

Neurotoxicities in Infants Seen With the Consumption of Star Anise Tea

Diego Ize-Ludlow, MD*; Sean Ragone, MD†; Isaac S. Bruck, PhD§; Jeffrey N. Bernstein, MD‡; Michael Duchowny, MD||; and Barbara M. Garcia Peña, MD, MPH¶

ABSTRACT. Chinese star anise (*Illicium verum* Hook f.) is a well-known spice used in many cultures. Many populations use it as a treatment for infant colic. Japanese star anise (*Illicium anisatum* L), however, has been documented to have both neurologic and gastrointestinal toxicities. Recently, concern has been raised regarding the adulteration of Chinese star anise with Japanese star anise. We report 7 cases of adverse neurologic reactions in infants seen with the home administration of star anise tea. In addition, we have found evidence that Chinese star anise has been contaminated with Japanese star anise. More strict federal regulation of the import of star anise into the United States is warranted. Star anise tea should no longer be administered to infants because of its potential danger in this population. *Pediatrics* 2004; 114:e653–e656. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0058; star anise, neurotoxicity, colic, infants.

ABBREVIATION. GC-MS, gas chromatography–mass spectroscopy.

Chinese star anise (*Illicium verum* Hook f.) is a well-known spice used in many cultures. Caribbean and Latino populations typically use a tea infusion of its 8-pointed stellate fruit (Fig 1) as a carminative and sedative for the treatment of infant colic. Because of its long history of herbal and culinary uses, Chinese star anise has been commonly regarded as being safe and nontoxic. A closely related species, Japanese star anise (*Illicium anisatum* L, syn. *I japonicum* Sieb, syn. *I religiosum* Sieb et Zucc), has been well documented to cause both neurologic and gastrointestinal toxicities.^{1–5}

All *Illicium* species contain sesquiterpene lactone compounds,^{6–12} a large and diverse group of biologically active plant chemicals, most containing a number of secondary metabolite products related to anisatin, neoanisatin, and pseudoanisatin, the potent neurotoxins found in Japanese star anise.^{13,14} Although Chinese star anise is considered safe for consumption, this species also contains toxic com-

pounds named veranisatins A, B, and C.¹⁵ Although these veranisatins are not as potent as anisatin itself, neurologic symptoms are observed at higher doses.¹⁵ Anisatin compounds are thought to act as potent noncompetitive γ -aminobutyric acid antagonists.^{16–20}

Concern has been raised regarding the adulteration of *I verum* with *I anisatum* and has led to recalls of these products in other countries, including Spain, France, Scotland, China, Japan, and Netherlands.^{21–23} In this communication, we report 7 cases of adverse neurologic reactions associated with the home administration of star anise tea to young infants seen during the past 2 years at Miami Children's Hospital. In addition, we have discovered adulteration of several of the Chinese star anise samples with *I anisatum*.

METHODS

Clinical Cases

Over a 2-year period, infants with signs and symptoms of star anise intoxication were identified in the emergency department of Miami Children's Hospital. Miami Children's Hospital is a large, urban, pediatric teaching hospital with an emergency department that sees 87 000 patients per year. Signs and symptoms of star anise intoxication include jitteriness, hyperexcitability, nystagmus, vomiting, myoclonic movements, and seizures. We included patients who experienced an otherwise unexplainable acute onset of 1 or more signs of star anise intoxication after the ingestion of star anise tea.

Analysis of Samples

Samples were obtained and analyzed from 3 of the patients (5, 6, and 7) to determine whether readily available herbal packages of *I verum* had been contaminated with the toxic *I anisatum*. Samples from the remaining 4 patients were not available for analysis. Three samples of Chinese star anise were also purchased from local stores for comparative morphologic and chemical analysis. All fruits were inspected for the defining structures of *I verum* and *I anisatum*.

