The Relative Safety of Ephedra Compared with Other Herbal Products

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Background: **Ephedra is widely used in dietary supplements that are marketed to promote weight loss or increase energy; however, the safety of this product has been questioned because of numerous case reports of adverse events.**

Objective: **To compare the risk for adverse events attributable to ephedra and other herbal products.**

Design: **Comparative case series.**

Setting: **American Association of Poison Control Centers Toxic Event Surveillance System Database Annual Report, 2001.**

Measurements: **The relative risk and 95% confidence interval for experiencing an adverse reaction after ephedra use compared with other herbs. This risk was defined as the ratio of adverse reactions to ephedra versus other products, divided by the ratio of their relative use in the United States.**

Results: **Products containing ephedra accounted for 64% of all adverse reactions to herbs in the United States, yet these products represented only 0.82% of herbal product sales. The relative risks for an adverse reaction in persons using ephedra compared with other herbs were extremely high, ranging from 100 (95% CI, 83 to 140) for kava to 720 (CI, 520 to 1100) for *Ginkgo biloba*.**

Conclusions: **Ephedra use is associated with a greatly increased risk for adverse reactions compared with other herbs, and its use should be restricted.**

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An Asian ephedra species has been used for thousands of years in Traditional Chinese Medicine herbal formulas designed to treat asthma and other respiratory diseases (1, 2). The herb extract is known as ma huang and contains several ephedra alkaloids, including the primary active constituent, ephedrine, as well as smaller amounts of pseudoephedrine, phenylpropanolamine, methylephedrine, methylpseudoephedrine, and norpseudoephedrine (cathine, a controlled substance) (3). These drugs have sympathomimetic activity and lead to various physiologic responses, including vasoconstriction; bronchodilation; and increases in blood pressure, heart rate, cardiac contractile force, and automaticity (4). Ephedra gained widespread medical use in the United States in the 1920s as a nasal decongestant, central nervous system stimulant, and asthma treatment, but use declined substantially in the following decade because of safety concerns and the availability of safer alternatives (5, 6).

Recently, ephedra has become a common ingredient in many dietary supplements that are promoted to increase energy or assist with weight loss. Since herbs are regulated as dietary supplements in the United States, these ephedra-containing products can be sold without approval by the U.S. Food and Drug Administration (FDA) (7).

Numerous case reports have documented adverse effects in persons using ephedra (8–11). In the largest published case series, Haller and Benowitz (8) reviewed 140 adverse event reports involving ephedra that were submitted to the FDA. They concluded that 43 were definitely or probably related to ephedra and another 44 were possibly related. However, there are certain limitations in determining causality from case reports, the foremost of which is the inability to determine relative risk.

The primary obstacle to determining a relative risk is that underreporting of adverse reactions prohibits a calculation of their true incidence. A recent report from the Office of the Inspector General of the U.S. Department of Health and Human Services (12) concluded that current surveillance systems for identifying adverse reactions from dietary supplements probably detect less than 1% of adverse reactions.

One option for estimating the safety of ephedra-containing herbs is to compare the relative frequency of adverse reactions attributable to ephedra with that of other commonly used herbs. Based on the assumption that persons using various herbal products will have a similar tendency to report adverse reactions associated with their use, a comparison of the frequency of adverse reactions per unit sold can help determine their relative safety. This technique is commonly used in postmarketing surveillance of pharmaceutical drugs (13). Using data obtained by the Toxic Event Surveillance System of the American Association of Poison Control Centers, we examined the risk for adverse reactions per unit of ephedra sold compared with the risk among users of other herbal products.

Methods

Adverse Reactions

Adverse reactions to ephedra and other herbal products during 2001 were documented by the Toxic Event Surveillance System, a database maintained by the American Association of Poison Control Centers that contains standardized information on approximately 96% of all poison center contacts in the United States (14). For each inquiry to a participating poison control center, a specialist in poison control information determined whether an adverse reaction that could be attributed to a specific agent occurred. An adverse reaction was defined as "an adverse event occurring with normal, prescribed, labeled, or recommended use of the product, as opposed to overdose, misuse, or abuse" (14).

