Fatal Seizures Due to Potential Herb-Drug Interactions with Ginkgo Biloba

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Abstract

Alternative therapy including herbal drugs and complementary medicine is becoming increasingly popular. However, the rise in the incidence of herb-drug interactions is causing concern, especially in the absence of warning labels addressing potential adverse effects. We present the case of a 55-year-old male who suffered a fatal breakthrough seizure, with no evidence of non-compliance with his anticonvulsant medications. The autopsy report revealed subtherapeutic serum levels for both anticonvulsants Depakote® and Dilantin®. Concomitant with his prescribed medications, the decedent was also self-medicating with a cornucopia of herbal supplements and nutraceuticals, prominent among which was Ginkgo biloba. Ginkgo, an herbal extract from the leaves of the Ginkgo biloba tree, has been used medicinally for centuries and has been touted as a cure for a variety of medical conditions. The induction of Cytochrome P450 enzymes by components of herbal drugs has been known to affect the metabolism of various drugs. Dilantin is primarily metabolized by CYP2C9, and secondarily metabolized by CYP2C19. Valproate metabolism is also modulated in part by CYP2C9 and CYP2C19. A recent study revealed significant inductive effect of ginkgo on CYP2C19 activity. CYP2C19 induction by ginkgo could be a plausible explanation for the subtherapeutic levels of Dilantin and Depakote. Additionally, ginkgo nuts contain a potent neurotoxin, which is known to induce seizure activity. Evidence of other herbal drugs diminishing the efficacy of anticonvulsant medication does exist; however, there has been only one other documented instance of ginkgo potentiating seizure activity in the presence of anticonvulsant therapy. Highlighting the potential adverse effects and drug interactions of ginkgo on the packaging of the drug may help prevent inadvertent use in vulnerable individuals.

Introduction

Alternative therapy including herbal drugs and complementary medicine are becoming increasingly popular in the Western world. Although some of these drugs have potential benefits, there is an erroneous public perception that these herbal drugs are benign and without adverse effects (1). However, as is being documented, herb-drug interactions are becoming alarmingly frequent, especially considering the absence of a label addressing the possibility of adverse effects. The incidence of herb-drug reactions are generally based on two factors, that is, factors related to drug and factors related to the individual. Drug-related factors are dose, dosing regimen, route of administration, pharmacokinetics, and therapeutic range. Patient associated factors are genetic polymorphisms, age, gender, and pathology (2). The following case is about a 55-year-old patient, compliant with his seizure medications, suffering a fatal breakthrough seizure. The autopsy report revealed subtherapeutic serum levels of both the anticonvulsants, Depakote and Dilantin. Concomitant with his prescribed medications, the patient was also self-medicating with a cornucopia of herbal supplements and nutraceuticals, prominent among which was ginkgo biloba. Ginkgo is an herbal extract from the leaves of the Ginkgo biloba tree, and has been used medicinally for centuries (3). It has been credited with increasing cerebral blood flow, and the herbal extract is used to treat a variety of conditions including post-thrombotic syndrome, peripheral vascular disease, difficulties with memory, confusion, anxiety, headache, tinnitus, etc. (3-5). In 1998, more than $649 million was spent on medicinal herbs in the United States (6), and ginkgo biloba was the top seller with reported retail sales of $150 million. The biologically active components of ginkgo biloba include the ginkgo-flavone glycosides or flavonoids (e.g., bilobetin, ginkgetin, sciadopitin, quer cetin, etc.) and the terpenoids (e.g., bilobalides and ginkgolides) (2,5-7). Ginkgolides are potent inhibitors of platelet aggregating factors, which explains the purported pharmacologic actions of ginkgo (i.e., increased vasodilation and peripheral blood flow rate) (2). Reports of serious adverse effects such as prolonged bleeding times and spontaneous subdural hematomas have been associated with the anti-platelet aggregating factor activity of ginkgo (3,8). Ginkgo has also been reported to interfere with platelet function and has been associated with bleeding, even in the absence of anti-coagulants (2). Some of the possible drug interactions of ginkgo include aspirin, warfarin, ticlopidine, clopidogrel, and dipyridamole (9). Although there has been documented evidence of an herbal agent (shankapulshpi) causing diminished effectiveness of anticonvulsant medication (phenytoin), there has been only one other reported instance of ginkgo potentiating seizure activity in the presence of anticonvulsant medication (3,8).
Case History

