Black Cohosh

UK Public Assessment Report

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Summary

Black cohosh (*Cimicifuga racemosa* Nutt) is used traditionally as a herbal remedy for rheumatism, rheumatoid arthritis, intercostal myalgia (pain in the rib muscles), sciatica (pain in the lower back), whooping cough, chorea (loss of nervous-system function), tinnitus, dysmenorrhoea (painful menstruation), and uterine colic (painful cramps of the muscle of the uterus). At present, black cohosh is commonly used for treatment of symptom relief during and after the menopause (eg, flushes and sweats, joint aches, and headaches). Estimates suggest that in the UK 9 million treatment days for this product were purchased in 2004.

Published literature suggests that large doses of black cohosh might be associated with gastrointestinal irritation, headache, dizziness, and vomiting. The long-term safety of black cohosh is not known. Since 2002, the Medicine and Healthcare products Regulatory Agency (MHRA) has been monitoring reports of adverse liver reactions associated with the use of black cohosh.

This report discusses an assessment of the adverse liver reactions associated with black cohosh that were identified from: spontaneous reports received through the UK Yellow Card Scheme (see www.yellowcard.gov.uk); similar reporting schemes in other countries; and cases reported in the published literature.

Of 21 UK reports of liver reactions received in total up to March 31, 2006, 14 cases report an association between black cohosh and adverse effects on the liver (hepatotoxicity). Of the UK reports, 13 are reported as recovered or recovering after stopping the drug and did not require medical intervention.

The Herbal Medicines Advisory Committee and the Commission on Human Medicines—two panels of independent expert advisors to the MHRA—were informed of the continuing concern about black cohosh and its effects on the liver in May and June 2006.

The Committees concluded that the available evidence supports an association between black cohosh and risk of hepatotoxicity. In light of the number of reports of liver disorders and the use of this herbal product in the UK, they considered it important to inform users of black cohosh of this potential risk, and that warnings about rare adverse reactions in the liver should be added to the product information for all black-cohosh products.

Introduction

1. The issue

Black cohosh (*Cimicifuga racemosa* Nutt) is used traditionally as a herbal remedy for rheumatism, rheumatoid arthritis, intercostal myalgia (pain in the rib muscles), sciatica (pain in the lower back), whooping cough, chorea (loss of nervous-system function), tinnitus, dysmenorrhoea (painful menstruation), and uterine colic (painful cramps of the muscle of the uterus). At present, black cohosh is commonly used for treatment of symptom relief during and after the menopause (eg, flushes and sweats, joint aches, and headaches). Estimates suggest that in the UK 9 million treatment days for this product were purchased in 2004.

Published literature suggests that large doses of black cohosh might be associated with gastrointestinal irritation, headache, dizziness, and vomiting. The long-term safety of black cohosh is not known. Moreover, there has been a growing concern worldwide about the risk of adverse effects on the liver (hepatotoxicity) associated with use of black cohosh.

This Public Assessment Report presents the evidence for an association between black cohosh and adverse effects on the liver, which culminated in the recommendation by independent experts (the Herbal Medicines Advisory Committee and the Commission on Human Medicines) to add warnings about rare adverse liver reactions to the product information for all black-cohosh products

2. Background

Black-cohosh products

At present, 27 products that contain black cohosh are licensed in the UK, including 11 homeopathic products. Of the 16 non-homeopathic products, only one product consists solely of black cohosh; all other products are combinations of various herbal active ingredients. Most non-homeopathic products are licensed for symptomatic relief of rheumatic pain; others are used for various ailments such as cough, stomach cramps, menstrual pains and bloatedness, and tenseness or irritability.

The number of unlicensed black-cohosh products that are marketed in the UK and their usage is not known by the MHRA, who therefore approached the herbal sector in 2005. More than a dozen companies provided useful information. There are a range of products available, including combination products and single-herb products. These are available as tinctures (an alcoholic extract), tablets, or capsules; some contain powdered root, others are extracts.

Calculation of the usage of black cohosh is difficult. According to information provided by the herbal sector, however, for single-herb tablets and capsules at least 9 million treatment-days' or 25 000 treatment-years' worth of black cohosh were purchased in the UK in 2004. These are only estimates, true usage may be higher.

Information provided by a few companies in the herbal sector suggests that the use of single-constituent black-cohosh products has been rising steadily since the late 1990s, peaking in 2003. Although sales of this product are high, they seemed to decrease slightly in 2004, but this may in part be due to incomplete information. Media coverage of potential side-effects with herbal productsincluding black cohosh might have had a minor effect on sales.

Adverse effects on the liver

Concerns about adverse liver reactions suspected to be associated with the use of black cohosh were first brought to the attention of the MHRA in 2002 through cases in the published literature. In October 2003, media activity surrounded the publication of a case in the USA, in which a woman developed liver failure and required a liver transplant after using a herbal remedy that contained black cohosh.

