

Suspected caffeine and ephedrine toxicosis resulting from ingestion of an herbal supplement containing guarana and ma huang in dogs: 47 cases (1997–1999)

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Objective—To describe the clinical signs following ingestion of an herbal supplement containing guarana and ma huang in dogs, estimate minimum dose at which clinical signs of toxicosis and death were reported, and evaluate treatment options.

Design—Retrospective study.

Animals—47 dogs with evidence of ingestion of an herbal supplement containing primarily guarana and ma huang.

Procedure—Records of dogs that had ingested an herbal supplement containing ma huang and guarana between July 1997 and October 1999 were retrieved from the National Animal Poison Control Center database. Data were retrieved and reviewed regarding signalment, dose ingested, clinical signs, laboratory test results, treatment, and final outcome. Cases were assessed by staff veterinarians as toxicosis or suspected toxicosis on the basis of strength of evidence supporting a diagnosis.

Results—Most dogs (80%) developed clinical signs of toxicosis within 8 hours of ingestion, and clinical signs persisted for up to 48 hours. Hyperactivity, tremors, seizures, and behavior changes were reported in 83% of dogs; other signs included vomiting (47%), tachycardia (30%), and hyperthermia (28%). Seventeen percent of the dogs died or were euthanized. Estimated doses of guarana and ma huang ranged from 4.4 to 296.2 mg/kg (1.98 to 133.2 mg/lb) and 1.3 to 88.9 mg/kg (0.58 to 40.0 mg/lb) of body weight, respectively; minimum dose at which death was reported was 19.1 mg of guarana/kg (8.7 mg/lb) and 5.8 mg of ma huang/kg (2.6 mg/lb).

Conclusions and Clinical Relevance—Accidental ingestion of herbal supplements containing primarily guarana and ma huang in dogs can lead to a potentially lethal condition that may require prompt detoxification and supportive treatment for several days. Most dogs recovered with supportive treatment. (*J Am Vet Med Assoc* 2001;218:225–229)

The use of medicinal plants and herbal medicine in humans has increased in the past decade around the world, including the United States. In 1997, the herbal medicine industry alone generated approximately \$3.24 billion in sales.¹ Herbal medications are marketed as nutritional or dietary supplements and are not required

to be clinically evaluated and labeled, as are prescription drugs.² Many herbal medications are claimed to be natural and safe by the manufacturer, while promising to provide energy, euphoria, and weight loss.

Information on toxicity of herbal medications in the veterinary literature is scarce. However, clinical studies reveal that many of these medications may have undesirable adverse effects in humans and laboratory animals.³ In many instances, the container does not have adequate warnings, is not childproof, and may have a blanket safety claim. Consequently, many people do not regard these products as hazardous. It is not uncommon for pet owners to leave these products within reach of their pets and, therefore, toxicosis from herbal medications is likely to result when pets accidentally ingest these medications.

An herbal medicine^a that primarily contains guarana (*Paullinia cupana*), a natural source of caffeine, and ma huang (*Ephedra sinica*), a natural source of ephedrine, is marketed in various places as a weight loss and energy supplement. Caffeine and ephedrine in this product are believed to be derived from guarana and ma huang, respectively, and amounts are standardized such that each capsule contains 40 mg of caffeine and 12 mg of ephedrine. Some of the other ingredients listed are chromium picolinate, chelated zinc and magnesium, vitamin E, and bee pollen. Herbal products containing guarana (caffeine) and ma huang (ephedrine) as active ingredients have raised interest and controversy in human medicine, because these 2 ingredients have been associated with many harmful adverse effects, including acute hepatitis (it was suspected that an unknown contaminant may have led to acute hepatitis),⁴ nephrolithiasis,⁵ hypersensitivity myocarditis,⁶ and death.⁷

When dogs accidentally ingest guarana and ma huang, many adverse effects are to be expected. Recently, the American Society for the Prevention of Cruelty to Animals National Animal Poison Control Center (NAPCC) has received 47 reports of dogs that ingested their owner's herbal supplement containing guarana and ma huang. The purposes of the study reported here were to describe the clinical signs of toxicosis following ingestion of an herbal supplement containing guarana and ma huang in dogs, estimate minimum dose at which clinical signs of toxicosis and death were reported, and evaluate treatment options.

