Spontaneous bleeding associated with Ginkgo biloba: a case report and systematic review of the literature

Bent S, Goldberg H, Padula A, Avins A L

CRD summary
The authors concluded that published case reports suggest the possibility of a causal association between the use of Ginkgo biloba and bleeding events, but further research is required. Given the low evidence level studies and the difficulty of establishing causal associations in general and in the included studies, the conclusions should be regarded with caution.

Authors' objectives
To collate evidence about the association between Ginkgo biloba (ginkgo) and bleeding from case reports and to evaluate a causal relationship.

Searching
MEDLINE, EMBASE, IBIDS and the Cochrane CENTRAL Register were searched without any language restrictions (from 1966 to October 2004); the search terms were reported. In addition, reference lists from the identified studies were screened. The authors also included one of their own case reports (full details were given in the same article as the review).

Study selection
Study designs of evaluations included in the review
Case reports were eligible for inclusion in the review.

Specific interventions included in the review
Studies of ginkgo were eligible for inclusion. Where reported in the included studies, the daily dose of ginkgo ranged from 75 to 600 mg and the duration of use ranged from 1 week to 2.5 years.

Participants included in the review
Studies of patients taking ginkgo were eligible for inclusion; no further inclusion criteria were specified. The patients in the included studies were aged from 33 to 78 years (most were aged 56 to 78).

Outcomes assessed in the review
Studies that reported bleeding, risk or complications were eligible for inclusion. Most of the included studies reported serious medical bleeding, most commonly intracranial bleeding.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies.

Assessment of study quality
Two reviewers independently assessed the following five published elements to establish causality from case reports: timing of the event relative to drug exposure; presence or absence of other factors that might cause the event; the result of withdrawing the drug (dechallenge); the result of reintroducing the drug (rechallenge); other data supporting the association. Any disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted the data onto a structured form and resolved any disagreements through
Methods of synthesis
How were the studies combined?
The studies were grouped according to the causality assessment elements and combined in a narrative.

How were differences between studies investigated?
Differences between the studies were discussed with respect to participants.

Results of the review
Fourteen case reports describing 15 incidences of bleeding were included.

None of the identified cases appeared to fulfill all five causality criteria.

Timing of event relative to drug exposure.

Twelve cases provided data on timing, in eight of these ginkgo was taken for more than 6 months before the bleeding event. In two cases (both intracerebral bleeding) ginkgo was used for less than 2 months and in the other two cases (both spontaneous hyphema) ginkgo was used for less than 2 weeks.

Presence or absence of other factors that might cause the event.

All but two cases (one subdural haematoma and one post-operative bleeding) had other risk factors for bleeding (age in thirteen cases, other drugs known to increase bleeding in five cases, and a fall, cirrhosis and intracerebral mass in one case each).

Dechallenge.

Six cases reported explicitly stopping ginkgo; none had recurrent bleeding over follow-up periods ranging from 3 months to 4 years. All three cases that measured bleeding times reported shorter bleeding times when ginkgo was not being taken.

Rechallenge.

The only case report that reintroduced ginkgo reported an increased bleeding time from 5 to more than 15 minutes (normal range: 2.5 to 9.5 minutes) when ginkgo was restarted.

Authors’ conclusions
Published case reports suggest the possibility of a causal association between using ginkgo and bleeding events, but further research is required.

CRD commentary
The review addressed a difficult research question; some inclusion criteria were clearly defined. The review was restricted to low evidence studies (case reports only) and the reasons for this were not clear. Several relevant sources were searched and attempts were made to minimise language bias. The authors acknowledged that they made no attempt to minimise publication bias. Methods were used to minimise reviewer errors and bias in the selection of studies, the assessment of causality and the extraction of data. The evidence from the included studies was discussed under the criteria used in the review to assess causality but the results were not always clearly reported. Given the restriction to very low evidence level studies, the difficulty of establishing a causal association and the fact that none of the included studies appeared to meet all the causal relationship criteria, the conclusions have to be regarded with caution.
Implications of the review for practice and research
Practice: The authors stated that patients taking ginkgo should be warned about the potentially increased risk of bleeding. Research: The authors stated that the safety of ginkgo should be further evaluated using large cohort studies with adequate follow-up and high-quality case-control studies that carefully assess use of ginkgo.

Bibliographic details

PubMedID
16050865

DOI
10.1111/j.1525-1497.2005.0121.x

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Bleeding Time; Ginkgo biloba /adverse effects; Hemorrhage /chemically induced; Humans; Male; Memory Disorders /drug therapy; Phytotherapy /adverse effects; Plant Preparations /adverse effects

AccessionNumber
12006003523

Date bibliographic record published
31/01/2008

Date abstract record published
31/01/2008

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.