Translated from ***Rev Prescrire*** **August 2007 ; 27 (286): 618-619**

Haemorrhage due to Ginkgo biloba?

● **About 20 detailed reports of haemorrhage (usually cerebral, ocular, or post-surgical) in patients using *Ginkgo biloba* extracts have been published. One-third of these patients were also taking drugs that increase the risk of bleeding (anticoagulants or antiplatelet drugs).**

● **Some substances contained in *Ginkgo biloba* have been shown to have an antiplatelet effect.**

● **In practice, patients with risk factors for bleeding (anticoagulant or antiplatelet treatment, surgery, etc.) should avoid using *Ginkgo biloba* extracts.**

Extracts from the leaves of the *Ginkgo biloba* tree are marketed in a variety of formulations with differences in administrative status (**a**). In France, the best-known extract is Tanakan°, which corresponds to a standardised *Ginkgo biloba* leaf extract (24% of flavonoids and 6% of terpenoids, including ginkgolides) (1). Various "dietary supplements" are also marketed for different uses: as "vasodilators", to improve cognitive functions, reduce tinnitus, relieve lower limb arterial disease, etc. (2).

About twenty cases of haemorrhagic adverse effects linked to *Ginkgo biloba* extracts have been published in detail.

Potentially severe haemorrhage. These reports include eight cases of cerebral haemorrhage, four cases of ocular haemorrhage, and several cases of post-operative bleeding (2-11). Surgery was sometimes needed to remove a haematoma or stop bleeding (2). One case of cerebral haemorrhage was fatal (4).

Bleeding time was reported in only three of these cases, and in all three cases bleeding time was reduced when *Ginkgo biloba* was withdrawn and increased again when *Ginkgo biloba* was reintroduced (2,7).

Uncertainties in the role of *Ginkgo biloba*. About one-third of these patients were also taking drugs that could potentially cause haemorrhage or interact with *Ginkgo biloba*: anticoagulants (warfarin), antiplatelet drugs (aspirin), and non-steroidal antiinflammatory drugs (ibuprofen) (**b**)(2-4,7,9,10).

Unfortunately, the reports are incomplete: the composition of the extract used was not specified in more than half the cases; no information was provided in some cases on the duration of treatment or on *Ginkgo biloba* withdrawal after the patient began to haemorrhage. Coagulation status was not studied in most cases.

An antiplatelet effect (through inhibition of platelet activating factor, PAF) was observed with a mix of three ginkgolides given at doses of 80 mg and 120 mg to six healthy volunteers (12). This effect cannot be extrapolated to the *Ginkgo biloba* extracts used by patients, however, because the composition of the extracts was not specified in more than half the reported cases, and, when a standardised extract was specified, the ginkgolide content was only 3.1%, for a usual dose of 120 mg/day (i.e. a daily ginkgolide dose of less than 4 mg).

A small placebo-controlled study in 12 healthy volunteers, lasting 3 months, showed a slight inhibitory effect of 120 mg standardised extract on the synthesis of a platelet clotting factor (thromboxane B2) (13).

However, a double-blind placebo-controlled trial in 32 healthy volunteers showed no statistically significant difference between 3 doses of standardised *Ginkgo biloba* extract (120 mg, 240 mg, and 480 mg/day) on coagulation status and platelet aggregation after 14 days of treatment (14). A double-blind placebo-controlled trial in 50 young healthy volunteers showed no statistically significant difference between 240 mg/day of standardised *Ginkgo biloba* extract (twice the usual daily dose) and placebo on coagulation status and platelet aggregation after 7 days of treatment (15).

In practice: caution. Cases of haemorrhage in patients taking *Ginkgo biloba*, together with the known antiplatelet effect of some standardised *Ginkgo biloba* extracts, call for caution. The latest French summary of product characteristics for Tanakan° does not mention a risk of bleeding, but this risk is mentioned in Martindale The Complete Drug Reference (1,16).

