COMMENTS AND RESPONSES

The Relative Safety of Ephedra Compared with Other Herbal Products

TO THE EDITOR: In their Brief Communication concerning the safety of the dietary supplement ephedra (1), Bent and colleagues compared the 2001 Toxic Event Surveillance System (TESS) report with ephedra sales data provided to them by various sources (2). The design and conclusions of their study have several fundamental flaws.

Clinical trials of drugs and herbal products provide a basis for understanding the potential for serious adverse events as well as the intended population. The TESS data indicate that 55.5% of all reports related to ma huang (ephedra) alone or in combination with another herb involved people younger than 19 years of age. In addition, 27.9% of exposures were in children younger than 6 years of age (3). People younger than 19 years of age should not take ephedra; there simply have been no studies performed on the herb ephedrine in that age group. Bent and colleagues’ data are therefore misleading to the intended consumer. Furthermore, Bent and colleagues mistakenly stated that ephedra accounts for 64% of all herb-related adverse reactions. However, hundreds of herbal products are sold in the United States, not 12 as the TESS report stated (Watson B. Personal communication. 22 February 2003).

It is important to know the direct evidence about the safety of ephedra. We must not fail to use the available published, peer-reviewed clinical studies. According to the TESS data, ephedra has a mortality rate of 0.000757% (6 deaths in 7927 exposures), while kava has a mortality rate of 0.002976% (1 death in 336 exposures). Using these data, one could conclude that kava has a mortality rate of 0.000757% (6 deaths in 7927 exposures), while kava has a mortality rate of 0.002976% (1 death in 336 exposures). Using these data, one could conclude that kava has a mortality rate of 0.002976% (1 death in 336 exposures). Using these data, one could conclude that kava has a mortality rate of 0.002976% (1 death in 336 exposures). Using these data, one could conclude that kava has a mortality rate of 0.002976% (1 death in 336 exposures). Using these data, one could conclude that kava has a mortality rate of 0.002976% (1 death in 336 exposures). Using these data, one could conclude that kava has a mortality rate of 0.002976% (1 death in 336 exposures).

Perhaps a less negative conclusion would not have served the purpose of Bent and colleagues’ study. The manipulative presentation of their data appears to have influenced media reports regarding the potential danger of ephedra compared with other herbs. The audience, both the scientific and lay press, deserves the absolute facts.

Disclosure: Mr. Kalman has testified in cases related to ephedra on behalf of CytoDynite Technologies, Inc. Dr. Antonio is also employed by MET-Rx, a dietary supplement company that formerly sold ephedra products. Dr. Kreider has served as an expert in litigation for Metabolife.

References

IN RESPONSE: While our study certainly has some limitations, the letter from Mr. Kalman and his colleagues is unfortunately characterized by incorrect statements and invalid analyses of the data. They initially refer to the age distribution of “reports” related to ephedra. However, as we clearly stated, our analysis was limited to adverse reactions, which are defined as “adverse events occurring with normal, prescribed, labeled, or recommended use” (1). Fewer than 25% of these occur in persons younger than 20 years of age (2). Although the TESS annual report lists only nine herbs, it includes totals for all single-herb and multitherb products. Ephedra-containing products accounted for 64% of all herb-related adverse reactions in the 2001 report, as reported in our paper.

Mr. Kalman and colleagues then made the mistake of determining mortality rates to be the number of herb-related deaths divided by the number of contacts to poison control centers. A mortality rate is determined by the number of deaths divided by the total exposed population in 1 year, and the exposed population can be estimated only from sales data or population-based surveys. The correct statement extrapolated from the TESS data would be that ephedra accounted for six deaths and less than 5% of herbal product sales in 2001, whereas all other herbs accounted for one death (from kava) and more than 95% of herbal product sales. Because spontaneous reporting has been estimated to detect less than 1% of all reactions to herbal products (3), these deaths associated with ephedra may be merely the “tip of the iceberg.” Mr. Kalman and colleagues also referred to adverse reaction frequency as the proportion of adverse reactions among reports to poison control centers; however, this statistic has no relevance for comparing the safety of herbal products.