In February 2004, this issue was discussed at the Committee on Safety of Medicines Sub Committee on Pharmacovigilance (CSM SCOP, a panel of independent advisory experts). At that time, the MHRA had received 4 UK spontaneous case reports of liver reactions

associated with the use of this drug. This Committee concluded that there was insufficient information to support regulatory action being taken, but recommended the publication of an article about this issue in Current Problems in Pharmacovigilance. This article was published in October 2004 (*Current Problems in Pharmacovigilance* 2004; **30:** 10, see http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON007447&ssTargetNodeId=368).

At the time of publication of this article, 7 UK cases of adverse liver reactions associated with black cohosh had been received through the Yellow Card Scheme. The MHRA received further reports after publication of the article, which may reflect the public's increased awareness of the issue and the possible increase in the use of alternative treatments for menopausal symptoms after concerns over the safety of hormone-replacement therapy.

As of March 31, 2006, 21 UK cases of adverse effects on the liver associated with the use of black cohosh have been received through the Yellow Card Scheme, one of which required a liver transplantation.

At present, the mechanism by which black cohosh might cause liver injury is unknown. In addition to releasing guidance about the warnings that should be placed on black-cohosh products about liver injury, the MHRA and its expert advisory Committees are keeping the safety of this product under close review.

3. Questions posed by the current evidence for black cohosh

- What is the estimated risk, if any, of developing liver injury when using black cohosh?
- If black cohosh is associated with adverse effects on the liver, how can the health of those who wish to use this product be safeguarded?

Evidence for an association between black cohosh and liver injury

The MHRA assessed reports of adverse reactions reported with products that contained black cohosh obtained from: spontaneous reports received through the UK Yellow Card Scheme; similar reporting schemes in other countries; and cases reported in the published literature.

1. Spontaneous UK reports

As of March 31, 2006, 21 UK reports of adverse liver reactions associated with black cohosh had been received through the Yellow Card Scheme. The total number of reports (any reaction) for this herbal medicine was 31—ie, more than two thirds of the reports received for black cohosh related to reactions in the liver.

Information received through the Yellow Card Scheme implies that mainly products containing only black cohosh are associated with liver reactions: only 1 of the 21 reports suggested that a multi-ingredient product had a role in development of adverse liver reactions.

These 21 cases were split into three groups: those that seemed to support a relation between liver injury and black cohosh; those with an unclear relation; and those that cannot be assessed meaningfully because of limited information. These groupings were done on the basis of two classification systems developed by the World Health Organization (WHO) and by the Council of International Organizations of Medical Sciences (CIOMS), respectively, which help determine the likelihood that a particular drug caused a particular adverse reaction. In general, the MHRA focused its assessment on WHO criteria because the CIOMS classification system (called RUCLAM) requires that liver-function tests are done at specific time points. Although this information may be easy to capture during a clinical trial, it may not be available for case reports that arise during routine clinical practice. Thus, RUCLAM has limitations when used for assessment of new safety signals.

Cases that appear to support a relation between black cohosh and liver damage

- There were 14 cases in this category. The brands of black cohosh involved are mainly unknown.

- Of the 14 cases, 4 had hepatitis; 9 had abnormal or raised liver-function tests; and 1 had jaundice. 11 recovered after stopping black cohosh; 2 recovered after stopping treatment; and the outcome of 1 person was unknown.

- According to the classification of the WHO, black cohosh was "probably" thought to have caused liver injury in 10 people, and "possibly" thought to have caused liver injury in 4.

- According to the CIOMS classification system (ie, RUCLAM), 3 cases were "unlikely" to have had liver injury because of taking black cohosh; 5 cases "possibly" had liver injury as a result of taking black cohosh; and 6 cases could not be assessed.

For a further 6 cases, the relation between black cohosh and liver damage is unclear, and one case could not be assessed meaningfully because of limited information.

The table below shows the outcome for the 21 UK cases as at March 31, 2006:

Recovering after withdrawal of black cohosh	6
Recovering after treatment	2
Recovering	1
Recovered after withdrawal of black cohosh	7
Recovered within 1 month	2
Recovered within 3 months	1
Recovered between 6 months and 12 months	2
Duration of recovery not stated	2
Recovered after treatment	2
Reactions continuing	3

Table: Outcome of 21 cases of adverse liver reactions associated with black cohosh

2. Cases reported in published literature

The following published reports presented and reviewed evidence for an association between black cohosh and adverse effects on the liver:

A systemic review of the safety of black cohosh (Huntley A, Ernst A. *Menopause* 2003; **10:** 58–64*).*

This comprehensive review of the literature, spontaneous reports, and company data up to October 2001 reports that adverse reactions with black cohosh are rare, mild, and reversible with gastrointestinal upsets and rashes being the most common reactions. This review acknowledges the serious reports of liver reactions associated with black cohosh from spontaneous-reporting systems, but states that it is not possible to say black cohosh causes the liver injury. The authors also note that they did not identify any serious reactions with black cohosh from the literature.

