Original Article

Black Cohosh Hepatic Safety: Follow-up of 107 Patients Consuming a Special Cimicifuga racemosa rhizome Herbal Extract and Review of Literature

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European Medicines Agency (EMEA) and the Committee on Herbal Medicinal Products (HMPC) on July 2006 have released an alert to get European sanitary authorities aware of 42 cases of suspected hepatotoxic reactions in patients consuming Cimicifuga racemosa rhizome. In the public statement EMEA itself considered reliable as hepatotoxic reactions only four cases, on the base of RUCAM score: two were considered possible and two probable. Lacking in almost all of them a precise description of cases, especially a botanical-chemical analysis of the suspected substance, we think there is no real proof of supposed C. racemosa rhizome hepatotoxicity. In our department we administer from about 10 years C. racemosa as special herbal dry extract as single substance or mixed with other medicinal plants at the dose of 500–1000 mg daily, for treatment of menopause related disorders without any reported adverse effect. After EMEA’s official signal we have contacted all our patients using a C. racemosa herbal extract continuously from more than 12 months to verify possible hepatotoxic effects. We followed-up 107 women, and asked them by telephone (33/107) and/or after anamnesis and clinical examination (74/107) to undergo a blood sample examination. In all the patients there was no sign of hepatic disease, or worsening of already altered but stable parameters. We think on the base of these data and current literature C. racemosa rhizome extract should not be considered a potential hepatotoxic substance.

1. Introduction

Currently hormone replacement therapy (HRT) is commonly used to reverse symptoms and diseases associated with falling oestrogen and progesterone levels. However HRT is associated with adverse effects and an increased risk of breast cancer [1]. Many women therefore take a dislike to HRT and choose to employ herbal remedies for menopausal symptoms, one of most used worldwide is Black Cohosh.

Cimicifuga racemosa Nuttal (syn. Actaea racemosa L) common name Black Cohosh (Ranunculaceae; Figure 1), is an herbaceous perennial plant of North America. It is a coarse, perennial, woodland herb with large compounds leaves, and a thick, knotted, rhizome system [2]. Traditionally it was used by Native Americans (Penobscot, Winnebago and Dakota) [3] for the treatment of coughs, colds, constipation, fatigue and rheumatism and to stimulate lactation. Since 1832 a hydroalcoholic extract was described as treatment for pain and inflammation in endometriosis and dysmenorrhea [3]; and a fluid extract was listed in the US National Formulary from 1840 until 1946 [4]; and was a major constituent of the once popular patent medicine “Lydia Pinkham’s Vegetable Compound” used for treatment of “painful complaints and weakness” in females. Actually, C. racemosa is widely employed in various pharmaceutical–industrial preparations often mixed with other medicinal plants to alleviate menopausal and post-menopausal symptoms, including hot flushes, profuse sweating, sleep disturbances, anxiety and depression.

Safety data from post-marketing surveillance study have generally found very few serious adverse events, nevertheless the lack of placebo or positive control arms in main studies, the lack of serious adverse events suggests that C. racemosa has a very good safety profile [4] as confirmed in a review of more than 3800 climateric women [5].

Recently the European Medicines Agency (EMEA) and the Committee on Herbal Medicinal Products (HMPC) on July 2006 have released a public statement [6], although
lacking of many data on patients and herbal extracts, to get European sanitary authorities aware of 42 (34 directly reported from European national competent authorities and 8 published) cases of suspected hepatotoxic reactions in patients, probably all women and for treatment of menopause related disorders, consuming C. racemosa often mixed with other medicinal plants. Following the review of available data, the statement considered real a potential connection between herbal medicinal products containing C. racemosa and human hepatotoxic reaction. Nevertheless this highly authoritative review of such a number of cases, in the summary EMEA states that “overall, all discussed cases of literature and pharmacovigilance reports are poorly documented. In many cases there is not even information about the time frame of treatment with Cimicifuga containing products or about the relation to the onset of reaction available. Therefore, they are insufficiently documented according to RUCAM score. The Non-EU cases are not validated by a health care professional but reported by patients” [6]. Because C. racemosa extracts are sold as OTC integrators, Italian sanitary authorities decided a precautionary withdrawal from the national market, that later has been reversed, and stringent label warnings have been introduced for C. racemosa extracts in United Kingdom. So actually there are some concerns about C. racemosa extracts safety especially in patients suffering of liver disease.