While not mentioned in Mr. Kalman and colleagues’ letter, an important limitation of our study was the difficulty in estimating ephedra’s percentage of herbal product unit sales. For this reason, we included a sensitivity analysis in our study that varied this percentage from 0.82% to 13.5%. Our estimation that ephedra was responsible for 0.82% of the herbal product market in 2001 was based on unit sales of products that were identified as “herbal formulas or singles” by a natural products information company (SPINS, Inc., San Francisco, California). After the article was published, the company realized that information about some products, which contain ephedra and other herbs but which the company classifies as “vitamins/supplements” or “grocery” items rather than “herbal products,” had not been provided to us. When information from these additional categories was included, ephedra’s percentage of herbal sales was 4.3% rather than 0.82% (the figure we originally published). Of note, the 4.3% figure is well within the range used in our original sensitivity analysis. When this higher estimate was used, the relative risk for an adverse reaction from ephedra compared with all other herbs decreased from 220 (95% CI, 200 to 240) to 40 (CI, 37 to 44). The natural products company has contacted us and verified that all of

Douglas S. Kalman, MS, RD
Miami Research Associates
Miami, FL 33143

Jose Antonio, PhD
Florida Atlantic University
Boca Raton, FL 33431-0991

Richard B. Kreider, PhD
Baylor University
Waco, TX 76798-7313

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their ephedra and other herb sales data are captured within the three categories that were used to obtain the lower estimate.

We stand by our original conclusions: The risk for adverse reactions with ephedra is dramatically elevated compared with other herbs. Our results are consistent with a recently published systematic review, which found that ephedra is associated with an elevated risk for nausea, vomiting, psychiatric symptoms, autonomic hyperactivity, and palpitations (4).

Stephen Bent, MD
San Francisco Veterans Affairs Medical Center
San Francisco, CA 94121

Thomas N. Tiedt, PhD
Med-Tox Group
Longboat Key, FL 34228

Michelle Odden, BS
Michael G. Shlipak, MD, MPH
San Francisco Veterans Affairs Medical Center
San Francisco, CA 94121

References

TO THE EDITOR: We read with interest the article by Phillips and colleagues (1) and the accompanying editorial (2). One of us (Dr. Torgovnick) developed low-grade myopathy while receiving statin therapy. Atorvastatin, 5 mg (0.5 tablet), was started in September 1999. Nonspeciﬁc aches and pains were noticed, but no clear weakness was evident and Dr. Torgovnick continued regular exercise. On several occasions, a burning sensation beyond what was anticipated developed in the muscles after exercise. Low-grade myopathy was considered in June 2000, and creatine kinase level was checked. The result, 3.14 µkat/L, was normal (reference range, 0 to 3.34 µkat/L), and atorvastatin therapy was continued.

In early May 2002, 24 hours after exercise, creatine kinase level was checked and was found to be 4.8 µkat/L. Atorvastatin was withdrawn, and the aches, pains, and burning sensation gradually resolved. After vigorous exercise, several weeks after atorvastatin was discontinued, the creatine kinase level was 3.19 µkat/L. On a repeated test, serum cholesterol level was signiﬁcantly elevated and pravastatin was introduced. Symptoms recurred but were tolerated. While Dr. Torgovnick was taking pravastatin, the creatine kinase level was 4.98 µkat/L shortly after exercise.

Phillips and colleagues’ patients ranged in age from 62 to 76 years, and no information was given on their level of activity or their muscle mass, both of which can affect creatine kinase levels. In the current author’s case, it was clear that something was wrong, but the creatine kinase level rose only with exercise provocation. The message of the article by Phillips and colleagues is clear and important. As more patients with this syndrome are identiﬁed, perhaps less invasive evaluation might include the use of exercise provocation to watch for an increase in creatine kinase level. Alternatively, simple serial measurement of creatine kinase levels to establish a baseline and subsequent reevaluation after a speciﬁed period (or withdrawal of the agent and a demonstrated decrease in creatine kinase level, particularly if associated with resolution of symptoms) would be useful.

