Transpl Int (2002) 15: 377–379
DOI 10.1007/s00147-002-0432-y

BRIEF REPORT

Debra Hauser
Timothy Gayowski
Nina Singh

Bleeding complications precipitated by unrecognized *Gingko biloba* use after liver transplantation

Received: 22 June 2001
Revised: 28 February 2002
Accepted: 15 March 2002
Published online: 19 June 2002

D. Hauser · T. Gayowski · N. Singh (✉)
VA Pittsburgh Healthcare System,
Infectious Disease Section,
University Drive C, Pittsburgh,
PA 15240, USA
E-mail: nis5+@pitt.edu
Tel.: +1-412-688-6179
Fax: +1-412-688-6950

D. Hauser · T. Gayowski · N. Singh
Thomas E. Starzl Transplantation Institute,
Pittsburgh, Pennsylvania, USA

Abstract Because of its neurocognitive enhancing effects, *Gingko biloba* has emerged as amongst the most commonly used herbal products. We report a liver transplant recipient with potentially life-threatening toxicity resulting from Gingko biloba use. Seven days after a second liver transplantation for recurrent hepatitisB virus infection, subphrenic hematoma was documented in a 59-year-old Korean patient. Failure to control bleeding with CT-guided drainage necessitated exploratory laparotomy for the evacuation of a large subphrenic hematoma. Three weeks later, an episode of vitreous hemorrhage was documented. Unbeknownst to his care providers, the patient had been consuming *Gingko biloba* throughout the postoperative period. No further bleeding episodes occurred after the cessation of *Gingko biloba* use. Unrecognized use of herbal products may be associated with serious side effects and adverse clinical sequelae in transplant recipients. Given their increasing popularity, the use of herbal products should be routinely sought as part of the history in transplant recipients.

Keywords Alternative therapies
Transplants · Herbal products

Introduction

Use of alternative therapies, including herbal products, has increased exponentially in recent years. An estimated 42% of American adults are proposed to be consuming herbal medicines [8]. Notably, physicians were unaware of the herbal medicine use in up to 70% of the cases [9]. Currently, requirements documenting the efficacy of herbal remedies are not mandated [22], and little is known about their safety [3, 10]. Thus, potentially harmful drug interactions may be unappreciated and result in serious side-effects. We report a liver transplant recipient in whom hemorrhagic diathesis in the post-transplant period may have been precipitated by unrecognized use of *Gingko biloba*.

Case report

A 59-year-old Korean male underwent a second liver transplant in October 1999 as a result of cirrhosis secondary to recurrent hepatitisB virus infection. A routine post-operative ultrasound of the liver 1day after transplantation revealed a fluid collection adjacent to the left hepatic lobe and in the gallbladder fossa. A repeat ultrasound 4days later was performed to evaluate an increasing total bilirubin. This ultrasound revealed probable subcapsular hematoma around the dome of the liver, probable peri-hepatic hematomas/seromas both in the gallbladder fossa and adjacent to the lateral segment of the left lobe of the liver, and patent vessels with normal direction flow. A T-tube cholangiogram on this same day revealed no biliary leak. A third ultrasound of the liver was done 8days following the transplant, revealing complex fluid collections surrounding the liver and patent vessels with normal direction flow. A CT scan of the abdomen on that same day confirmed a large hematoma in the subphrenic space and near the porta-hepatis. CT-guided drainage of these hematomas was then performed. The

following day, the patient's hematocrit further decreased from 34.3 to 20.5%. An exploratory laparotomy was performed with evacuation of the hematomas. A source for the bleeding was not identified. A liver biopsy was done during the exploratory laparotomy, revealing no acute cellular rejection and changes consistent with bile duct obstruction. The patient's platelet count following transplantation until the day of the exploratory laparotomy ranged from 28,000 to 173,000. Prothrombin and partial thromboplastin times were within normal limits during this period of time. Transaminases and caninicular enzymes were decreasing from the time of transplantation. On the day of the exploratory laparotomy, the total bilirubin was 18.9mg/dl, alanine aminotransferase was 98IU/l, and alkaline phosphate was 141IU/l.

