Neurotoxicities in Infants Seen With the Consumption of Star Anise Tea

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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 compounds 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-

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Accepted for publication May 25, 2004.
doi:10.1542/peds.2004-0058

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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-Cabrera[35] reported the frequent use of Chinese star anise in Mexico and described the appearance of similar neurologic symptoms. Johanns et al[4] 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 al[5] 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 al[36] 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.

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Pediatrics 2004;114;e653
DOI: 10.1542/peds.2004-0058 originally published online October 18, 2004;

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