Josh Torgovnick, MD
St. Vincent’s Hospital and Medical Center
New York, NY 10011
Edward Arsura, MD
Salem Veterans Affairs Medical Center
Salem, VA 24153

References

TO THE EDITOR: Phillips and colleagues (1) nicely documented biopsy-conﬁrmed myopathy in patients with normal creatine kinase levels in association with statin therapy. As they mentioned in their discussion, similar features are reported for coenzyme Q10 deﬁciency. It is known that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibition by statins inﬂuences not only the cholesterol synthesis but also that of proteins such as farnesylated and geranylgeranylated proteins and ubiquinones such as coenzyme Q10. Similar to cholesterol synthesis, the primary regulation of coenzyme Q10 biosynthesis is the HMG-CoA reductase reaction, providing its

Mark H. Hyman, MD
University of California, Los Angeles
Los Angeles, CA 90025

References
TO THE EDITOR: Phillips and colleagues (1) posited that myopathy with normal creatine kinase levels may occur in patients receiving statin therapy. Patients with muscular pain or weakness but without elevated enzyme levels pose an important clinical problem, although the exact incidence of this disorder is not known. Phillips and colleagues did not discuss a potential mechanism or mechanisms. However, they reported 3-methylglutaconic aciduria consistent with re- liability (2). The American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute clinical advisory states that ubiquinone (coenzyme Q10) deficiency could be a possible mechanism, although no conclusive data support this hypothesis (3). The synthesis of coenzyme Q10 in cells involves pathways that are blocked by the statins. A recent review of statin myopathy (4) discusses this and other topics.

Members of the complementary and alternative medicine community have been advocating the concomitant use of coenzyme Q10 with statins, although this practice has not been accepted by most mainstream physicians. Data on whether statins lower coenzyme Q10 levels are contradictory. However, certain persons with a genetic, biochemical, or other cause of decreased levels of coenzyme Q10 levels in tissue, such as increasing age (5), may experience statin-induced decreases in muscle coenzyme Q10 levels as a cause of the myopathy. Of note, the patients in Phillips and colleagues’ study were 62 to 76 years of age. Do the authors have any information on serum or muscle coenzyme Q10 levels or coenzyme Q10 use in these patients?

I believe the clinical and pathologic data in Phillips and colleagues’ study, coupled with other reports in the peer-reviewed literature, suggest an etiologic role of coenzyme Q10 deficiency in some patients with statin-induced myopathy. Although isolated case reports have supported this hypothesis, we need large randomized, controlled studies studying the concomitant administration of coenzyme Q10 and statins to prevent or treat muscle symptoms, with or without muscle enzyme elevations. Only then will we be able to address this important controversy.

Louis Evan Teichholz, MD
Hackensack University Medical Center
Hackensack, NJ 07601

References
5. Bhuyen J, Secombe DW. The effects of 3-hydroxy-3-methylglutaryl-CoA reductase inhibition on tissue levels of carnitine and carnitine acyltransferase activity in the rabbit. Lipids. 1996;31:867-70. [PMID: 8869889]

IN RESPONSE: Dr. Hyman asks whether other biochemical markers might identify patients with statin-induced myopathy. Levels of aldolase and myoglobin, which would be released by disrupted myocyte membranes, have been normal whenever we have tested them in our patients. We are currently testing other indicators of the metabolic defect associated with this muscle toxicity (1).

Drs. Torgovnick and Arsura inquire about the relation of this toxicity to exercise. Postexercise creatine kinase level is more sensitive than resting creatine kinase level in assessing muscle toxicity. The latter is related to membrane disruption but has not met with much success in assessing statin toxicity (2, 3). We required that all study patients maintain a consistent exercise and dietary regimen during the 5-month evaluation. Although all of the creatine kinase evaluations were performed after exercise, they were not performed late enough (6 to 12 hours later) to make this a sensitive test. We believe that the preoccupation with muscle membrane abnormalities and

