Status Epilepticus Associated with Borage Oil Ingestion

Wafa'a A. Al-Khamees · Michael D. Schwartz ·
Saleh Alrashdi · Adam D. Algren · Brent W. Morgan

Published online: 9 March 2011
© American College of Medical Toxicology 2011

Abstract The use of herbal and complementary medicine is common. Many herbal products are known to produce serious adverse effects. Borage oil is derived from the seeds of the borage plant (*Borago officinalis*) an abundant source of gamma-linolenic acid (GLA), and Borage oil has been promoted as a treatment for rheumatoid arthritis, atopic dermatitis, diabetic neuropathy, and menopause-related symptoms. We report a case of status epilepticus in a patient who consumed borage oil for one week.

Keywords Borage oil · Gamma-linolenic acid · Status epilepticus · Herbal

Background

Complementary and alternative medicine (CAM) use has increased significantly in the past few decades [1, 2].

Previous presentation Poster Presentation North American Congress Clinical Toxicology 2006: Status Epilepticus Associated with Borage Oil. Clinical Toxicology. 2006; 44:642–43 (abstract).

W. A. Al-Khamees · M. D. Schwartz · S. Alrashdi · B. W. Morgan
Georgia Poison Center, Grady Health System,
Atlanta, GA, USA

W. A. Al-Khamees · M. D. Schwartz · S. Alrashdi · B. W. Morgan
Emory University School of Medicine,
Atlanta, GA, USA

A. D. Algren
Departments of Emergency Medicine and Pediatrics,
Truman Medical Center and Children's Mercy Hospital,
University of Missouri–Kansas City School of Medicine,
Kansas City, MO, USA

B. W. Morgan (✉)
The Hurt Building, Suite 600, 50 Hurt Plaza,
Atlanta, GA 30303, USA
e-mail: bmorg02@emory.edu

Herbal medicine is one of the most popular forms of CAM and the use of herbal remedies and dietary supplements is widespread throughout the world, in part because of its perceived benefit by the consumer and a belief that it is inherently safe [3, 4]. Patients with chronic medical conditions frequently turn to CAM without physician knowledge and people with epilepsy are no exception in this regard. One survey showed that nearly one in six adults in the USA taking prescription drugs is also taking at least one herbal remedy, and 24% of patients in tertiary-care epilepsy clinics reported using CAMs [5, 6]. This creates a potential for adverse effects as many herbal and dietary supplements are known to have interactions with prescription medications. Inappropriate use of CAM may induce seizures among individuals predisposed to epilepsy, or worsen seizure control in those with a known seizure disorder [2].

There are a number of herbs that potentially contain neurotoxic compounds [1]. Borage seed oil is derived from the seeds of the borage plant (*Borago officinalis*). Borage seed oil, which contains gamma-linolenic acid (GLA) and linoleic acid (LA), is popular because of its use medicinally as an anti-inflammatory for treating arthritis, as well as for the treatment of certain skin conditions (e.g., atopic dermatitis), menopause-related symptoms and diabetic neuropathy [7]. We report a case of status epilepticus temporally associated with the use of borage seed oil.

Case Report

A 41-year-old previously healthy female, presented to a medical facility with continuous seizure activity. She was noted to be confused with episodes of inappropriate staring and laughing (gelastic seizures; laughter without mirth) that progressed to generalized tonic-clonic seizures. One week prior to presentation, she began taking between 1,500 and 3,000 mg of borage oil a day. She was also regularly taking

several other supplements including vitamin B and E complexes, ascorbylpalmitate, coenzyme Q10, and L-carnitine. She did not take any prescription medications and did not drink alcohol or use illicit drugs. She worked as an interior decorator and there were no reported hobbies that would expose her to neurotoxins. There was no family history of epilepsy.

