Bradycardia in a patient taking black cohosh

Scott C McKenzie and Atifur Rahman

Cimicifuga racemosa, better known as black cohosh, has been widely used in Western cultures as a herbal treatment for relieving symptoms of menopause. It has previously been linked to cases of liver toxicity. We report a case of reversible complete heart block in a woman who had recently begun taking a herbal supplement containing black cohosh. We review the known side effect profile of black cohosh and its relationship to our case. ***(MJA 2010; 193: 479-481)***

Clinical record

In April 2009, a 59-year-old woman presented to a hospital emergency department after experiencing three episodes of syncope. She had never experienced cardiac ischaemic symptoms and there was no identifiable precipitant for a vasovagal event. She had no history of thyroid disease, hypertension, hyperlipidaemia or diabetes. Her personal and family medical histories were unremarkable, and she was a lifelong non-smoker and non-drinker. She had no recent febrile illness. She took no regular medications, but 2 weeks earlier had commenced taking one tablet daily of Remifemin (Schaper & Brümmer, Salzgitter, Germany; distributed by SciNat Australia, Gold Coast, Qld), a herbal preparation for the alleviation of menopausal symptoms.

While undergoing cardiac monitoring in the emergency department, the patient experienced a further episode of syncope. Telemetry (Box 1, A) and an electrocardiogram (ECG) (Box 1, B) demonstrated complete heart block. An atropine bolus was administered and an isoprenaline infusion commenced. The initial ECG performed after commencement of isoprenaline demonstrated 2:1 heart block. The patient's serum electrolyte levels were normal.

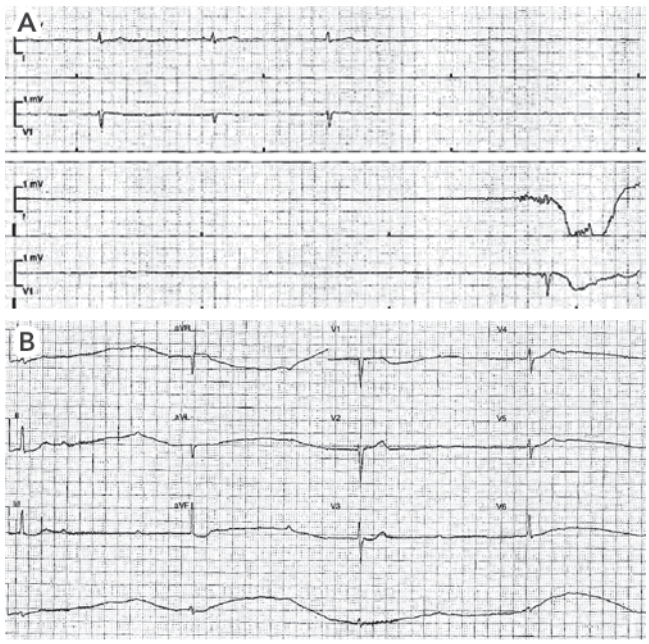
Further symptomatic complete heart block occurred while the patient was receiving the isoprenaline infusion (10 µg/min). A temporary pacing wire was placed, with reliable capture at a rate of 60 beats/min, an output of 0.5 V and reliable sensing at greater than 10 mV. Remifemin was ceased. Measures of thyroid function and serial serum cardiac troponin I levels were within normal ranges. Echocardiography demonstrated a structurally and functionally normal heart.

The patient required intermittent pacing for heart block throughout the next 2 days, after which pacing was no longer required, and she was successfully discharged on Day 5 with normal sinus rhythm. She underwent 24-hour ECG Holter monitoring 1 week after discharge, which confirmed no further episodes of heart block. She did not recommence Remifemin treatment and, 12 months later, reported no further episodes of syncope.

Discussion

The only listed active ingredient of Remifemin is isopropanolic *Cimicifuga racemosa* root extract, also known as *Actaea racemosa* and most commonly known as black cohosh (BC). Remifemin contains the most thoroughly researched formulation of BC.[1] BC was traditionally used by Native Americans of Canada and the eastern United States to treat malaria, impaired kidney function, sore throat, rheumatism, menstrual irregularities, and pain during childbirth.[2] Recently, there has been interest in its use in the treatment of menopausal symptoms.