Emil Toma, MD, DSc, FRCP(C)
Hôpital-Dieu Hospital
Montreal, Quebec H2W 1T8, Canada

References
5. Bhuyen J, Secombe DW. The effects of 3-hydroxy-3-methylglutaryl-CoA reductase inhibition on tissue levels of carnitine and carnitine acyltransferase activity in the rabbit. Lipids. 1996;31:867-70. [PMID: 8869889]
elevation of creatine kinase levels as indicators of toxicity has delayed the detection of the metabolic toxicity we described. Other afflictions with similar pathologic characteristics—mitochondrial myopathies, for example—cause significant abnormalities in muscle function without disrupting membranes sufficiently to elevate creatine kinase levels. We suspect that further evaluation of metabolic defects in patients with statin myotoxicity will prove more fruitful than repeated attempts to evaluate this abnormality from the perspective of muscle membrane toxicities or rhabdomyolysis.

The comments of Dr. Toma and Ms. Loignon and Dr. Tichholz regarding the possible relationships of carnitine and coenzyme Q10 to statin myotoxicity are correct. While we found no depression in either serum or muscle carnitine levels in our patients, measurement of coenzyme Q10 may be more productive. Muscle coenzyme Q10 levels correlated with toxicity in one of the three patients in our study who underwent muscle biopsy, both while myopathic and again when toxicity had resolved. We have a report in preparation that discusses measurement of coenzyme Q10 level in a series of 50 muscle biopsy specimens from patients under evaluation for statin myotoxicity. The results of that study should provide further impetus for future trials assessing coenzyme Q10 and carnitine.

Statins are the best therapy available to reduce cardiovascular end points in patients with atherosclerotic risks. The optimal use of these agents requires a thorough understanding of their toxicities as well as of their efficacy. We agree that we know too little about the mechanism and pathophysiology of statin myotoxicity and that further clinical evaluations and biochemical description are essential.

Paul S. Phillips, MD
Scripps Mercy Hospital
San Diego, CA 92103

Richard H. Haas, MD
University of California, San Diego
La Jolla, CA 92039-0935

References

The In-Training Examination in Internal Medicine

TO THE EDITOR: Since the In-Training Examination in Internal Medicine (IM-ITE) is administered to many internal medicine residents in categorical programs for 3 consecutive years, it is possible that repeated test-taking itself contributes in part to the improved performance seen in postgraduate year (PGY) 2 and PGY3. Certainly, ongoing training in internal medicine must have a substantial effect. Garibaldi and colleagues (1) report that IM-ITE performance correlates well with the cumulative number of internal medicine rotations undertaken. In addition, annual increments in scores were lower for medicine–pediatrics residents (who receive half the annual internal medicine training of categorical internal medicine residents) and for all residents during the shorter inter-test interval in 1999 to 2000, when examination administration was moved up to October (1).

Repetition of any task can improve performance. Since 25% to 50% of questions on the IM-ITE are selected from examinations given 2 or more years previously, the potential for learning how to take the test (as opposed to simply learning more about internal medicine) may be higher than if the test were totally new each year. Even when questions are not identical, many are very similar from year to year, since there are a finite number of core “testable” concepts. Indeed, having taken the IM-ITE examination myself for 3 years during residency, I recall that there were several questions on the PGY1 examination that I went home and read about because I was uncertain about my answer, only to see a similar question the next year or the identical question 2 years later.

Are there enough residents who took the examination only during the PGY2 or PGY3 years to determine whether their scores more closely approximate those of their training-year colleagues instead of the scores of first-time test-takers in general (mostly PGY1 residents)? Are any data available for performance specifically on questions repeated on the PGY3 examination from the PGY1 examination?

David P. Steensma, MD
Mayo Clinic
Rochester, MN 55905

Reference

TO THE EDITOR: I was somewhat surprised by the conclusion reached by Garibaldi and colleagues (1) about why international medical graduates perform better than U.S. graduates on the IM-ITE. The authors stated, “Improvement in performance occurred almost exclusively in international graduates; in particular, it occurred in residents for whom English was not their native language.” They went on to conclude that international medical graduates did better on the examination because they got more time to complete it. Because international medical graduates were unfamiliar with the English language, the additional time allowed them to perform better at the end of the examination and thus score better.