Several doses of lorazepam failed to control the seizures. The patient was intubated for airway protection and she was loaded intravenously with fosphenytoin. A lumbar puncture was reportedly normal but the patient was started empirically on acyclovir to treat possible herpes encephalitis. The patient was admitted to the ICU on a propofol drip for sedation. Recurrent seizures developed and the patient was loaded with valproic acid prior to transfer to our tertiary referral hospital.

Upon arrival at our facility, she was intubated and sedated with lorazepam. Her temperature was 37.8 C, pulse 96 bpm, BP 141/79 mmHg, RR 12/m. Head exam revealed normocephaly and no signs of trauma. The pupils were 5 mm bilaterally and sluggishly reactive. The neck was supple without meningismus. Cardiopulmonary and abdominal exam were normal. Extremities showed no cyanosis or edema. Pulses were equal and no skin rashes or abrasions were noted. The patient remained persistently altered and would not open eyes or follow commands. She would minimally withdraw to pain in all extremities. An MRI of the brain was normal and serial EEG monitoring confirmed right temporal lobe status epilepticus. Because of the continued status epilepticus, the patient was placed in a pentobarbital-induced coma. The acyclovir and the phenytoin were continued.

Her complete blood count, serum chemistries, and thyroid studies were unremarkable. A repeat lumbar puncture was performed on the third day at our hospital. Cerebral spinal fluid analysis revealed WBC 7, RBC 8, protein 31 mg/dl, and glucose 65 mg/dl. Bacterial, fungal, mycobacterial cultures, Lyme antibodies, and the VDRL were negative. Viral studies for HSV, varicella, CMV, West Nile, Enterovirus, St Louis, Eastern and Western equine encephalitis were negative. Serologies were negative for rickettsia, ehrlichiosis, hepatitis A, B, C, and toxoplasmosis.

A urine gas chromatography-mass spectrometry (GC/MS) screen was negative. Urine drug immunoassay was negative for propoxyphene, opiates, cocaine, amphetamines, methadone, and phencyclidine. Heavy metal testing results revealed blood lead, 0.8 mcg/dl; 24 h urine for mercury and arsenic, 2 and 12.5 mcg/L, respectively.

With the history of borage seed oil use, measurements of GLA and LA were made on a whole blood sample that was obtained on her first day at our hospital and a cerebrospinal fluid (CSF) sample from day 3 at our hospital. The concentrations of fatty acids (expressed as a wet lipid weight

basis) were: GLA 345 µg/g of blood (Control 191 µg/g), and LA 259 µg/g of blood (control 165 µg/g). Expressed as a whole blood concentration (SI units), the GLA concentration was 1,165 µmol/L and linoleic acid concentration was 871 µmol/L. Analysis of the CSF sample was negative for GLA and LA.

The analytical method involved serial extraction of 1 g of the blood sample with methyl-t-butyl ether (MTBE). The MTBE layer was dried over anhydrous sodium sulfate. The MTBE layer was concentrated to near dryness and derivatized using diazomethane. The sample was blown down to near dryness and brought up to 1.0 ml in MTBE. Twenty microliters of internal standard (1,030 ppm d10-phenanthrene) was added and the extract was analyzed via GC/MS. A calibration standard was also prepared using: 100 µL of linoleic acid (100 ppm) and 100 µL of linolenic acid (128 ppm).

The seizures were controlled with pentobarbital but would reoccur as pentobarbital dosing was reduced. Levetiracetam was instituted. After roughly 10 days in the pentobarbital coma, the pentobarbital was tapered and her neurological status rapidly improved. The patient developed an increase in transaminases and the phenytoin was discontinued. She was transferred to a rehab facility. While at the rehab facility, she developed two brief seizures that resolved spontaneously. Carbamazepine was added and she had no further seizure activity. At 4-months follow-up, she reported no convulsive seizures but was occasionally having simple partial seizures which involved a familiar-sounding tone that can be triggered by loud noises. She also reported short-term memory and word-finding impairment. At that point, she transferred her care to a neurologist closer to her home and was lost to follow-up.