2. Methods

2.1. Participants. In our department we administer C. racemosa rhizome extract regularly for treatment of menopause related complaints, from about 10 years to 798 patients as only substance or mixed with other medicinal plants like Glycine max isoflavones, Trifolium pratense and, Medicago sativa, at the dose of 500 or 1000 mg daily as dry extract, standardized and titrated in 2.5% of actein, a triterpene glycoside (Figure 2), for treatment of menopause related disorders like anxiety, depression, flashes and myalgia. We regularly exclude from the treatment patients affected by cancer of sexual organs: breast, ovaries, uterus and hypophysis, unless already treated with conventional therapy from more than 7 years and considered recovered. In our experience we had no report of adverse reaction to C. racemosa extracts, both as single prescription either mixed with other medicinal plants extracts, but minor complaints.

After EMEA’s official statement indicating a possible risk of hepatotoxicity in patients assuming extract of C. racemosa, we have contacted all our available patients consuming the extract continuously from at least 12 months. So we considered 158 patients eligible, for control of a possible hepatotoxic adverse reaction to C. racemosa herbal extract to whom it was prescribed following our patterns. Of our contact list 107 climacteric women were followed-up by telephone or direct clinical examination in our department.

2.2. Study Protocol. Baseline characteristics of study participants are available in Table 1. They were an heterogeneous group of patients in different phases of menopause and most of them asked a complementary treatment for menopause related anxiety and depression because of unsatisfied or fear of synthetic drugs. Most of them were in good health, but complaints referred to menopause. Only five patients were suffering of chronic hepatobiliary disease (four patients suffering of benign hepatic disease and one chronic toxic hepatitis). We excluded from follow-up patients who had suspended the treatment for more than 15 days, also non-consecutive, or had spontaneously reduced the dose prescribed.

We followed-up 107 women asking them by telephone (33/107) and/or after clinical examination (74/107), to undergo a blood sample examination to control main laboratory parameters to evaluate liver function.

As shown in Table 2 patients underwent a blood sample examination to evaluate: total leukocyte count, hepatic transaminases, γ-glutamyltranspeptidase, alkaline phosphatase, albumin, coagulation and total bilirubin. By telephone the patients were questioned if they were still regularly consuming the herbal extract and they were asked some question on the base of the same check-list used during clinical examination in hospital.

3. Results

In all the patients (comprehending four patients suffering of benign hepatic disease and one suffering of chronic toxic
Table 1: Baseline characteristics of study participants.

| Characteristics          | N = 107 (%) |
|--------------------------|-------------|
| Age                      | 48 (SD 4.24) |
| Menopause                |             |
| Spontaneous premature    | 7 (6.5)     |
| Perimenopause            | 29 (27.1)   |
| Menopause from >3 years  | 55 (51.4)   |
| Menopause from >6 years  | 10 (9.3)    |
| Surgical menopause       | 6 (5.6%)    |
| Treatment                |             |
| Cimicifuga racemosa herbal extract titrated in 2.5% of actein |             |
| 500 mg daily             | 49 (45.8)   |
| 500 mg + other plants    | 33 (30.9)   |
| 1000 mg daily            | 11 (10.3)   |
| 1000 mg + other plants   | 14 (13)     |
| Clinical history         |             |
| Depression or anxiety    | 89 (83.1)   |
| Moderate alcohol consumption | 86 (80.3) |
| Chronic headaches        | 27 (25.2)   |
| Dyspepsia                | 16 (15)     |
| Hypertension             | 12 (11.2)   |
| Thyroid disease          | 8 (7.4)     |
| Hepatobiliary disease    | 5 (4.6)     |
| Allergies                | 5 (4.6)     |
| Previous cancer non genital organ | 3 (2.8) |
| Major heart disease      | 2 (1.8)     |
| Autoimmunity disease     | 1 (0.93)    |
| Major psychiatric diseases | 0         |
| Alcohol abuse            | 0           |
| Previous idiosyncratic reactions to drugs | 0 |
| Concomitant medication   |             |
| Antacids                 | 26 (24.3)   |
| NSAID                    | 25 (23.3)   |
| HRT                      | 17 (15.9)   |
| Hypotensive              | 12 (11.2)   |
| Hormone thyroid therapy  | 8 (7.5)     |
| Botanicals               | 5 (4.6)     |
| Administration of blood product | 0 |
| Antiestrogen drugs       | 0           |
| Vitamins                 | 0           |

hepatitis) there were no sign of hepatic disease neither alteration of plasma hepatic parameters, or worsening of already altered but stable parameters. Only nine patients were suffering of minor transient complaints (see Figure 2) and after 1 month underwent by telephone a new follow-up with a blood sample control that was negative for any disease.