The volatile fraction from each sample was then examined by gas chromatography–mass spectroscopy (GC-MS) techniques for the presence of safrole and eugenol, compounds found in all toxic *Illicium* species but not in *I verum*.^{24–28} The samples were also examined for the presence of anethole, found in *I verum* in concentrations of 72% to 92%.^{24–28} Other *Illicium* species typically have anethole concentrations <40%.^{29,30} The isolation and characterization of anisatin and neoanisatin^{31–33} using liquid chromatography–mass spectroscopy techniques was also performed. The method of the liquid chromatography–mass spectroscopy and GC-MS analyses are described elsewhere.³⁴

RESULTS

Clinical Cases

Seven cases of infants who were aged 2 to 12 weeks and had signs of acute star anise intoxication were identified over a 2-year period. The cases are presented in Table 1. Symptoms included seizures, jitteriness, irritability, hyperexcitability, emesis, ver-

From the *Department of Pediatrics, Miami Children's Hospital, Miami, Florida; †Florida Poison Control Center, Jackson Memorial Hospital, University of Miami School of Medicine, Miami, Florida; ‡Center for Ethnobiology and Natural Products, Florida International University, Miami, Florida; §Department of Neurology, Miami Children's Hospital and the University of Miami School of Medicine, Miami, Florida; and ¶Division of Emergency Medicine, Miami Children's Hospital, Miami, Florida.

Accepted for publication May 25, 2004.

doi:10.1542/peds.2004-0058

Reprint requests to (B.M.G.P.) Division of Emergency Medicine, Miami Children's Hospital, 3100 SW 62nd Ave, Miami, FL 33155. E-mail: barbara.pena@mch.com

PEDIATRICS (ISSN 0031 4005). Copyright © 2004 by the American Academy of Pediatrics.



Fig 1. Morphology of Chinese anise star fruit.

tical nystagmus, and myoclonic movements. The dose of star anise varied from 1 star to 6 stars boiled in varying ounces of water administered as little as once per day to as much as every 4 hours. The duration of exposure varied from a 1-time exposure to a 2-week exposure. On physical examination, all of the patients exhibited neurologic signs as described in the table. Laboratory work, electroencephalogram findings, and neuroimaging studies were normal in all of the patients. Each patient experienced a complete recovery to neurologic baseline within 48 hours of treatment.

Analysis of Samples

Initially, all samples were examined microscopically for distinguishing morphologic characteristics. Features such as beaked follicles, broad dehiscence, size, and color did not prove suitable for a definitive determination of *I anisatum* adulteration because of the inherent variation observed in the hundreds of *I verum* fruits examined. Thus, plant material obtained from our patients was inadequate for making a determination on the basis of morphology, because we lacked complete fruits for some samples and others contained fruits that had characteristics from both species.

In the GC-MS analysis of patient 7, anethole was found to compose at least 75% of the essential oil.³⁴ It was not possible to discern whether safrole was present in low concentration, because the equipment cannot resolve the safrole peak from anethole, when such high concentrations of anethole are present.²⁴ GC analysis of patient 5 samples was able to detect eugenol; however, anethole, again, was found in high concentrations, preventing the identification of safrole. The volatile compound profile in patient 6 was significantly different from that of patients 5 and 7 as a result of the presence of safrole and eugenol with a low concentration of anethole. The 3 samples purchased from local stores showed GC spectra similar to patient 7.³⁴

Liquid chromatography analysis of the sesquiter-

TABLE 1. Cases of Star Anise Intoxication Seen in the Miami Children's Hospital Emergency Department

Patients	Symptoms	Tea Amount and Preparation	Duration of Exposure	Physical Examination	Labs, EEG	Additional Neurologic Episodes on Follow-up?
Patient 1: 12-wk-old girl	Right arm shaking followed by generalized tonic-clonic movements	Four stars boiled in 8 oz of water; given 3 oz every 4 h	3 d	Normal but had second tonic-clonic seizure in ED	Normal	No at 2 y
Patient 2: 5-wk-old boy	Irritability, jitteriness, and tonic posturing	Six stars in 2–3 oz of water per day	1 wk	Jitteriness and episode of tonic posturing in ED	Normal	No at 2 y
Patient 3: 10-wk-old boy	Emesis, myoclonic movements, recurrent tonic posturing, back arching	Four stars boiled in 8–12 oz of water; given 1 oz	Once	Intermittent myoclonic movements of all extremities	Normal	No at 2 y
Patient 4: 6-wk-old girl	Emesis, jitteriness, hyperexcitability, eye-rolling movements	Unknown	Once	Jitteriness and roving eye movements	Normal	No at 1 y
Patient 5: 3-wk-old boy	Emesis, jitteriness, shaking, and upward gaze deviation	Two to 3 stars in 6 oz of water; given 1–2 oz several times weekly	2 wk	Jitteriness, bilateral clonus, and increased deep tendon reflexes	Normal	No at 1 y
Patient 6: 2-wk-old girl	Emesis, upward gaze deviation, generalized myoclonic movements, pallor	Five stars boiled in 8 oz of water; given 1 oz	Once	Myoclonus and vertical nystagmus	Normal	No at 6 mo
Patient 7: 3-wk-old girl	Irritability, lethargy, jitteriness, myoclonic movements of the left leg	One star boiled in 7 oz of water; given 1–2 oz 3–4 times per day	6 d	Jitteriness with weak cry	Normal	No at 3 mo