Discussion

Numerous herbal medicines have effects in the central nervous system and have the potential for adversely affecting patients with epilepsy [1]. New-onset seizures have been reported to occur in patients taking CAM when no other cause has been found [2]. We report a case of status epilepticus associated with the ingestion of borage oil. Borage (*B. officinalis*) oil has been used for the treatment of depression, inflammation, fevers, and coughs, although these uses have not been empirically tested. GLA, a polyunsaturated fatty acid, is the ingredient of borage seed oil that is reported to be responsible for its beneficial, specifically anti-inflammatory health effects [7, 8]. Borage oil products typically contain 20–27% GLA [7].

Borage seed oil is a significant source of gamma-linolenic acid, C18:3(n-6), which is converted to dihomo-gamma-linolenic acid (DGLA) a precursor to a variety of the 1-series prostaglandins and 3-series leukotrienes.

GLA is thought to exert its therapeutic effect in rheumatologic and dermatologic conditions by inhibiting leukotriene synthesis, resulting in anti-inflammatory and anti-thrombotic effects [7, 8]. Borage seed oil has been estimated to contain the highest amounts of GLA: 23% compared to black currant seed oil or evening primrose oil, both of which are also well known herbal supplement sources of GLA [7]. Borage seed oil also contains high concentrations (up to 35–38%) of LA, another omega-6 fatty acid, and a precursor to GLA in normal fatty acid metabolism. Two putative toxic minor metabolites of LA, leukotoxin diol (LTX), and isoleukotoxin diol (iLTX), may result from the activity of epoxidehydrolase on LA [9]. In normal fatty acid metabolism, LA is converted to GLA by means of a $\Delta 6$ -desaturase in the rate-limiting step of essential fatty acid metabolism. GLA is then converted to DGLA and then to arachidonic acid (AA). In a single-dose study of radio-labeled LA metabolism in healthy subjects, the percent of LA recovered as AA was very low (0.05% of the radio-labeled dose) [10].

In our literature review of central nervous system (CNS) effects related to GLA or LA, we found only two reports describing a total of five cases of purported GLA-induced seizures. Three patients with schizophrenia developed EEG-confirmed temporal lobe epilepsy after starting treatment with evening primrose oil. All patients improved after withdrawal of primrose oil and institution of carbamazepine treatment [11]. Generalized tonic-clonic seizures were described in two further schizophrenic patients after starting treatment with evening primrose oil [12]. However, one recent study has called these two earlier case series into question [13]. It should be noted that all five cases used evening primrose oil rather than Borage oil, which was used by our patient. Borage oil may have the potential to lower the seizure threshold although some studies report anti-epileptic effects of fatty acids GLA and LA [4, 6]. Research in this regard is mixed and so no certain conclusions can be drawn. These herbal preparations may best be avoided by epilepsy patients at least until this issue is clarified [1, 14].

In a review of the toxicity of LA, the two monoepoxide metabolites (LTX diol and iLTXdiol) resulting from the action of epoxidehydrolase rather than $\Delta 6$ -saturase, showed significant cytotoxic effects in a number of *in vitro* and *in vivo* test systems. Cytotoxic mechanisms included: reduced mitochondrial oxygen consumption and loss of cellular membrane potential. Organ effects included smooth muscle relaxation (porcine stomach), ARDS-like pulmonary injury (rats), and depressed cardiac function (dogs) [9, 15]. In addition, polyunsaturated fatty acids can be oxidized in cells and tissues to oxygenated α, β -unsaturated aldehydes [15]. These putative toxins have been implicated in a number of pathological conditions including chronic

inflammation, neurodegeneration, and cancer [16]. Their role in seizures is unclear.

Analysis of a blood sample obtained on admission from our patient demonstrated an elevated concentration of GLA (1,165 $\mu\text{mol/L}$) but a low level of LA (871 $\mu\text{mol/L}$). Reference ranges (>18 years of age) for essential fatty acid analyses give a range of 16–150 $\mu\text{mol/L}$ for GLA and 2,270–3,850 $\mu\text{mol/L}$ for linoleic acid. (Information provided courtesy of Mayo Medical Laboratories, Rochester, MN, USA).