I believe this is too simplistic an explanation. For the past 5 years, international medical graduates have consistently outperformed U.S. graduates on the IM-ITE. The test results show that international medical graduates are better prepared to be internists than U.S. graduates. It is high time that internal medicine educators address the inherent problems in medical education and correct them before it is too late. Internal medicine was traditionally considered the intellectually challenging branch of medicine that emphasized skills in physical diagnosis, cognitive and analytical clinical skills, knowledge of pathophysiology, and expertise in clinical decision making. As the most intellectually challenging specialty, it attracted the best and the brightest from our medical schools. This is no longer the case. The best and brightest of our graduating classes now seek residencies in radiology, emergency medicine, and orthopedics.
For many of them, internal medicine is no longer an attractive career choice. The best of the international medical graduates, on the other hand, cannot get into the highly competitive specialties and thus choose internal medicine instead.

What is actually happening in our medical schools and training programs is that our technology is overshadowing the basic skills that are the hallmark of internal medicine. Imaging studies are replacing physical diagnostic skills, clinical pathways are replacing clinical reasoning, and algorithms are replacing clinical decision making. Is it surprising that international medical graduates who do not have easy access to technologies are better prepared in basic skills? Are not echocardiograms replacing good cardiac examinations, magnetic resonance imaging replacing good neurologic examinations, and computed tomography scans replacing good abdominal examination? Educators in internal medicine need to do some soul-searching regarding the poor performance of U.S. graduates.

Joseph J. Nidiry, MD
Howard University
Washington, DC 20060

Reference

TO THE EDITOR: We read with interest that international medical graduates now consistently outperform U.S. medical graduates on the IM-ITE (1). We propose that the difference in scores may reflect residency program directors’ use of U.S. Medical Licensing Examination (USMLE) scores when selecting international medical graduates. In the past decade, program directors have increasingly relied on USMLE scores for recruiting residents. The Residency Review Committee for Internal Medicine of the Accreditation Council for Graduate Medical Education continues to increase the board pass rate on the American Board of Internal Medicine Certifying Examination that is required for program accreditation, and USMLE scores, like IM-ITE results, are believed to predict passage (2, 3). The Electronic Residency Application Service has made it easy to screen applicants by using USMLE scores and numbers of attempts.

International medical graduates have gotten the message. The applicant pool knows that there is a virtually insurmountable barrier to obtaining a residency with low USMLE scores. Furthermore, the high cost of taking the Clinical Skills Assessment examination and the increased availability of H-1B visas for residency training, which require passing USMLE Step 3, have selected out a higher-scoring group.

On the other hand, few U.S. graduates will find low USMLE scores to be a barrier to obtaining an internal medicine residency position. The paradox of limiting training opportunities for international medical graduates, who now score better than U.S. medical graduates on the IM-ITE, has been noted (4). Although the very best medicine programs recruit highly competitive U.S. graduates, the oversupply of medicine residency positions makes many programs a safe choice for less competitive students. Most program directors with both international and U.S. graduates in their programs are acutely aware of the “book knowledge gap.” To narrow the gap (although it is not yet reflected in American Board of Internal Medicine Certifying Examination pass rates [5]), residency programs will have to develop creative ways to motivate U.S. medical graduates to acquire the type of knowledge tested on standardized examinations.