The decedent, a 55-year-old male, was swimming at a health club with an attendant walking alongside as he swam, when he suddenly went underwater and lost consciousness. The two life-guards at the pool immediately pulled him out, and one of them initiated CPR; paramedics were summoned. There was an initial report of a seizure in the pool, but it could not be corroborated. During the time that the paramedics attempted resuscitation, they encountered a pulseless rhythm, ventricular fibrillations, and ventricular tachycardia. The patient received defibrillation and intravenous advanced cardiac life support medications including epinephrine, bicarbonate, and normal saline. At the ER, he was observed to be lifeless and cyanotic, with an absence of spontaneous movements or respirations. Pulmonary sounds were symmetric, with bilateral coarse rales and rhonchi. The pupils were fixed and dilated with an absence of corneal and doll's eye reflexes. The nail beds were cyanotic, and the patient was flaccid with an absence of neurological responses. The patient was pronounced dead, and an autopsy was indicated. Autopsy results revealed evidence of an old cerebral infarct and severe coronary vascular disease, as well as an old myocardial infarct and prior bypass surgery. The toxicological analyses involved a broad-based gas chromatography (GC) screen for acidic/neutral drugs, with confirmation by GC–mass spectroscopy (MS). Trinders' test was used to check for salicylates, and headspace GC was used for analysis of volatiles. Chem-Elut columns were used for GC. The toxicological analysis revealed a femoral blood valproic acid (Depakote) level of less than 26 μg/mL and a phenytoin (Dilantin) level of 2.5 μg/mL. Caprilic acid and para-methyl phenytoin were used as internal standards for valproic acid and phenytoin, respectively. Both the anti-epileptic drugs were considered to be subtherapeutic at the time of death.

Table I. Fluctuations in the Dilantin Levels

<table>
<thead>
<tr>
<th>Date</th>
<th>Dilantin Level</th>
<th>Therapeutic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/24/00</td>
<td>4.1 mg/L</td>
<td>10 to 20 mg/L</td>
</tr>
<tr>
<td>5/3/00</td>
<td>10.4 mg/L</td>
<td></td>
</tr>
<tr>
<td>7/21/00</td>
<td>14.0 mg/L</td>
<td></td>
</tr>
<tr>
<td>8/4/00</td>
<td>9.6 mg/L</td>
<td></td>
</tr>
<tr>
<td>8/14/00</td>
<td>10.6 mg/L</td>
<td></td>
</tr>
<tr>
<td>8/25/00</td>
<td>13.7 mg/L</td>
<td></td>
</tr>
<tr>
<td>9/29/00</td>
<td>21.2 mg/L</td>
<td></td>
</tr>
<tr>
<td>10/20/00</td>
<td>14.1 mg/L</td>
<td></td>
</tr>
<tr>
<td>11/30/00</td>
<td>13.9 mg/L</td>
<td></td>
</tr>
</tbody>
</table>

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Discussion

Herbal products have long been popular, and some of their modern derivatives constitute highly prescribed medications (e.g., the evolution of digoxin from foxglove). Although many herbs have been evaluated in randomized controlled trials, the limitations of poor design, small samples, and uncertain composition of products make any reliable interpretation impossible. Furthermore, the absence of advisory warning labels addressing possible adverse effects of these nutraceutical agents, make it imperative to study and document any possible drug interactions. The U.S. Food and Drug Administration's Special Nutritional Adverse Effect Monitoring System (SN/AEMS) described seven reports of seizures associated with ginkgo. Four reports were associated with multi-ingredient products and three were associated with single-ingredient preparations, each from different manufacturers. Several reports in the literature indicate that consumption of ginkgo nuts might induce seizure activity. After the consumption of ginkgo nuts, a previously healthy 36-year-old woman without any past or family history of epilepsy developed vomiting and generalized tonic and clonic convulsions (11). Ginkgo nuts contain a potent neurotoxin, 4'-O-methoxypyriddoxine (4'-MPN), which is known to indirectly inhibit the enzyme activity of glutamate decarboxylase, resulting in decreased levels of γ-aminobutyric acid (GABA) (12). GABA is an inhibitory neurotransmitter, and a reduced concentration of GABA may lead to seizure induction (11). The leaves of the ginkgo tree are a source of extracts for commercial ginkgo products. Although the majority of commercial ginkgo products may not contain sufficient 4'-MPN to cause seizures, depending on the harvest season and the potential introduction of contaminants, 4'-MPN may be present in amounts sufficient to cause seizures in a vulnerable populace, such as infants or individuals with known seizure disorders (13). Arenz et al. (14) documented the occurrence of 4'-MPN in ginkgo leaves and some commercially available ginkgo preparations. Manocha et al., (15,16) proposed an alternative mechanism for the putative seizure activity of ginkgo biloba. They found that ginkgo, a platelet-aggregating factor (PAF) antagonist, facilitated strychnine-induced convulsions in mice. This study emphasized the possible modulating effect of ginkgo biloba on the inhibitory neurotransmitter glycine because strychnine competes with glycine, thus exerting a central stimulant effect through in-
hibitory blockade (15,16). Additionally, the prior administration of ginkgo to mice potentiated the seizure activity of picrotoxin, a GABA antagonist, in the presence of the anti-convulsant drugs sodium valproate and carbamazepine. This was possibly because of the anti-GABAergic activity of ginkgo components (15,16).