In a study of essential fatty acid levels in normal controls ($n=31$), asthma/allergic rhinitis patients ($n=35$), and atopic dermatitis patients ($n=35$), the control levels of LA were $2,902.65 \pm 742.25$ $\mu\text{mol/L}$ and control levels of GLA were 22.07 ± 15.65 $\mu\text{mol/L}$ [17]. Another study of the pharmacokinetics of gamma-linolenic acid in healthy volunteers after evening primrose oil ingestion found levels of LA and GLA to be 327.3 ± 155.2 $\mu\text{g/ml}$ (1167.0 ± 553.4 $\mu\text{mol/L}$) and 11.4 ± 9.7 $\mu\text{g/ml}$ (40.9 ± 34.8 $\mu\text{mol/L}$), respectively [18]. By contrast, in our patient, the non-lipid adjusted concentrations of LA and GLA were 244 $\mu\text{g/ml}$ (871 $\mu\text{mol/L}$) and 324 $\mu\text{g/ml}$ (1,163 $\mu\text{mol/L}$).

The reasons for the non-detection in CSF in our patient may include methodological limitations, reduction in GLA and LA concentrations due to a delay in lumbar puncture (which occurred 2 days after the blood sample that was analyzed for GLA and LA) and the possibility that an unmeasured toxic metabolite of GLA or LA (such as an oxygenated α, β -unsaturated aldehyde or diol) was present in CSF in greater quantity compared to GLA or LA. GLA and LA, along with a host of other polyunsaturated free fatty acids (palmitic, oleic, myristic) are present in normal CSF: a study of traumatic brain injury and healthy controls found a mean concentrations of LA in spinal fluid of 356 $\mu\text{mol/L}$ (error range not provided) in controls [19]. The presence of detectable levels of polyunsaturated free fatty acids in CSF in healthy individuals suggests methodologic failure as the likeliest explanation for the undetectable concentrations of GLA and LA in that matrix in our patient.

The ingestion of borage seed oil likely explains the high blood level of GLA detected in our patient. In normal fatty acid metabolism, dietary LA is converted to GLA by means of $\Delta 6$ -saturase. Exogenous GLA, from ingestion of borage seed oil for example, would bypass this rate-limiting step and could lead to the very high level of GLA (relative to LA) found in our patient. The LA concentration in our patient was found to be lower than the LA concentrations found in control subjects during an atopic dermatitis-GLA treatment trial and in a pharmacokinetic study of GLA metabolism [17, 18]. Other explanations for the high levels of GLA and low levels of LA found in our patient could be unique to the

product she ingested. Unfortunately, the herbal preparation which our patient started was never recovered and thus an analysis of the GLA and LA content could not be performed. A compounding or other formulation error could have resulted in excessive doses of GLA being administered. The high level of GLA found in our patient, the proximity of her consumption of borage seed oil 1 week before her seizures developed, and the limited case series describing temporal lobe seizures developing following GLA administration reported in the literature, suggest that consumption of borage seed oil was associated with our patient's illness either by directly causing or unmasking an undiagnosed seizure disorder. It is equally possible that some as yet un-identified toxin in *B. officinalis* could be responsible for the development of seizures either after excessive borage oil ingestion, or perhaps in a subset of those who use it therapeutically.

We attempted to obtain a complete list of supplements taken by the patient from her husband. Upon awakening from the pentobarbital-induced coma, it was difficult for the patient to provide any additional information because of short-term memory impairment. Two of her supplements, Coenzyme Q10 and L-carnitine have rarely been associated with seizures but not of the temporal lobe variety. It is possible that some non-reported supplement could have contributed to her illness either directly or via interacting with the borage oil.