To our patients we administered very high doses respect to median dose used in clinical trials (median range 40–80 mg daily) [7, 8], but after 12 months of regular use there were no laboratory data, neither clinical signs, referring to a possible hepatic adverse reaction.

Table 2: Follow up of patients assuming Cimicifuga.

| Parameter                     | Values         |
|-------------------------------|----------------|
| Physical examination          |                |
| BMI                           | 28.5 (SD 0.71) |
| Blood pressure                |                |
| systolic                      | 125 (SD 7.07)  |
| diastolic                     | 75 (SD 21.21)  |
| Heart rate                    | 76.5 (SD 0.71) |
| Few patients (9/107) were suffering of minor complaints, that revalued after 1 month did not show any sign of liver disease. |
| Abdominal pain                | 5 (4.6%)       |
| Paresthesias                  | 3 (2.8%)       |
| Fatigue                       | 2 (1.8%)       |
| Anorexia                      | 1 (0.9%)       |
| Myalgia                       | 1 (0.9%)       |
| Malaise                       | 1 (0.9%)       |
| Pruritus                      | 1 (0.9%)       |
| Fever                         | 0              |
| Skin rash                     | 0              |
| Jaundice                      | 0              |
| Laboratory findings           |                |
| Leukocyte total count         | 4250 mm³ (SD 1060) |
| Bilirubin                     | 0.75 mg dl⁻¹ (SD 0.07) |
| AST                           | 29.5 U l⁻¹ (SD 10.61) |
| ALT                           | 15.5 U l⁻¹ (SD 17.68) |
| Alkaline Phosphatase          | 135 U l⁻¹ (SD 63.64) |
| GGT                           | 28 U l⁻¹ (SD 7.07) |
| Albumin                       | 3.75 g dl⁻¹ (SD 0.49) |
| INR                           | 1 (SD 0.14)    |

Few patients (9/107) were suffering of minor complaints, like fatigue, aspecific abdominal pain and paresthesias, (Table 2), controlled again after 1 month did not show any sign of liver disease.

4. Discussion

4.1. Hepatotoxic Drug Reactions. Between 0.1 and 3% of all hospital admissions are related to drug toxicity, but it is suspected that many cases are not recognized. Since liver is central to the metabolic disposition of virtually all drugs, drug-induced hepatic injury is a potential complication of nearly every medication. Fortunately adverse hepatic drug reactions are relatively uncommon in comparison with the number of drug prescriptions. In majority of the cases, hepatic drug reactions present as acute hepatitis, which is usually reversible and relatively benign; however, the spectrum of liver disease may range from mild biochemical abnormalities to acute hepatic failure.

When a drug is found to cause even rare hepatotoxicity but is used by millions, it may disproportionally be removed from the market, although this substance is a real danger only for few patients. And should be stressed that to incriminate
any drug in an episode of liver dysfunction is a difficult step-by-step process that requires: high degree of suspicion, compatible chronology, awareness of its hepatotoxic potential, competent exclusion of alternative causes of liver damage and the ability to detect the presence of subtle data that favors a toxic etiology [9].

It is very important in the step-by-step process to rule out other causes of liver injury including hepatic infections, alcoholic and autoimmune hepatitis, biliary tract disorders and hemodynamic based diseases [10]. Finally, genetic and metabolic disorders may produce liver injury such as hemochromatosis and Wilson’s disease. Liver injury in the absence of other known causes may be drug-related and requires additional information, such as that obtained through a careful drug history, in relation to the onset of injury [10].

In respect to the hepatotoxic potential of screened drugs, their potential for causing liver damage is not the same, and almost all marketed medications have been incriminated in incidences of hepatotoxicity [9, 11]; probably because the most important factor for hepatotoxicity is genetic variability [12]. Genetic polymorphisms have a strong influence on drug metabolism and may increase the risk of hepatotoxicity [13].

The main causative group of drugs, in a large cohort of hepatotoxicity cases collected in the Spanish registry, were antibiotics followed by non-steroidal anti-inflammatory drugs [14]; and statins have been shown to cause elevations of aminotransferase levels and severe liver injury in animals; while in humans such elevations are common but rarely if ever, lead to clinically significant hepatotoxicity [15]. All drugs that are well known hepatotoxic, and well stable in the market, thanks to their therapeutic advantages, as such as paracetamol, one of main causes worldwide of liver transplant, nevertheless sold over-the-counter in many Western countries.