Criteria for Selection of Cases

Clinical and epidemiologic information was retrieved from the NAPCC computerized case record

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database. The NAPCC is a 24-hour consultation service that receives phone calls on incidents of animal poisonings throughout the United States and Canada from veterinarians and pet owners. On receiving a reported incident, the NAPCC veterinary staff collects the following information: species, breed, sex, age, weight, number of animals at risk, exposed and affected animals, source of exposure, approximate amount of toxin ingested (dose), and assurance of exposure (whether observed or evidenced). Information on time of onset, type and duration of clinical signs, laboratory results, serum biochemical alterations, treatment administered, and pathologic findings are also recorded. Follow-up calls are made as needed to update records for progression of clinical signs, response to treatment, and final outcome. Information included here has not been recorded by direct observation or confirmed using analytic methods.

On the basis of clinical, temporal, and exposure histories, the NAPCC veterinarian assessed each incidence of guarana and ma huang ingestion as either a toxicosis, suspected toxicosis, possible toxicosis, doubtful toxicosis, or exposure only. Assessments were made on the basis of expected clinical signs of guarana (caffeine) and ma huang (ephedrine) toxicosis, as described in the literature, temporal and dosage consideration, and previous experience dealing with the agent. A case was defined as an exposure to guarana or ma huang when no clinical signs of toxicosis were present at the time of call, and none were reported on follow-up. A case was assessed as toxicosis when all temporal, clinical, and historic data were consistent with the expected syndrome; as suspected toxicosis if clinical signs were characteristic of the expected syndrome but some data such as amount (dose) or time of onset of clinical signs were not available; as possible toxicosis when only few signs were consistent with the expected syndrome; and doubtful when exposure history and clinical signs were not consistent with the expected syndrome.

Results

Records pertaining to 47 incidents of guarana and ma huang ingestion in dogs were retrieved between July 1997 and October 1999 from the NAPCC database. Of these, 3 involved ingestion of multiple agents and were not included in this study. The yearly distribution of cases revealed 3 instances of toxicosis in 1997, 6 in 1998, and 38 in the first 10 months of 1999. No incidents of accidental exposure to supplements containing guarana and ma huang were found in the database prior to July 1997. Dogs were the only species involved.

Clinical signs of toxicosis were reported in all 47 (100%) dogs; 23 (49%) of these were assessed as toxicoses, 20 (43%) as suspected toxicoses, and 4 (9%) as possible toxicoses. The most commonly involved breeds were Labrador Retrievers (9), mixed breeds (8), and German Shepherd Dogs (5). Weights of dogs ranged between 4.1 and 52.2 kg (9.0 and 114.8 lb), and ages ranged between 3 months and 12 years. Information regarding sex was available in 33 dogs; 22 were females, and 11 were males. A veterinarian (either

Table 1—Clinical signs of guarana and ma huang toxicosis in 47 dogs

| Clinical signs | No. of dogs affected (%) |
|---------------------|--------------------------|
| Vomiting | 22 (47) |
| Hyperactivity | 20 (43) |
| Tachycardia | 14 (30) |
| Hyperthermia | 13 (28) |
| Mydriasis | 10 (21) |
| Tremors | 7 (15) |
| Behavioral changes | 6 (13) |
| Seizure | 6 (13) |
| Tachypnea/panting | 6 (13) |
| Weakness | 5 (11) |
| Signs of depression | 5 (11) |
| Apprehensiveness | 5 (11) |
| Anorexia | 5 (11) |

as an original caller or on follow-up) was involved in 87% of the cases.

The amount of guarana and ma huang ingested by dogs was estimated in 39 (83%) dogs and ranged between 80 and 3,600 mg of guarana and 24 and 1,080 mg of ma huang. Doses of guarana and ma huang at which signs of intoxication were reported ranged between 4.4 and 296.2 mg/kg (1.98 and 133.2 mg/lb) of body weight and 1.3 and 88.9 mg/kg (0.58 and 40 mg/lb), respectively. The minimum dose at which death was reported in a dog was 19.1 mg/kg (8.5 mg/lb) of guarana and 5.8 mg/kg (2.61 mg/lb) of ma huang.