Extensive clinical investigations in our patient failed to identify an alternate infectious or toxicological cause of her seizures. If anything, our case serves to highlight the uncertainties that surround herbal and CAM usage and the clinical and analytical challenges that face the medical toxicologist in approaching a possible case of botanical or herbal poisoning.

Conclusion

Available evidence suggests that herbal medicines may have the potential for adverse effects in people with seizure disorders. Many herbs are known to affect the central nervous system, some with sedative effects and others stimulating the CNS. The link between herbal remedies and seizure activity is suggestive and many knowledge gaps exist. Limited human case reports have been published and we add this case in which Borage oil ingestion was temporally associated with the development of temporal lobe and gelastic seizures progressing to status epilepticus. Herbal products and

alternative medicines should be considered in the differential diagnosis of status epilepticus.

Source of funding None.

Conflicts of Interest None.

References

1. Spinella M (2001) Herbal medicines and epilepsy: the potential for benefit and adverse effects. *Epilepsy Behav* 2(6):524–532
2. Tyagi A, Delanty (2003) Herbal remedies, dietary supplements, and seizures. *Epilepsia* 44(2):228–235
3. Abbot NC, Ernst E (1997) Patients' opinions about complementary medicine. *Forschende Komplementärmedizin* 4:164–168
4. Ernst E, White A (2000) The BBC survey of complementary medicine use in the UK. *Complement Ther Med* 8:32–36
5. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA (2002) Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *JAMA* 287:337–344
6. Peebles CT, McAuley JW, Roach J, Moore JL, Reeves AL (2000) Alternative medicine use by patients with epilepsy. *Epilepsy Behav* 1:74–77
7. Barre D (2001) Potential of evening primrose, borage, black currant, and fungal oils in human health. *Ann Nutr Metab* 45(2):47–57
8. Belch J, Hill A (2000) Evening primrose oil and borage oil in rheumatologic conditions. *Am J Clin Nutr* 71(suppl):352S–356S
9. Greene JF, Hammock BD (1999) Toxicity of linoleic acid metabolites. *Adv Exp Med Biol* 469:471–477
10. Vermunt SHF, Mensink RP, Simonis MMG, Wagenmakers AJM, Hornstra G (2001) The metabolism of linoleic acid in health subjects after intake of a single dose of 13 C linoleic acid. *Eur J Clin Nutr* 55:321–326
11. Vaddadi KS (1981) The use of gamma-linolenic acid and linoleic acid to differentiate between temporal lobe epilepsy and schizophrenia. *Prostaglandins Med* 6(4):375–379
12. Holman C, Bell A (1983) A trial of evening primrose oil in the treatment of chronic schizophrenia. *J Orthomol Psychiatry* 12:302–304
13. Puri BK (2007) The safety of evening primrose oil in epilepsy. *Prostaglandins Leukot Essent Fat Acids* 77(2):101–103, Epub 2007 Aug 30
14. Miller LG (1998) Herbal medicinals: selected clinical considerations focusing on known or potential drug–herb interactions. *Arch Intern Med* 158:2200–2211
15. Guillen MD, Goicoechea E (2008) Toxic oxygenated α , β -unsaturated aldehydes and their study in foods: a review. *Crit Rev Food Sci Nutr* 48:119–136
16. Esterbauer H, Schaur RJ, Zollner H (1991) Chemistry and biochemistry of 4-hydroxy-2-nonenal, malonaldehyde and related aldehydes. *Free Radical Biol Méd* 11:81–128
17. Yen CH (2008) Linoleic acid metabolite levels and transepidermal water loss in children with atopic dermatitis. *Ann Allergy Asthma Immunol* 100:66–73
18. Martens-Lobenhoffer J, Meyer FP (1998) Pharmacokinetic data of gamma-linolenic acid in healthy volunteers after the administration of evening primrose oil. *Int J Clin Pharmacol Therap* 36(7):363–366
19. Pilitsis JG, Coplin WM, Regan MH et al (2003) Free fatty acids in cerebrospinal fluid from patients with traumatic brain injury. *Neurosci Lett* 349:136–138