EEG indicates electroencephalogram; ED, emergency department.

pene lactone fraction of each sample was performed for the presence of anisatin and neoanisatin in addition to veranisatins A, B, and C. The mass spectral pattern of each sample was similar in the number of compounds, type of compounds, and concentration of each.³⁴ Sesquiterpene lactone extracts from patient 6 only faintly resembled the other sample spectra in compound distribution or concentration, suggesting the presence of another *Illicium* species besides *I verum*.³⁴

DISCUSSION

Several reports documenting clear instances of clinical toxicity with star anise have been described. Montoya-Cabrera³⁵ reported the frequent use of Chinese star anise in Mexico and described the appearance of similar neurologic symptoms. Johanns et al⁴ reported 63 adults who experienced symptoms of general malaise, nausea, and vomiting 2 to 4 hours after consuming an herbal tea of star anise. Twenty-two of the subjects required hospitalization, and 16 experienced generalized seizures. Vandenberghe et al⁵ reported a 23-year-old man who experienced headache and epigastric pain 4 hours after ingesting 3 glasses of "vin chaude" prepared with star anise. Eight hours later, he developed generalized tonic-clonic seizures. Guerrero Fernandez et al³⁶ from Spain reported 9 infants aged 5 to 45 days with excessive crying, irritability, and vertical nystagmus after ingesting Chinese star anise tea. Physical examination, electroencephalogram, and neuroimaging studies were normal in all patients. Another group from Spain reported a series of 18 infants with irritability, abnormal movements, vomiting, and nystagmus after receiving star anise tea and found evidence of contamination of *I verum* with *I anisatum*.³

Our patients presented with evidence of central nervous system hyperexcitability including jitteriness, irritability, sleeplessness, and seizures. Although these symptoms are nonspecific and can occur in response to ingestion of substances other than Chinese star anise, the history of recent star anise ingestion and the known effects of its administration strongly implicate star anise as the cause. The speed of recovery is also indicative of a pharmacologic source given the resolution of all symptoms within 48 hours after appropriate symptomatic and supportive care.

I verum has been considered safe as a food or medicine because it contains veranisatins in low concentrations. However, significant quantities in infants may be enough to produce adverse neurologic reactions. On the basis of the results of our chemical analysis, the symptoms that we describe in this report may be attributed to an overdose of *I verum*, contamination with *I anisatum*, or a combination of the two. It is worth noting that the material from patient 6, the sample most clearly indicative of adulteration with *I anisatum*, is associated with the fewest doses and fastest onset of convulsive symptoms.

The ingestion of star anise should be considered in the differential diagnosis of infants who present with

the acute onset of unexplained irritability, vomiting, and seizures, particularly in the Latino population. Although the cases that we report here are associated with members of the Cuban and Central and South American population of southern Florida, star anise is widely used by all Latino groups. On the basis of these cases and the finding of contamination of *I verum* in the United States, we strongly believe that star anise should no longer be administered to infants. Pursuant to our findings, the Food and Drug Administration has recently issued a warning for consumers not to drink teas that are brewed from star anise fruits. The retail of star anise products in the United States warrants additional investigation and stricter federal regulation given the neurotoxic effects of the adulterated product and the potential danger to infants and children.