Another putative hypothesis in the current case was the induction of the Cytochrome P450 (CYP) enzyme system by nutraceutical ingredients, causing extensive metabolism of the anticonvulsant medications, thus leading to seizure induction due to the subtherapeutic levels of these drugs. Zhou et al. (2) describe the induction and inhibition of CYP enzyme system by various components of herbal drugs. If the CYP enzymes metabolizing a certain drug are induced, they will hasten its elimination from circulation, thereby diminishing its therapeutic benefit (17). Dilantin is primarily metabolized by CYP2C9 and secondarily metabolized by CYP2C19 (18). Additionally, valproate is also metabolized by CYP2C9 and CYP2C19; however, these enzymes account for a relatively minor portion of its excretion (19). A recent study by Yin et al. (20) found significant inductive effect of ginkgo on CYP2C19 activity. They concluded that co-administration of ginkgo with a CYP2C19 substrate may significantly reduce the effect of the drug. CYP2C19 induction by ginkgo could be a plausible explanation for the subtherapeutic levels of Dilantin and Depakote.

Granger (1), in what is probably the only other documented case of ginkgo precipitating seizure activity in the presence of anticonvulsant medications, describes two patients with well-controlled epilepsy, compliant with their anti-epileptic medication (sodium valproate), who developed seizures within two weeks of using ginkgo products. After cessation of the herbal remedy, both the patients remained seizure-free without any increase in the dosage of antiepileptic medication (1). Other reports of ginkgo include an elderly female with elevated blood pressure who was treated with a thiazide diuretic and later began taking ginkgo biloba. After one week, her blood pressure increased further and remained increased for a few weeks. After stopping ginkgo and the diuretic, blood pressure returned to pretreatment level. Furthermore, in patients with epilepsy, there have been also reports of breakthrough seizures occurring with the combination of valproate and phenytoin (13). The absence of federal mandate and the lack of a warning label may endanger individuals afflicted with epilepsy. Miller (8) advises against the use of ginkgo products in epileptic patients, as the use of anticonvulsants. Tyagi et al. (21) suggest that the use of ginkgo may lower the seizure threshold, and they advise against its use with antiepileptic medications. Ginkgo is known to provide some therapeutic benefit in cerebral ischemia, memory deficiency, and other cerebral disorders; however, a co-morbid seizure disorder may also be present in these individuals. For them, any possible benefit with ginkgo could be offset by potential interactions with anticonvulsant medications. In his report, Granger (1) emphasizes the need for highlighting the seizure potential and other possible adverse effects of ginkgo on the packaging of the drug.

Conclusions

Currently, there are no means to ascertain that the ginkgo product is free of the seizure-inducing neurotoxin. In the present case, the fluctuations in the concentrations of Dilantin and Depakote could not be definitively attributed to herb-drug interactions. However, in the absence of an alternative hypothesis, it is our belief that the nutraceutical product contributed to breakthrough seizures in the decedent. Although the association is not conclusive, the literature reports have sufficient probative value to suggest caution in the use of ginkgo products by individuals with a history of convulsive disorders. A balance is sought between the proven benefits and the suspected adverse effects of ginkgo. However, without a qualifying label or a standardized quality control process, use of some nutraceutical products may prove to have hazardous consequences in susceptible individuals.

References

16. A. Manocha, K.K. Pillai, S.Z. Husain. Effect of ginkgo biloba on