4.2. Safety of Black Cohosh in Experimental Trials. A study in vitro on HepG2 cells and in vivo on rats to evaluate potential hepatotoxicity of C. racemosa; showed cytotoxic reactions in vivo at concentrations of 75 μg ml−1; and significant initial mitochondrial swelling in rats fed with 100 and 300 mg kg−1 daily of C. racemosa extract, while clear microvesicular steatosis of the hepatocytes and fragmentation of the rough endoplasmic reticulum at 1000 mg kg−1 daily [16]. The Authors conclude that toxicity is not clinically relevant for most patients but may become important in patients with underlying risk factors [16], as like as for any drug; moreover a dose of 100 mg kg−1 is very high and corresponds in a woman of 50 kg at 5 g of extract daily.

Natural and synthetic estrogens are known to alter hepatobiliary physiology, and certain genetically susceptible women become icteric during pregnancy, when high serum oestrogen levels are present. Although not all the mechanisms responsible for hepatic injury produced by estrogens are known, it is consistently reported that Black Cohosh extracts and isolated compounds do not posses estrogenic activity, regardless of source, extraction procedure, dose or length of exposure [17].

Chronic toxicity was not observed in rats at a dose of 500 mg kg−1 per day for 27 weeks or in dogs at 400 mg kg−1 per day for 26 weeks [18]. Furthermore, a 40% 2-propanol extract of Black Cohosh was negative in the Ames test [18]. In mice, the LD50 of a Black Cohosh extract was 7.7 g kg−1 for intragastric administration and 1.1 g kg−1 for intravenous administration [18].

4.3. Safety of Black Cohosh in Humans. In clinical trials only minor adverse side effects have been reported, including nausea, vomiting, head-aches and dizziness: a review of eight clinical trials concluded that extracts of the rhizome of C. racemosa might be a safe alternative for women seeking alternative estrogen replacement therapy [19].

Black Cohosh also contains several catechols, such as caffeic acid, piscidic acid and fukiic acid esters that exhibit some antioxidant properties, including fukinolic acid, cimicifugic acid A and cimicifugic acid B [20]. Such catechols could be of significant concern in toxicology because of the possibility that they could be activated, either metabolically or chemically, to electrophilic quinones. The potential of such quinones to cause toxicity and carcinogenesis is well documented, and can occur via arylation of cellular proteins and DNA or redox cycling leading to the formation of reactive oxygen species such as the hydroxyl radical [21]. Nevertheless has been shown in six perimenopausal women after administration of a single dose of either 32, 64 or 128 mg of C. racemosa that no corresponding mercapturic acids were found in the urine [22]. In a previous study, potential toxicity was suspected because catechols from Black Cohosh are activated to quinoid metabolites, but catechols are not absorbed across the bowel [23].

In a recent trial on 351 randomized women, placebo controlled, Black Cohosh both used as single substance and mixed in multi herbs remedies after 12 month of treatment, did not show any effect on lipids, glucose, insulin and fibrinogen [24].

Instead an important issue about safety is probably the interaction with synthetic drugs because of the interference with the metabolic pathway of cytochrome P4503A4 [25], a potential cause of important adverse reactions, especially in patients assuming multi drug regimen therapies as confirmed by a recent work in which ethanol and isopropanol extract induced inhibition of CYP1A2, 2C9, 2D6, 3A4.

To be added a case of cutaneous pseudolymphoma in a patient assuming a commercial extract of C. racemosa has been reported recently [26]; and a case of muscle damage with asthenia, high levels of creatine phosphokinase and lactate dehydrogenase following assumption of a dietary supplement derived from C. racemosa has also been reported [27].

4.4. The EMEA and HMPC Signal of Hepatic Toxicity. The EMEA and the HMPC have been made aware of a number of case reports of hepatotoxicity (liver injuries) in patients using C. racemosa rhizome. Following review of all available data, the HMPC considered that there is a potential connection between herbal medicinal products containing C.
and contradictory, while the follow-up publication includes more (although to some extent contradictory) therapy information.

(a) This a well-documented case (RUCAM Score 6) [30]. The admitted amount was 500 mg drug per day. The reaction was described as hepatocellular, other causes for acute hepatitis were excluded. The provisional clinical diagnosis was autoimmune hepatitis. Therapy was started with 60 mg prednisone/day for 5 weeks. Liver enzymes improved, but due to worsening coagulopathy and encephalopathy the patient underwent an orthotopic liver transplantation. In the explanted organ, histologically features of acute hepatitis, fibrous linkage of portal tracts and cholestasis were seen after 5 weeks on corticosteroids. Nevertheless in this case too, the exact content of the remedy based on Black Cohosh is not known: was it an extract or crude drug? Did it contain other toxic substances? Heavy metals? Later on nevertheless Levitsky et al. [30] reported that the patient did not drink, use drugs or take any other medication; but in a US District Court proceeding the woman testified that she regularly drank wine, and used both prescribed and non-prescribed pharmaceuticals [31].