Patients with risk factors for bleeding such as anticoagulant or antiplatelet therapy and surgery should avoid using *Ginkgo biloba* extracts. For an assessment of clinical efficacy, see *Prescrire Int* 91, p. 205 - Ginkgo and Alzheimer's disease.

a- About 30 oral extracts of Ginkgo biloba are sold in France for therapeutic purposes, but with "dietary supplement" status. The composition of extracts with dietary supplement status is not controlled (ref 17).

b- One placebo-controlled trial assessed a standardised extract of Ginkgo biloba (240 mg/day) for 7 days in 50 healthy volunteers who were also taking 500 mg of aspirin a day. There was no statistically significant difference between the groups in terms of clotting factor levels. However, because of the small size of the study population, changes in some patients cannot be ruled out (ref 18).

Selected references from Prescrire's literature search.

1- "Tanakan°". In French datasheet compendium "Dictionnaire Vidal" Vidal, Issy-Les-Moulineaux, 2007: 2115-2116.
2- Bent S et al. "Spontaneous bleeding associated with Ginkgo biloba" *J Gen Intern Med* 2005; **20**: 657-661.
3- Matthews MK "Association of Ginkgo biloba with intracerebral haemorrhage" *Neurology* 1998; **50**: 1933-1934.
4- Meisel C et al. "Fatal intracerebral mass bleeding associated with Ginkgo biloba and ibuprofen" *Atherosclerosis* 2003; **167**: 367.
5- Vale S "Subarachnoid haemorrhage associated with Ginkgo biloba" *Lancet* 1998; **352**: 1145-1146.
6- Mac Vie OP "Vitreous haemorrhage associated with Ginkgo biloba use in a patient with age related macular disease" *Br J Ophthalmol* 2005; **89**: 1378-1379.
7- Rosenblatt M and Mindel J "Spontaneous hyphema associated with ingestion of Ginkgo biloba extract" *N Engl J Med* 1997; **336**: 1108.
8- "Postoperative Blutungen unter Ginkgo biloba Extracten (Tebonin)" *Arznei-telegramm* 2004; **35** (6): 62.
9- Hauser D et al. "Bleeding complications precipitated by unrecognized Ginkgo biloba use after liver transplantation" *Transplant* Int 2002; **15**: 377-379.
10- Bebbington A et al. "Ginkgo biloba: persistent bleeding after total hip arthroplasty caused by herbal self-medication" *J Arthroplasty* 2005; **20** (1): 125-126.
11- Destro MWB et al. "Bilateral haematoma after rhytidoplasty and blepharoplasty following chronic use of Ginkgo biloba" *Br J Plast Surg* 2005; **58**: 100-101.
12- Chung KF et al. "Effect of a Ginkgolide mixture (BN52063) in antagonising skin and platelet responses to platelet activating factor in man" *Lancet* 1987; **i**: 248-251.
13- Kudolo GB et al. "The ingestion of Ginkgo biloba extract (EGb 761) inhibits arachidonic acid-mediated platelet aggregation and thromboxane B2 production in healthy volunteers" *J Herb Pharmacother* 2004; **4** (4): 13-26.
14- Bal Dit Sollier C et al. "No alteration in platelet function or coagulation induced by EGb761 in a controlled study" *Clin Lab Haematol* 2003; **25** (4): 251-253.
15- Köhler S et al. "Influence of a 7-day treatment with Ginkgo biloba special extract EGb 761 on bleeding time and coagulation: a randomized, placebo-controlled, double-blind study in healthy volunteers" *Blood Coagul Fibrinolysis* 2004; **15** (4): 303-309.
16- "Ginkgo biloba". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com/mc/martindale consulted on 18 May 2007: 3 pages.
17- Prescrire Rédaction "Compléments alimentaires: la passoire administrative" *Rev Prescrire* 2006; **26** (276): 656- 657.
18- Wolf HR "Does Ginkgo biloba special extract Egb761 provide additional effects on coagulation and bleeding, when added to acetylsalicylic acid 500 mg daily?" *Drugs RD* 2006; **7**: 163-172.