REFERENCES

1. Read BE. Bastard anise poisoning and its antidotal measures. *Chinese J Physiol.* 1926;1:15-22
2. Biessels GJ, Vermeij FH, Leijten FS. Epileptic seizure after a cup of tea: intoxication with Japanese star anise. *Ned Tijdschr Geneesk.* 2002;146:808-811
3. Garzo Fernandez C, Gomez Pintado P, Barrasa Blanco A, Martinez Arrieta R, Ramirez Fernandez R, Ramon Rosa F. [Cases of neurological symptoms associated with star anise consumption used as a carminative.] *An Esp Pediatr.* 2002;57:290-294
4. Johanns ES, van der Kolk LE, van Gemert HM, Sijben AE, Peters PW, de Vries I. An epidemic of epileptic seizures after consumption of herbal tea. *Ned Tijdschr Geneesk.* 2002;146:813-816
5. Vandenberghe N, Pittion-Vouyouvitch S, Flesch F, Wagner M, Godet E. An inaugural generalized tonic-clonic convulsive crisis following ingestion of Japanese star anise. *Presse Med.* 2003;32:27-28
6. Liu JS, Zhou QR. The toxic principle of *Illicium henryi* Diels and structure of 6-deoxypseudoanisatin. *Yaoxue Xuebao.* 1988;23:221-223
7. Kouno I, Baba N, Hasimoto M, et al. Isolation of three new sesquiterpene lactones from the pericarps of *Illicium majus*. *Chem Pharm Bull.* 1989;37:2448-451
8. Yang CS, Wang JL, Zhang ZL, Kouno I. Studies on the toxic constituents of *Illicium simonsii* Maxim. *Yaoxue Xuebao.* 1991;26:128-131
9. Wang JY, C.S. Yan, R.N. Yao, B. Yang, X.B. Sesquiterpene lactones from *Illicium minwanense*. *Yaoxue Xuebao.* 1994;29:693-696
10. Schmidt TJ, Schmidt HM, Muller E, et al. New sesquiterpene lactones from *Illicium floridanum*. *J Nat Prod.* 1998;61:230-236
11. Schmidt TJ, Okuyama E, Fronczek FR. The molecular structure of 2-gammahydroxyneoanisatin and structure-activity relationships among convulsant sesquiterpenes of the seco-prezizaane and picrotoxane types. *Bioorg Med Chem.* 1999;7:2857-2865
12. Huang JM, Fukuyama Y, Yang CS, Minami H, Tanaka M. Three new sesquiterpene lactones from the pericarps of *Illicium merrillianum*. *Chem Pharm Bull (Tokyo).* 2000;48:657-659
13. Yamada K, Takada S, Nakamura S, Hirata Y. The structures of anisatin and neoanisatin: toxic sesquiterpenes from *Illicium anisatum* L. *Tetraedron.* 1968;24:199-229
14. Kouno I, Mori K, Akiyama T, Hashimoto M. Two sesquiterpene lactones from *Illicium anisatum*. *Phytochemistry.* 1991;30:351-353
15. Okuyama E, Nakamura T, Yamazaki M. Convulsants from star anise (*Illicium verum* Hook. F.). *Chem Pharm Bull (Tokyo).* 1993;41:1670-1671
16. Kudo Y, Oka JI, Yamada K. Anisatin, a potent GABA antagonist, isolated from *Illicium anisatum*. *Neurosci Lett.* 1981;25:83-88
17. Shinozaki H, Ishida M, Kudo Y. Effects of anisatin on the GABA action in the crayfish neuromuscular junction. *Brain Res.* 1981;222:401-405
18. Matsumoto K, Fukuda H. Anisatin modulation of GABA- and pentobarbital-induced enhancement of diazepam binding in rat brain. *Neurosci Lett.* 1982;32:175-179
19. Ikeda T, Ozoe Y, Okuyama E, et al. Anisatin modulation of the gammaaminobutyric acid receptor-channel in rat dorsal root ganglion neurons. *Br J Pharmacol.* 1999;127:1567-1576
20. Ikeda T. Electrophysiological study of the mechanism of action of insecticides activity on ion channels. *Nippon Noyaku Gakkaishi.* 2002;27:310-319

