (10%) were reported in relation with the use of CO (Table 3).

The WHO–UMC causality assessment (WHO, 2000) was employed for each case (Table 2), and the results were "possible" in 24 cases, "probable" in 4 cases, "unlikely" in 1 case and "unassessable" in 1 case.

4. Discussion

Cade oil derived from *J. oxycedrus* (family Cupressaceae) is commonly used in Moroccan folk medicine. The oil contains phenols (17–26%) mainly guaiacol (12%) and cresol, cadinene (a sesquiterpenoid), and cardinol (an alcohol) (Bellakhdar, 1997). There are no human exposure case reports that can provide a basis for identifying the toxicity profile or side effects of the guaiacols. The toxicity profile of guaiacols (guaiacol, methylguaiacol and ethyl guaiacol) may be similar to that of the related phenolic compounds phenol and cresol.

In Morocco, CO is accessible to consumers without a prescription and is known to be used externally for skin disorders in dermatology and hair care, essentially for scalp care, eczema, scale affections, loss of hair, and psoriasis. The oil is also used as a vermifuge. The cases reported here have shown that CO is used also against "evil eye", abdominal pain and diarrhea, psychiatric disorder, cancer, fever, cephalgia, angina, weight decrease, the common cold, and hypotonia, without any scientific evidence to support these uses despite such common use. In the literature, CO has been shown to have many medicinal properties such as activity as a keratolytic, antipruritic, and antimicrobial agent *in vitro* (Leung and Foster, 1996). Guaiacol and cresol have been shown to suppress contractions of intestinal smooth muscle (Ogata et al., 1992) and fluid secretion induced by enterotoxin (Ataka et al., 1996).

Table 1
Route of administration, period of use, and dose of cade oil used in patients.

Cases	Route of administration[a]	Period of use[a]	Dose used[a]
1	Oral ingestion	One time	Unspecified single dose
2	Topical application	One time	Unspecified single dose
3	Oral ingestion	One time	Unspecified single dose
4	Oral ingestion	21 days	Unspecified single dose per day
5	Oral ingestion	One time	One teaspoon
6	Oral ingestion	One time	Two teaspoon
7	Oral ingestion	3 days	Unspecified single dose per day
8	Topical application	One time	Unspecified single dose
9	Oral ingestion	One time	Half a glass
10	Topical application	One time	Unspecified single dose
11	Oral ingestion	Many days	5 ml per day
12	Topical application	Many days	Unspecified high quantity doses
13	Topical application	One time	Unspecified single dose
14	Topical application	2 weeks	Unspecified single dose per week
15	Topical application	One time	Unspecified single high dose
16	Oral ingestion	One time	half a glass
17	Topical application	Many days	Unspecified many doses
18	Topical application	One time	Unspecified single dose
19	Oral ingestion	One time	Unspecified single dose
20	Topical application	One time	Unspecified single dose
21	Topical application	One time	Unspecified single dose
22	Nasal and topical application	One time	Unspecified single dose
23	Topical application	Many days	Unspecified many doses
24	Oral ingestion	Many days	One teaspoon each day
25	Topical application	5 days	Half a glass per day
26	Topical application	Many days	Unspecified many doses
27	Topical application	One time	Unspecified single dose
28	Topical application	3 days	Unspecified single dose per day
29	Topical application	Many days	Unspecified many doses
30	Topical application	One time	Unspecified single dose

[a] Data as reported to the Moroccan Pharmacovigilance Center.