The estimated numbers of units of herbal products sold during 2001 were determined by an independent natural products consulting agency that conducted a probability-based sampling of all natural product retail stores in the United States (SPINS, Inc., San Francisco, California). These include natural product supermarkets and mainstream food, drug, and mass merchandise stores. The total population of natural product stores was divided into cells based on ZIP codes, and sample stores in each cell were selected by using probability-based systematic sampling. Estimates of unit sales for herbal products are reported to have a standard error of ±6%. As an alternative source to our best estimate for ephedra sales, we identified a second sales estimate from an annual natural products survey of retail stores (15).

Statistical Analysis

We calculated the relative risk and 95% CIs for an adverse reaction attributable to ephedra compared with other herbs. Relative risk was defined as the number of adverse reactions per unit sales of ephedra divided by the number of adverse reactions per unit sales of the comparison herb. Confidence intervals were calculated by using the method of Tubert-Bitter and colleagues (13), which assumes a Poisson distribution for the number of adverse reactions observed for a given number of herbal units sold. All analyses were conducted by using Microsoft Excel 2000 (Microsoft Corp., Redmond, Washington).

Since the determination of relative risk for adverse reactions after use of ephedra and other herbs depends heavily on an accurate estimation of their relative sales, we performed a sensitivity analysis around the fraction of all herbal product sales that contained ephedra. Our two best estimates described above were based solely on retail herb sales, which make up approximately 75% of all herb sales (SPINS, Inc.). As an extreme "high-end" estimate for our sensitivity analysis, we assumed that half of all nonretail herb sales were of ephedra-containing products.

Table. **Relative Risk for an Adverse Reaction to Ephedra Compared with Other Commonly Used Herbal Products in the United States in 2001**

Herb	Adverse Reactions, *n*	Herbal Product Sales in United States, %*	Relative Risk (95% CI)†
Ephedra‡	1178	0.82	1.0
Ginkgo biloba	28	14.05	720 (520–1100)
St. John's wort	31	7.98	370 (270–570)
Echinacea	69	16.62	350 (280–450)
Ginseng	46	10.45	330 (250–460)
Valerian	44	4.78	160 (120–220)
Kava	59	4.30	100 (83–140)
Yohimbe	10	0.75	110 (66–280)
All herbal products (excluding ephedra)	654	99.18	220 (200–240)

* Sales percentage is calculated on the basis of units of the herbal product sold (SPINS, Inc., San Francisco, California).
† Relative risk is defined as the number of adverse reactions per unit sales of ephedra divided by the number of adverse reactions per unit sales of the comparison herb.
‡ Includes all ephedra products (single and combinations with other herbs and substances).

Context

Ephedra (ma huang) is used in dietary supplements to "promote weight loss and enhance energy." Is it safe?

Contribution

This study, based on data from U.S. poison control centers and sales information, shows that products containing ephedra accounted for 64% of all reported adverse effects from herbs even though they represented less than 1% of total herbal product sales. The relative risk for an adverse effect from ephedra was 100 (95% CI, 83 to 140) compared with kava and 720 (CI, 520 to 1100) compared with *Ginkgo biloba*.

Implications

Ephedra is associated with greatly increased risk for adverse effects compared with other herbs.

–The Editors

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The funding sources had no role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

Results

The **Table** shows numbers of adverse reactions adjudicated by poison control centers in the United States in 2001 to be attributable to several commonly used herbal products. Products containing ephedra alone or combined with other herbs or substances accounted for 64% of all adverse reactions, yet these products represented only 0.82% of herbal product sales. The relative risks for an adverse reaction in persons using ephedra compared with other herbs are extremely high (**Table**), ranging from 100 (95% CI, 83 to 140) for kava to 720 (CI, 520 to 1100) for *Ginkgo biloba*. The relative risk for ephedra-containing products was markedly elevated in comparison with all other individual herbs and the category of all herbal products.