21. Badiane et risque convulsif. L'Agence française de sécurité sanitaire des produits de santé (Afssaps); 2001. Available at: agmed.sante.gouv.fr/hm/10/filcoprs/011103c.htm. Accessed April 22, 2003
22. Mise en évidence de la contamination de la badiane de Chine (*Illicium verum* Hooker f.) par d'autres espèces de badiane. Laboratoires de la DGCCRF. Marseille, France; 2003. Available at: www.finances.gouv.fr/DGCCRF/activites/labos/2001/badiane.htm. Accessed April 22, 2003
23. 2002/75/EC: Commission Decision of 1 February 2002 laying down special conditions on the import from third countries of star anise (text with EEA relevance) (notified under document number C(2002) 379). *Off J Eur Commun*. 2002;L:33–34
24. Sun L. Studies on the chemical constituents of the volatile oil of *Illicium verum* Hook. f. grown in Shanyou. *Youji Huaxue*. 1990;10:183–186
25. Jiang Z, Li R. Aroma constituents of *Illicium verum*-containing condiment oil. *Shipin Kexue*. 1992;156:2–10
26. Quoc Tuan D, Ilangantileke SG. Liquid CO₂ extraction of essential oil from star anise fruits (*Illicium verum* Hook. f.). *J Food Eng*. 1996;31:47–57
27. Yan J, Xiao X, Huang K. Component analysis of volatile oil from *Illicium verum* Hook. F. *J Central South Univ Technol (English Ed)*. 2002;9:173–176
28. Small J. Star anise. *Food*. 1943;12:97–100
29. Agarwal SK, Siddiqui MS, Jain SP, Sushil-Kumar, Kumar S. Chemotaxonomical study of Indian *Illicium griffithii* and *Illicium verum* fruits. *J Medicinal Aromatic Plant Sci*. 1999;21:945–946
30. Saltron F, Langella C, Guerere M. Detection of contamination of Chinese star anise by other *Illicium* species. *Ann Fals Expert Chim Toxicol*. 2001;94:397–402
31. Niwa H, Tsukada I, Nisiwaki M, Yamada K. Further chemical studies on anisatin, a neurotoxic sesquiterpenoid having a β -lactone. *Bull Chem Soc Jpn*. 1991;64:2860–2862
32. Niwa H, Yamada K. Synthesis of anisatin, a neurotoxin of plant origin. *Farumashia*. 1991;27:924–927
33. Niwa H, Yamada K. Synthesis of (–)-neoanisatin, a neurotoxic sesquiterpenoid having a novel spiro β -lactone. *Chem Lett*. 1991;4:639–640
34. Ize-Ludlow D, Ragone S, Bruck I, Bernstein J, Duchowny M, Garcia Pena B. Chemical composition of Chinese star anise (*Illicium verum*) and neurotoxicity in infants. *JAMA*. 2004;291:562–563
35. Montoya-Cabrera MA. Poisoning by star anise (*Illicium verum*) tea. *Gac Med Mex*. 1990;126:341–342
36. Guerrero Fernandez J, Valle Sanchez A, Garcia Garcia S. Nueve casos de intoxicación por anís estrellado. *Rev Esp Pediatr*. 2002;58:111–114

Neurotoxicities in Infants Seen With the Consumption of Star Anise Tea
Diego Ize-Ludlow, Sean Ragone, Isaac S. Bruck, Jeffrey N. Bernstein, Michael
Duchowny and Barbara M. Garcia Peña

Pediatrics 2004;114:e653

DOI: 10.1542/peds.2004-0058 originally published online October 18, 2004;

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/114/5/e653>

References

This article cites 34 articles, 0 of which you can access for free at:
<http://pediatrics.aappublications.org/content/114/5/e653#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Fetus/Newborn Infant
http://www.aappublications.org/cgi/collection/fetus:newborn_infant_sub
Pharmacology
http://www.aappublications.org/cgi/collection/pharmacology_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Neurotoxicities in Infants Seen With the Consumption of Star Anise Tea
Diego Ize-Ludlow, Sean Ragone, Isaac S. Bruck, Jeffrey N. Bernstein, Michael
Duchowny and Barbara M. Garcia Peña

Pediatrics 2004;114:e653

DOI: 10.1542/peds.2004-0058 originally published online October 18, 2004;

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/114/5/e653>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2004 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