Central nervous system, cardiopulmonary, and gastrointestinal tract stimulation accounted for most clinical signs of toxicosis (Table 1). Commonly reported signs included vomiting, tachycardia (heart rate range, 100 to 260 beats/min), hyperthermia (rectal temperature range, 39.2 to 42.8 C [103.4 to 109.9 F]), and nonspecific behavioral changes such as snapping at the air, signs of nervousness, pacing, and head shaking. Information on laboratory results was available for 3 dogs; 2 of these dogs had hypokalemia, and 1 had hematuria. The time to onset of clinical signs after ingestion ranged between 30 minutes and 41 hours. However, clinical signs developed within 8 hours after ingestion in 80% of dogs. Duration of clinical signs ranged from 10 to 48 hours. Information regarding final outcome was available for 34 (72%) dogs; 26 dogs recovered with supportive treatment consisting of GI decontamination, stabilization of CNS and cardiovascular signs, and fluid diuresis; death or euthanasia was reported in 8 dogs.

Discussion

All dogs that ingested the herbal supplement containing guarana and ma huang in this study had adverse clinical signs that affected the gastrointestinal tract, CNS, or cardiopulmonary system. Although several other ingredients such as chromium picolinate, chelated zinc and magnesium, vitamin E, and bee pollen are listed in this herbal supplement, on the basis of rapid onset and type of clinical signs, we suspected these clinical signs developed primarily because of the high amount of guarana (caffeine) and ma huang (ephedrine) in the herbal supplement. Similar signs have been reported as a result of caffeine or ephedrine overdose in humans⁸⁻⁹ as well as other animals.¹⁰⁻¹¹ The

source of caffeine described in other reports of toxicosis in dogs has been through coffee, tea, chocolate, cola beverages, and human stimulant preparations,¹⁰ not through consumption of an herbal supplement as described here.

In our study, there did not appear to be a good correlation between the dose of guarana and ma huang ingested and severity of clinical signs. Some of the factors responsible for this poor dose-response relationship may have been attributable to differences in the amount of guarana and ma huang absorbed prior to detoxification, time between ingestion and treatment, and individual variation in sensitivity to guarana and ma huang.

Guarana contains high concentrations of caffeine; compared with coffee beans that contain 1.0 to 2.0% caffeine, guarana contains 3.0 to 5.0% caffeine.¹² In addition to caffeine, other chemical components of guarana may include carbohydrates, fats, and resins.¹³ Guarana is harvested from a South American woody shrub or sprawling vine, and native people use the seeds for their stimulant and prophylactic qualities. Guarana is believed to be useful in treating headaches, fever, gastrointestinal tract disturbances, neuralgia, arteriosclerosis, hemorrhage, muscular pain, and menstrual cramps. It is also believed to suppress appetite, decrease body fat, aid in diuresis, and act as a cerebral stimulant.¹⁴ Believers in herbal medicine claim that the use of guarana helps decrease signs of depression, increase optimism, develop mental fitness, and prevent fatigue. Guarana may also act as an aphrodisiac.¹⁴ However, these findings and claims could not be validated in controlled clinical studies.¹⁴⁻¹⁵

Caffeine is a methylated xanthine and exerts its effect through several mechanisms. It antagonizes cellular adenosine receptors and inhibits cellular phosphodiesterases, which leads to an increase in cAMP. Also, caffeine enhances the release of catecholamines and increases the entry of calcium while inhibiting calcium sequestration by the sarcoplasmic reticulum, leading to increased muscular contractility.¹⁰ The overall impact of this is a positive inotropic and chronotropic effect on the heart, cerebral vasoconstriction, renal vasorelaxation, smooth muscle relaxation in the gastrointestinal tract, and stimulation of gastric secretion.⁸

Ma huang is a dried stem of 1 of the 3 ephedra species indigenous to India, Pakistan, and China.¹⁶ The Chinese have used ma huang for thousands of years to treat asthma and hay fever, for its stimulant qualities, and for treating colds, influenza, chills, headache, edema, bronchial congestion, and aching joints and bones.¹⁷ In 1923, scientists discovered that the plant contains ephedrine and pseudoephedrine.¹⁶