Black cohosh and other herbal remedies associated with acute hepatitis (Whiting PW, Clouston A, Kerlin P. *Med J Aust* 2002; **117:** 440–43).

Whiting and colleagues report 6 patients in Australia who developed serious liver reactions after taking herbal remedies, two of whom had taken black cohosh. The first of these cases was a 47-year-old woman who developed sudden liver failure, requiring urgent liver transplantation, after using black cohosh alone for 1 week. No cause for liver disease other than the herbal remedy was found.

In the second case, a 43-year-old woman developed jaundice after taking a mixed herbal remedy that contained black cohosh. This herbal remedy also contained valerian and skullcap, which have been implicated in other cases of liver toxicity.

Acute liver failure associated with the use of herbal preparations containing black cohosh (Lontos S, Jones RM, Angus PW, Grow PJ. *Med J Aust* 2003; **179:** 390–91).

This letter reports a case of sudden-onset liver failure associated with the use of a herbal preparation taken for severe tinnitus that contained several ingredients including black cohosh; the other ingredients were *Nepeta hederacea* (ground ivy), *Hydrastis canadensis* (golden seal), and *Ginkgo biloba* (gingko). A 52-year-old woman had taken the herbal preparation for 3 months. 4 weeks after stopping the remedy, she developed sudden liver failure and required transplantation.

Autoimmune hepatitis associated with the use of black cohosh: a case study (Cohen SM, O'Connor AM, Hart J, Merel NH, Te HS. *Menopause* 2004; **11:** 575–77).

A 57-year-old woman developed drug-induced hepatitis associated with an inflammatory response against the body's own immune system 3 weeks after starting black cohosh. All other possible causes of hepatitis (eg, viral or other risk factors) were ruled out, although the patient had been taking other drugs for at least 2 years before the suspected reaction.

3. Worldwide reports

In addition to the 21 reports of adverse liver reactions associated with use of black cohosh that were received in the UK, a further 19 worldwide cases were included in a report by the German Federal Institute for Drugs and Medical Devices. These cases included 7 from Germany, 3 from the USA, and 6 from Sweden.

Furthermore, the Australian Therapeutic Goods Agency made reference to 9 cases in their announcement regarding a new warning statement to be put on black-cohosh products. In February 2006, this Agency in Australia announced that warning labels will be introduced to all black-cohosh products over a 12-month period. The warning states: "Black cohosh may harm the liver in some individuals. Use under the supervision of a healthcare professional". This decision was based on their assessment of 47 cases, including 20 from the UK.

The liver reactions reported worldwide include abnormal liver-function tests, jaundice, liver failure requiring a liver transplant, hepatitis, and liver disease (sometimes referred to as necrosis). In the UK, abnormal liver-function tests and hepatitis were the most commonly reported events.

In addition to the medical seriousness of the reaction, consideration of the severity of the reaction is also important. A measure of severity is whether the patient was admitted to hospital. Of 39 reports from the UK, Germany, Sweden, USA, and the literature, just over half (21) were admitted to hospital for adverse liver reactions. Of the 11 UK patients that were admitted to hospital, one required a liver transplant and 3 others required treatment with steroid hormones.

Establishment of a clear pattern in the onset of these liver reactions has not been possible because of incomplete information. However, the limited information suggests that most liver reactions occur within the first 3 months of starting black cohosh.

Discussion

Issues regarding the safety of herbal medicines are particularly difficult to assess in the UK. Most herbal products on the UK market are unlicensed, and as such the MHRA lacks even basic information about what products are being sold and their usage levels.

Information obtained by the MHRA from the herbal sector suggests that a wide variety of unlicensed black-cohosh products are being sold, most of which are single-ingredient black-cohosh extracts, and that its use to alleviate menopausal symptoms has become increasingly popular since the late 1990s.

Currently, 27 products that contain black cohosh are licensed in the UK, all but one are products that contain a range of other herbal ingredients. However, information received through the Yellow Card Scheme implies that mainly products containing black cohosh only are associated with liver reactions: only one of the 21 reports received suggested that a multi-ingredient product was involved.

Spontaneous case reports rarely contain all the information needed to make a thorough assessment of the drug and suspected reaction. From early 2004, the MHRA actively followed up all reports involving black cohosh for further information. Hospital reports have also been followed up with the patient's GP to obtain as complete information as possible.