1 Patient's telemetry and electrocardiogram (ECG) traces



Cardiac monitoring telemetry trace (A) and ECG (B) showing complete heart block. ◆

A recent systematic review identified over 72 studies of BC,[3] but only 13 of these were clinical studies involving BC-only preparations published since an earlier review in 2003.[4] Findings regarding adverse events were consistent with those of another earlier review, which had found that in more than 2800 patients, the rate of adverse events was about 5.4%, and over 97% of events were minor.[3] Most adverse events identified by the more recent review were gastrointestinal symptoms and musculoskeletal and connective tissue disorders.[3] Three recently published reviews have examined hepatotoxicity[3,5,6] — the most commonly reported serious adverse event associated with BC. They described seven, 42 and 31 cases of hepatotoxicity, respectively, but all three concluded that, in general, data supporting definite causality are lacking. The US Pharmacopeia Dietary Supplements Information Expert Committee, the European Medicines Agency, and the Australian Therapeutic Goods Administration (TGA) recommend that preparations containing BC should carry a warning of possible hepatotoxicity.[5-7] Other serious adverse events reported include anaphylaxis, cutaneous vasculitis and myotoxicity.[8-10]

Studies of BC for mutagenicity, teratogenicity and carcinogenicity have produced negative findings.[11]

A search of MEDLINE identified no reports of bradycardia due to BC in the literature. However, a Google internet search using the terms "black cohosh" and "heart rate" yielded numerous natural therapy websites describing "slow heart rate" as a side effect of BC. Slow heart rate is also described as a side effect of BC in the Micromedex AltMedDex System database (version 5.1; Thomson Reuters [Healthcare] Inc, Denver, Colo, USA).

We notified the TGA of this adverse event. The TGA has received 33 previous reports of suspected adverse events involving BC; none have involved bradycardia or syncope, and one involved hypotension (Rob Crowdy, Adverse Drug Reactions System Database Manager, TGA, personal communication, 3 June 2010).

The mechanism by which BC exerts its effects is uncertain. The rhizome of BC contains a number of biologically active constituents, including the triterpene glycosides actein, 27-deoxyactein and cimicifugoside, as well as long-chain fatty acids, resins, caffeic acids, isoferulic acids, phytosterin, fukinolic acid, salicylic acid, sugars and tannins.[12] To date, over 50 compounds derived from BC have been described.[13]

Serotonergic effects not due to serotonin selective reuptake inhibition have been demonstrated with BC preparations.[14,15] BC exhibits competitive binding to the 5-HT_{1A}, 5-HT_{1D} and 5-HT_7 receptors[14-16] and is a partial agonist at serotonin receptors.[17] This is noteworthy, as studies show that activation of 5-HT_{1A} receptors in the hypothalamus inhibit hypothalamus-mediated increases in heart rate and blood pressure.[18,19]

One study investigating the vasoactive effects of BC demonstrated that BC-derived cimicifugic acids inhibit noradrenaline-mediated contraction in rat aortas by inhibition of calcium influx.[20] In their 1993 review,[4] Borelli and colleagues described a 1935 study in which four glycosidic fractions obtained from the rhizome of BC were administered to dogs; the fraction insoluble in water was found to induce strong arterial hypotension, a decrease in cardiac contraction, and bradycardia to the point of death.

Based on the published pharmacology of the components of BC, it is difficult to provide a clear explanation as to how it mediates complete heart block. It is noteworthy that bradycardia is a widely listed side effect of BC in non-academic literature and that profound bradycardia has been documented in animal studies following administration of its extracts.[4] Applying the Naranjo algorithm to this case shows that BC was probably responsible for the presentation of our patient (Box 2).[21] Given the severity of the adverse reaction and the 2-week delay until its onset, reintroduction of BC while appropriately monitoring the patient to strengthen the argument for causality is not feasible.

Although BC is potentially useful in the treatment of menopausal symptoms, it has not been subjected to the extensive postmarketing surveillance that conventional pharmacological agents receive and has potential for numerous adverse effects. It should be considered as a potential cause of unexplained signs or symptoms of cardiac conduction disturbance.

Competing interests

None identified.

2 Application of the Naranjo algorithm[21] to this case

Criteria (score applied)	Score
1. Are there previous conclusive reports on this reaction? *Yes (+1) No (0) Do not know or not done (0)*	0
2. Did the adverse event appear after the suspected drug was given? *Yes (+2) No (– 1) Do not know or not done (0)*	2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? *Yes (+1) No (0) Do not know or not done (0)*	1
4. Did the adverse reaction appear when the drug was readministered? *Yes (+2) No (– 2) Do not know or not done (0)*	0
5. Are there alternative causes that could have caused the reaction? *Yes (– 1) No (+2) Do not know or not done (0)*	2
6. Did the reaction reappear when a placebo was given? *Yes (– 1) No (+1) Do not know or not done (0)*	0
7. Was the drug detected in any body fluid in toxic concentrations? *Yes (+1) No (0) Do not know or not done (0)*	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? *Yes (+1) No (0) Do not know or not done (0)*	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? *Yes (+1) No (0) Do not know or not done (0)*	0
10. Was the adverse event confirmed by any objective evidence? *Yes (+1) No (0) Do not know or not done (0)*	1
Total score*	6

* ⩾ 9 = definite adverse drug reaction (ADR); 5–8 = probable ADR; 1–4 = possible ADR; 0 = doubtful ADR. ◆

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