Three weeks after transplantation, the patient complained of visual blurring in his right eye. An ophthalmologic examination revealed a vitreous hemorrhage. The patient's platelet counts around the time of the visual blurring ranged from 102,000 to 174,000, and on the day the patient complained of visual blurring, the platelet count was 147,000. Prothrombin and partial thromboplastin times were within normal limits during this period. Transaminases and caninicular enzymes continued to decline further. On the day the patient complained of visual blurring, the total bilirubin was 2.5mg/dl, alanine aminotransferase was 23IU/l and alkaline phosphatase was 149IU/l. Shortly after this incident, the patient was noted to be consuming an unknown amount of *Gingko biloba* unbeknownst to his physicians and reported that he had indeed been consuming it during his recovery in the hospital and for an undetermined amount of time prior to transplantation. No further bleeding episodes were documented following the cessation of *Gingko biloba*. It is unknown whether this patient had been consuming any other herbal products. Of note, there were no unusual bleeding problems during the transplant procedure, and the patient did not have a history of a bleeding diathesis. At no time were anti-coagulants such as heparin ever used; however, 81mg aspirin daily was prescribed for this patient during the post-operative period.

Discussion

Herbal medicine use has been documented in up to 20% of solid organ transplant recipients [6]. Herbal products are perceived as "natural" and therefore generally considered safe and innocuous. However, their use in transplant recipients can be associated with potentially life-threatening adverse sequelae and drug interactions. St.John's wort has been associated with decreased cyclosporine levels [5, 15], resulting in rejection in kidney [2], heart [20], and liver [4, 13] transplant recipients. St.John's wort is proposed to be an inducer of CYP3A4 isoenzyme activity and P-glycoprotein expression. Since cyclosporine is metabolized by the same hepatic enzymes [5], the resultant interaction by enhancing the metabolism of cyclosporine can lead to decreased therapeutic immunosuppressive agent levels and allograft rejection [20].

Additionally, the quality, potency, and purity of the herbal products remains unstandarized and unregulated. In a bone marrow recipient, hepatic mucormycosis developed after ingestion of naturopathic herbal remedies. Arbitrary-primed PCR analysis revealed that the fungal isolate from the patient's liver aspirate and the herbal product were genotypically identical; therefore, it was thought that the mucor in the herbal product was the cause of hepatic mucormycosis in the patient [17].

Gingko biloba has long been used in Asia to treat a variety of ailments including asthma, cough, and urinary incontinence [7]. The popularity of this herb has grown substantially in the Western countries in recent years. An estimated 10 million Americans are believed to consume *Gingko biloba* and the total U.S. sales of this herb currently exceed $100 million [11]. The active ingredients of *Gingko biloba* preparations are flavone glycosides and terpene lactones. *Gingko biloba* functions as an antioxidant and free radical scavenger. Extracts of this herb are considered to have anti-stress and neuroprotective effects [1] and to lead to an improvement in cognitive performance [14].

Gingko biloba's primary biologic activity is proposed to result from inhibition of platelet-activating factor and, thus, platelet aggregation [16]. Use of *Gingko biloba* has been associated with subarachnoid haemorrhage [21], subdural hematomas [19], and bleeding in the anterior chamber of the eye [12, 18]. These side-effects can be particularly detrimental in liver transplant recipients since daily aspirin is prescribed routinely at many centers in the post-transplant setting. While a causal association between the use of *Gingko biloba* and bleeding in our patient cannot be proven, unexplained hemorrhages at multiple sites, lack of further recurrence of bleeding episodes after cessation of *Gingko biloba*, and the fact that bleeding is a recognized toxicity of this herb make it plausible that *Gingko biloba* was a contributory variable to our patient's bleeding episodes.

With the use of herbal products on the rise, it is increasingly likely that care providers may encounter potentially serious toxicity due to herbal therapies in the transplant setting. Patients should be cautioned against the use of these products, and consumption of herbal medicines should be sought as part of the history in transplant recipients.