Ephedrine is a sympathomimetic alkaloid with α -, β_1 - and β_2 -adrenergic agonist activity. Stimulation of these receptors by ephedrine can lead to increased diastolic and systolic blood pressure, bronchial smooth muscle dilatation, pupillary dilatation, and increased cardiac contractility and output.¹⁸ With long-term use, tachyphylaxis has been known to result.¹⁹ In humans, use of this drug may result in addiction or abuse. Ephedrine has a β -carbon hydroxylation, so it has less

CNS stimulatory effects than methamphetamine, but their structures are similar. Ephedrine is more potent than methamphetamine at increasing blood pressure and heart rate.⁹

The toxicity of ephedrine in humans is primarily manifested by cardiovascular and CNS effects.⁹ It has also been associated with nephrolithiasis and renal failure,⁵ acute hepatitis (it was suspected, however, that an unknown contaminant may have played a role in causing acute hepatitis),⁴ and death caused by cardiovascular failure.⁷ Consumers may be confused when purchasing the herb ma huang, not realizing that it is in the ephedrine family and is contraindicated in humans with hypertension, diabetes mellitus, and thyroid disease.¹ In the past few years, the FDA has administered warnings for consumers to avoid dietary supplements containing ephedrine.¹⁶

Time to onset of clinical signs of toxicosis in most dogs ($n = 38$) in our study was within 8 hours of ingestion of the herbal supplement. This is consistent with the pharmacokinetics of caffeine or ephedrine in dogs and humans. Caffeine is well-absorbed orally and has a plasma half-life of 4.5 hours in dogs.¹⁰ It is metabolized by the liver to methyluric acid and to methylxanthine, which are excreted through the urine. Ma huang is absorbed orally within 1.5 to 2 hours after administration in humans.¹⁶ One study revealed comparable pharmacokinetics between botanical ephedrine and synthetic ephedrine chloride in humans.²⁰ The elimination half-life of ephedrine is dependent on urinary pH; it is excreted unchanged in the urine.²¹

The minimum dose at which clinical signs of toxicosis were reported in the dogs of this study was 4.4 mg of guarana/kg (1.98 mg/lb) and 1.3 mg of ma huang/kg (0.58 mg/lb); the minimum dose at which death was reported in a dog was 19.1 mg of guarana/kg (8.6 mg/lb) and 5.8 mg of ma huang/kg (2.61 mg/lb). In dogs, the reported median lethal dose of caffeine is 140 mg/kg (63 mg/lb) when ingested orally.¹⁰ Signs of acute toxicosis in humans appear at 15 to 30 mg/kg (6.75 to 13.5 mg/lb), and the lethal dose for caffeine is estimated to be 100 to 200 mg/kg (45 to 90 mg/lb).⁸ It has been reported that dogs may have signs of toxicosis when they have been accidentally exposed to decongestants containing pseudoephedrine at 5 to 6 mg/kg (2.25 to 2.7 mg/lb); death may occur at 10 to 12 mg/kg (4.5 to 5.4 mg/lb).²² This suggests that caffeine and ephedrine or pseudoephedrine can act synergistically when ingested together and enhanced toxicosis may be seen, as in the dogs of this study. Caffeine, ephedrine, and pseudoephedrine are stimulants of the CNS and cardiovascular system and may have added or synergistic effects on these organ systems. Several investigators have suggested that, in humans, changes seen in blood pressure, as well as smooth and cardiac muscle stimulation, may be mild when caffeine or ma huang are used alone. However, when used together or in combination with other stimulants, or in patients with preexisting heart, liver, or kidney disease, these changes may be much more severe and life threatening.²⁰ In humans, numerous drug interactions have been reported between ephedrine or pseudoephedrine and digoxin, halothane, or monoamine oxidase inhibitors.²²

Treatment of guarana and ma huang toxicosis consists primarily of supportive care. The objectives of treatment are aimed at detoxification of the gastrointestinal tract, stabilization of CNS and cardiovascular signs, and maintenance of hydration and proper plasma electrolyte balance.