The markedly elevated relative risks observed with ephedra-containing products were stable over a wide range of estimates of ephedra sales (**Figure**). Even with an extreme high estimate for ephedra's share of the total herbal market (13.5%), the relative risks for adverse reactions among ephedra users were still 10- to 40-fold greater than the risk among users of other herbal products. Differential reporting of adverse reactions among users of ephedra and other herbs could potentially alter the calculated relative risks. However, to eliminate the observed statistically significant association of ephedra with adverse reactions, the reporting rate for nonephedra herbs would have to be 207-

fold less than the adverse reaction reporting rate for ephedra.

DISCUSSION

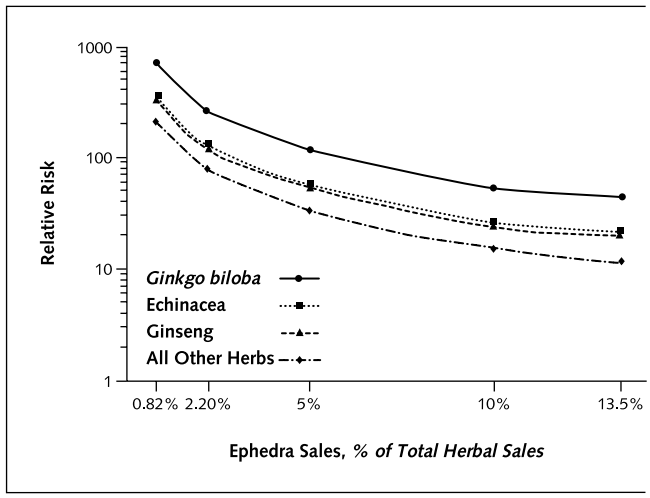
Ephedra is a common ingredient in many weight loss and energy-enhancing products but is extremely controversial. Several prominent medical organizations, including the American Medical Association and Health Canada, have recommended banning the sale of the herb (16). Numerous sports organizations, including the National Collegiate Athletics Association, the International Olympic Committee, and the National Football League, prohibit the use of ephedra-containing products. The FDA has issued several warnings regarding possible side effects from ephedra (17).

Some industry experts claim that ephedra is safe and note that the number of adverse reactions reported among users of ephedra may not be greater than the background rate of events in the population (18). This opinion had been difficult to challenge because no previous study had compared the risk for adverse reactions in ephedra users and nonusers.

In this study, we used a technique commonly employed to monitor the relative safety of pharmaceutical drugs to compare the safety of ephedra and other frequently used herbs. We found that the relative risk for an adverse reaction from ephedra was more than 100-fold higher compared with all other herbs. For example, persons using products containing ephedra were 720 times more likely to have an attributable adverse reaction to ephedra than persons using *Ginkgo biloba*.

Our study has several limitations. The number of adverse reactions used in this analysis is a fraction of all adverse reactions that occur with these herbs, and underreporting of adverse reactions may vary with the severity of the reaction. However, if persons using various herbs have similar likelihoods of reporting adverse reactions, then the relative risks that we generated should be valid. The relative risk calculations also assume that persons using these different herbs have similar general health. Differences in the characteristics of the populations using various herbs can affect both the likelihood of experiencing and reporting an adverse reaction. Whereas differences in the relative numbers of users of ephedra and other herbal products may somewhat affect the magnitude of the relative risks we calculated, we do not believe that characteristics of the users could explain the consistent finding of extreme increased risk of ephedra compared with all other herbs. Rather, these findings are most likely due to the toxicity of ephedra. These findings are consistent with those of a previous randomized, placebo-controlled trial of an ephedra product, in which 8 of 35 participants in the ephedra group (23%) compared with none of 32 participants in the placebo group (0%) abandoned therapy because of side effects (19).

Figure. **Sensitivity analysis showing the effect of variations in the estimate of ephedra's proportion of total herbal market sales on the relative risk for an adverse reaction with ephedra compared with other herbs.**



0.82% = best estimate from SPINS, Inc., San Francisco, California; 2.20% = *Whole Foods Magazine* survey estimate; 13.5% = high estimate assuming that ephedra sales represent half of all nonretail sales in addition to 0.82% of retail sales.

In conclusion, the risk for an adverse reaction after the use of ephedra is substantially greater than with other herbal products. The sale of ephedra as a dietary supplement should be restricted or banned to prevent serious adverse reactions in the general population.

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