4.5. The Problematics of Herb ADRs. We would like to remark that it is very important before an official statement about any adverse reaction referred to an herb based product to know the brand, dose of substance assumed, type of extract, content of possible contaminants (wrong plants, pesticides, heavy metals and aflatoxins) [32, 33]. When needed to establish a connection between herb consumption and an adverse reaction, especially if liver related, the same rules for conventional drugs can be followed [32] only if the case report deal with a single substance of a medicinal plant; while if it is a multitherb preparation a direct toxic connection with only one herb cannot be correctly established, unless it is a well known hepatotoxic substance for example, *Teucrium chamaedrys*; or it is contained in a very high ratio respect to other herbs. To date in our opinion paradoxically the EMEA statement could be regarded as the proof the risk of Black Cohosh hepatotoxicity is scarce, because actually there is not any full proved case of hepatotoxicity reported in front of millions of doses used yearly in the world (about 1 500 000 women are using *C. racemosae* extracts only in Europe) [34]; and its safety was already been sufficiently established by the fact that in over 3800 participants in clinical trials there were no hepatotoxic reactions reported [5].

In our series of patients assuming daily a very high dose of extract (much more than 40–80 mg used in most clinical trials and usually recommended) [7, 8, 23] for at least 12 months we did not find any clinical or laboratory proof of liver disease; but the five already suffering of chronic liver disease, that maintained stable clinical and laboratory parameters (Table 3).

In our series we had a relative low number of patients (32/107) assuming contemporary synthetic drugs to exclude
reliably an interference on hepatic metabolism, although they did not report any significant side effect.

5. Conclusions

A reporting rate higher than the background rate is taken as a “signal” of a possible causal relationship between the drug and the event [35], but in the EMEA statement the reported cases are so faintly circumstantiated that we think there is no evidence for an official signal. On the base of our data (although a small series of patients, but assuming high doses of C. racemosa extracts) and current literature, we think C. racemosa rhizome herbal extract should be considered safe concerning liver toxicity.

Table 3: Follow up of five patients suffering from stable chronic liver disease.

| Patients at baseline and control | 1 Baseline | 1 Control | 2 Baseline | 2 Control | 3 Baseline | 3 Control | 4 Baseline | 4 Control | 5 Baseline | 5 Control |
|---------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Leukocyte | 5780 mm³ | 6300 mm³ | 3990 mm³ | 4100 mm³ | 6700 mm³ | 6900 mm³ | 8000 mm³ | 7450 mm³ | 3450 mm³ | 4500 mm³ |
| Tot bilirubin | 1.4 mg dl⁻¹ | 1.3 mg dl⁻¹ | 0.9 mg dl⁻¹ | 0.9 mg dl⁻¹ | 0.7 mg dl⁻¹ | 0.6 mg dl⁻¹ | 0.2 mg dl⁻¹ | 0.3 mg dl⁻¹ | 0.4 mg dl⁻¹ | 0.5 mg dl⁻¹ |
| AST | 57 IU l⁻¹ | 52 IU l⁻¹ | 36 IU l⁻¹ | 33 IU l⁻¹ | 37 IU l⁻¹ | 35 IU l⁻¹ | 20 IU l⁻¹ | 18 IU l⁻¹ | 45 IU l⁻¹ | 42 IU l⁻¹ |
| ALT | 150 U l⁻¹ | 156 U l⁻¹ | 119 U l⁻¹ | 118 U l⁻¹ | 110 U l⁻¹ | 105 U l⁻¹ | 120 U l⁻¹ | 122 U l⁻¹ | 110 U l⁻¹ | 80 U l⁻¹ |
| Alkaline phosphatase | 55 IU l⁻¹ | 59 IU l⁻¹ | 22 U l⁻¹ | 25 U l⁻¹ | 35 U l⁻¹ | 32 U l⁻¹ | 45 U l⁻¹ | 44 U l⁻¹ | 48 U l⁻¹ | 35 U l⁻¹ |
| γGT | 3.5 g dl⁻¹ | 3.6 g dl⁻¹ | 4.1 g dl⁻¹ | 4.2 g dl⁻¹ | 3 g dl⁻¹ | 2.9 g dl⁻¹ | 3.8 g dl⁻¹ | 4 g dl⁻¹ | 4.2 g dl⁻¹ | 4.4 g dl⁻¹ |
| INR | 0.8 | 0.9 | 1.2 | 1.3 | 0.9 | 0.9 | 1.1 | 1.1 | 1 | 1.2 |

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