If exposure has occurred within 2 hours and no clinical signs of toxicosis are evident, emesis should be induced with 3% hydrogen peroxide (1.5 ml/kg [0.7 ml/lb], PO) or apomorphine (0.02 to 0.04 mg/kg [0.009 to 0.018 mg/lb], IM or IV). This should be followed by oral administration of activated charcoal (1 to 2 g/kg [0.45 to 0.9 g/lb]) and a cathartic such as 70% sorbitol (1 to 3 ml/kg [0.45 to 1.35 ml/lb]) or magnesium sulfate or sodium sulfate (250 mg/kg [112 mg/lb]). If the dog's condition contraindicates induction of emesis (presence of CNS signs or extreme tachycardia), gastric lavage should be performed. Gastric lavage should be performed with a cuffed endotracheal tube to decrease the risk of aspiration, and a dose of activated charcoal with a cathartic should be left in the stomach after lavage. Dogs with clinical signs such as hyperactivity, tremors, seizures, or tachycardia should be stabilized before attempting detoxification.

Controlling CNS signs may require the use of more than 1 anticonvulsant. The use of diazepam to control CNS signs should be avoided, because dissociative effects of benzodiazepines are generally exaggerated in pseudoephedrine toxicosis.²² In the authors' experience, use of diazepam, administered intravenously, in dogs to control hyperactivity following pseudoephedrine exposure led to exacerbation of clinical signs (increased hyperactivity, head bobbing, signs of aggression, and vocalization) in 5 dogs. Hyperexcitability, shaking, signs of nervousness, tremors, or seizures may be controlled with phenothiazine tranquilizers such as acepromazine (0.05 to 1.0 mg/kg [0.02 to 0.45 mg/lb], IV, IM, or SC) or chlorpromazine (0.5 to 1.0 mg/kg [0.22 to 0.45 mg/lb], IV or IM). In certain instances such as pseudoephedrine or amphetamine toxicosis, phenothiazines usually work well to control CNS effects, because the cause of seizure is not the same as in an animal with epilepsy.²² If this is ineffective, phenobarbital (3 to 4 mg/kg [1.35 to 1.8 mg/lb], IV) or pentobarbital, administered IV to effect, may be used. If CNS signs are uncontrolled from the preceding measures, administration of gas anesthetic such as isoflurane may be useful.

Propranolol (0.02 to 0.06 mg/kg [0.009 to 0.02 mg/lb], IV, q 6 h) or other β -adrenergic blocking agents can be used to control tachycardia. An α -adrenergic blocking agent such as prazosin (1 to 2 mg/animal, q 8 h) or phentolamine (0.1 mg/kg [0.05 mg/lb], IV, as needed) may also be used.¹¹ Blood pressure and electrocardiographic tracings should be monitored following this treatment. Body temperature should be monitored often and corrected as needed. Affected dogs may have hyperthermia initially, followed by exhaustion and hypothermia. Pulmonary edema, although rare, may develop because of prolonged hypertension.

After stabilization of adverse CNS and cardiovascular signs, measures should be taken to enhance guarana and ma huang excretion. Because caffeine and

ephedrine are primarily eliminated through the kidneys, fluid diuresis helps to enhance their excretion.⁸⁻⁹ Acidification of urine in humans is known to cause enhanced pseudoephedrine excretion.²³ Whether acidification of urine leads to enhanced excretion of ephedrine in dogs is not known. Fluid and electrolyte changes should be monitored and corrected as needed. Baseline serum electrolyte concentrations should be determined, and serum biochemical analyses should be performed and repeated in 1 to 3 days. Treatment and monitoring should continue until all clinical signs of toxicosis have resolved.

Diagnosis of guarana and ma huang toxicosis is usually made on the basis of history of exposure and type, onset, and duration of clinical signs. Presence of caffeine or ephedrine alkaloid in the urine of a dog with suspected toxicosis may support this diagnosis. Because of a substantial increase in the number of reported cases of guarana and ma huang toxicoses to the NAPCC in 1999, guarana and ma huang toxicosis should be included in the list of differential diagnoses in dogs with signs of CNS, gastrointestinal tract, and cardiopulmonary stimulation or abnormalities. Differential diagnoses should also include other toxic agents that cause CNS and cardiovascular stimulation such as amphetamines, cocaine, pseudoephedrine, metaldehyde, strychnine, lead, nicotine, chocolate, and some insecticides.

^{*}Metabolife 356, Metabolife International Inc, San Diego, Calif.

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