Worldwide, the liver reactions reported vary from abnormal liver-function tests and jaundice to liver failure. Just over half of the reactions reported resulted in admission to hospital. The limited evidence available suggests that the reactions occurred within three months of starting black cohosh.

Of the 21 UK reports received, 14 cases seem to support an association between adverse liver reactions and black cohosh. The period of onset of these reactions after taking black cohosh, the time of recovery on stopping treatment with black cohosh, and the exclusion of alternative causes of liver toxicity lend support to this association.

However, for UK 6 cases, the relation between black cohosh and liver injury is unclear, and 1 case lacks sufficient information for assessment. Moreover, 13 UK cases are reported as recovered or recovering after drug withdrawal, and did not require medical intervention.

In addition to the issues of obtaining all the required information in order to assess a case, the overall level of reporting adverse reactions for herbal products is very low—fewer than 150 reports every year. Therefore, although the reporting rate for black cohosh may have been stimulated by media coverage and the article in Current Problems in Pharmacovigilance (see page 4), the risk of liver reaction with this drug must be regarded as very important because currently 68% of reports received for black cohosh relate to liver reactions.

In the context of the usage information provided for the UK, liver reactions associated with black cohosh could be considered rare (occurring in more than 1 in 1000, but less than 1 in 10 000) or possibly very rare (occurring in more than 1 in 10 000). It is important to bear in mind that patients may be taking this treatment long term. However, adverse reactions associated with taking black cohosh could be under-reported, and its true usage may be unknown.

In addition to the lack of information about the number and usage of herbal remedies in the UK that contain black cohosh, more needs to be known about the brands that may be associated with liver toxicity. Because of a possible lack of knowledge about herbal medicine, many individuals (including healthcare professionals) might consider all products that contain the same active ingredient as essentially similar.

For worldwide cases where information about the brand has been provided there is one common feature—all were black-cohosh extracts standardised to contain 2·5% of a glycoside sugar called 27-deoxyacetin.

From the evidence obtained, it is difficult to determine if there is a risk of abnormal liver-function tests or hepatitis with all products that contain black cohosh, if these reactions are limited to extracts of black cohosh, or if the reports simply reflect the marketing of these products and the extracts account for the biggest proportion of the market.

Parallels with Kava-kava

It may be helpful to note comparisons with the safety issues concerning the herbal ingredient kava-kava. The sale, supply, and importation of Kava-kava as an unlicensed medicine for treatment other than for external use was prohibited in January 2003. As for black cohosh, no information is available regarding the possible mechanism of toxicity of Kava-kava.

When the Commission on Safety of Medicines (CSM) provisionally on a proposed ban on Kava-kava as unlicensed medicine in July 2002, CSM had assessed 68 case reports, including 3 UK reports of suspected hepatotoxicity associated with Kava-kava. Three of the 68 cases had a fatal outcome, and six resulted in liver transplantation. The CSM considered that there was evidence that Kava-kava was associated with rare cases of hepatotoxicity that may be serious in nature.

However, by contrast with Kava-kava, the hepatotoxicity noted in patients receiving black cohosh improved or completely recovered after they stopped taking it; this trend was not as predictable in those who reported liver injury with Kava-kava, which was associated with a stronger signal and greater severity.

Conclusions and recommendations

The Herbal Medicines Advisory Committee and the Commission on Human Medicines consist of a panel of experts that provide advice to the MHRA about the safety of herbal medicines.

The Committees were informed of ongoing concern about a possible association between black cohosh and adverse liver reactions. They were informed that Australia is to introduce warning labels about liver reactions for all black-cohosh products and that black-cohosh products in Germany already carry general warnings. In the UK, black-cohosh products do not contain any warnings about the risk of liver disease.

The Committees commented that many of the UK cases of raised or abnormal liver-function tests were asymptomatic, and that the 1 UK case of liver transplant reported in association with black cohosh had other factors that might exclude black cohosh as a cause of liver disease.

However, the Committees considered that the available evidence supported an association between black cohosh and risk of liver toxicity, even though the level of risk is difficult to determine. In light of the number of reports of liver disorders and the usage of this drug in the UK, it was considered important to inform users of black cohosh of this potential risk, and the following recommendations were made:

1. Warnings regarding rare adverse reactions in the liver should be added to the product information for black cohosh for both licensed and unlicensed products.

2. The issue of liver toxicity with black cohosh should be monitored closely, and further information should be gathered on the composition and quality of black-cohosh products available in the UK.

3. Licence holders of black-cohosh products should study the potential mechanism by which black cohosh is associated with liver injury.

Further information about herbal safety can be found on the MHRA website: http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=93. Anyone who has previously had any liver complaint or any other serious health complaint is advised not to take black cohosh without speaking with their doctor first.