References

1. Amri H, Ogwuegbu S, Boujrad N, Drieu K, Papadopoulos V (1996) In vivo regulation of peripheral-type benzodiazepine receptor and glucocorticoid synthesis by *Gingko biloba* extract EGb 761 and isolated gingkolides. Endocrinology 137:5707–5718
2. Barone GW, Gurley BJ, Ketel BL, Lightfoot ML, Abul-Ezz SR (2000) Drug interaction between St. John's wort and cyclosporine. Ann Pharmacother 34:1013–1016
3. Bauer BA (2000) Herbal therapy: what a clinician needs to know to counsel patients effectively. Mayo Clin Proc 75:835–841
4. Breidenbach T, Hoffmann MW, Becker T, Schlitt H, Klempnauer J (2000) Drug interaction of St. John's wort with cyclosporine. Lancet 355:1912
5. Breidenbach T, Kliem V, Burg M, Radermacher J, Hoffman MW (2000) Profound drop of cyclosporin A whole blood through levels caused by St. John's wort (*Hypericum perforatum*). Transplantation 69:2229–2232
6. Crone CC, Wise TN (1997) The survey of alternative medicine use among organ transplant patients. J Transplant Coord 7:123–130
7. Cuccinelli JH (1999) Alternative medicine *Gingko biloba*. Clin Rev 8:93–94
8. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL (1993) Unconventional medicine use in the United States: prevalence, costs and patterns of use. N Engl J Med 328: 246–252
9. Eisenberg D, Davis R, Ettner S, Appel S, Wilkey S, Rompay M, Kessler R (1998) Trends in alternative medicine use in the United States, 1990–1997. JAMA 280:1548–1553
10. Ernst E (1998) Harmless herbs? A review of the recent literature. Am J Med 104:170–178
11. Glisson J, Crawford R, Street S (1999) The clinical applications of *Gingko biloba*, St. John's wort, saw palmetto, and soy. Nurse Pract 24:28–46
12. Jancin B (1999) Gingko plus anticoagulation spells trouble. Med News 22:37
13. Karliova M, Treichel U, Malago M, Frilling A, Gerken G, Broelsch CE (2000) Interaction of *Hypericum perforatum* (St. John's wort) with cyclosporin A metabolism in a patient after liver transplantation. J Hepatol 33:853–855
14. Le Bars P, Katz M, Berman N, Itil T, Freedman A, Schatzberg A (1997) A placebo-controlled, double-blind, randomized trial of an extract of *Gingko biloba* for dementia. JAMA 278: 1327–1332
15. Mai I, Kruger H, Budde K, Johne A, Brockmoller J, Neumayer HH, Roots I (2000) Hazardous pharmacokinetic interaction of St. John's wort (*Hypericum perforatum*) with the immunosuppressant cyclosporine. Int J Clin Pharmacol Ther 38:500–502
16. Myerscough M (1998) Herbal remedies: how much do you know? Aust Fam Physician 11:1037–1040
17. Oliver MR, Van Voorhis WC, Boeckh M, Mattson D, Bowden RA (1996) Hepatic mucormycosis in a bone transplant recipient who ingested naturopathic medicine. Clin Infect Dis 22:521–524
18. Rosenblatt M, Mindel J (1997) Spontaneous hyphema associated with ingestion of *Gingko biloba* extract. N Engl J Med 336:1108
19. Rowin J, Lewis SL (1996) Spontaneous bilateral subdural hematomas associated with chronic *Gingko biloba* ingestion. Neurology 46:1775–1776
20. Ruschitzka F, Meier PJ, Turina M, Luscher TF, Noll G (2000) Acute heart transplant rejection due to St. John's wort. Lancet 355:548–549
21. Vale S (1998) Subarachnoid haemorrhage associated with *Gingko biloba*. Lancet 352:36
22. Winslow LC, Kroll DJ (1998) Herbs as medicines. Arch Intern Med 158: 2192–2199