Robin Dibner, MD
Julia Andrieni, MD
Lenox Hill Hospital
New York, NY 10021

Lawrence Smith, MD
Mount Sinai School of Medicine
New York, NY 10029

IN RESPONSE: Dr. Steensma is concerned about the carryover effect of reusing questions on the IM-ITE after a gap of 2 or more years. The operational practice of reusing items from previous examinations is similar for virtually all national examinations that use multiple-choice questions. The IM-ITE, however, is unique in that most examinees take the test in 3 consecutive years. The practice of reusing items provides the examination with a core group of questions that have performed well on psychometric evaluations in the past and have been demonstrated to be effective in distinguishing high scorers from low scorers. It also enables psychometricians to equate the scores of the examination from one year to the next. The previously used items that we include on the IM-ITE are from several different administrations and not from one single examination, with a gap of at least 1 year between use. Through internal audits, we have found no statistically significant difference in performance on new versus previously used items (Subhiyah RG, McGrenra CC. Comparison of performance of ACP/ASIM ITE candidates on new and used items. 1999, 2000, 2001. Unpublished data). Similar comparisons have been made for other programs, with similar results (Subhiyah RG, Hess B. Effect of item exposure on a take-home recertification examination. 2002. Unpublished data). Furthermore, in our paper, we noted a consistent increase in examination scores between the PGY1 and PGY2 years, when the examinations were totally different, and the PGY2 and PGY3 years, when some questions may have been repeated. We did not see a marked increase in scores in the PGY3 examination, which might have been anticipated if residents had actually remembered questions that had been asked previously.

Dr. Nidiry is concerned about our finding that international medical school graduates have outscored U.S. medical school graduates on the last seven IM-ITEs. Before 1995, unknown to the IM-ITE committee, the examination had been “speeded” for those less practiced in the English language. In 1995, the time allocated for...
the IM-ITE was lengthened from 6 hours to 7 hours. In that year, the scores of international graduates in all 3 training years increased substantially and exceeded those of U.S. graduates. International graduates have scored consistently higher on all subsequent examinations with the longer time for answering questions. These data suggest that graduates from international medical schools might be better trained than U.S. graduates or that they may have benefited from extra clinical experiences before entering a U.S. residency program. It is also possible, as Drs. Dihner, Andrieni, and Smith suggest, that international medical school graduates may have been selected specifically because of their success on a similar type of examination when they applied for residency training. Our data simply point out that international medical graduates were better able to demonstrate their medical knowledge when the time limit for the examination was increased sufficiently to enable them to complete the test.

The IM-ITE does not compare the performances of U.S. graduates in internal medicine training programs with those of U.S. graduates in other specialties in which the content differs. Thus, our study provides no insight into Dr. Nidiry’s idea that graduates of U.S. medical schools in internal medicine residency programs are less knowledgeable than those entering other residency programs.

Raja Subhiyah, PhD
National Board of Medical Examiners
Philadelphia, PA 19104

CLINICAL OBSERVATIONS

Fish Oil Therapy in Recurrent IgA Nephropathy

TO THE EDITOR: Background: IgA nephropathy is the most common type of glomerulonephritis worldwide and may lead to kidney failure in approximately 25% of patients (1). Histologic recurrence rates are very high in the transplanted kidney (60%) and, with long-term follow-up, graft loss due to recurrent disease is eventually seen in approximately 25% of patients (1). Histologic recurrence rates are very high in the transplanted kidney (60%) and, with long-term follow-up, graft loss due to recurrent disease is eventually seen in approximately 25% of patients (1). Histologic recurrence rates are very high in the transplanted kidney (60%) and, with long-term follow-up, graft loss due to recurrent disease is eventually seen in approximately 25% of patients (1).

Objective: To describe treatment of post-transplantation IgA nephropathy with fish oil.

Case Report: A 34-year-old pipefitter presented with microscopic hematuria in 1979. Over the next 7 years, his kidney function deteriorated; he required hemodialysis by March 1986. Two months later, he received a successful cadaveric kidney transplant. His immunosuppressive medications consisted of prednisone and cyclosporine. He did well until 1991, when he developed the nephrotic syndrome. Open kidney biopsy revealed progressive IgA nephropathy, presumably recurrent disease. One year later, without any additional specific therapy for IgA nephropathy, peritoneal dialysis was started. Five months after this, the patient received another successful cadaveric kidney transplant. His immunosuppressive medications were identical to those used after his first kidney transplantation.

In May 1997, 5 years after the second transplantation, the nephrotic syndrome again developed and kidney biopsy confirmed recurrent IgA nephropathy. Fish oil therapy with 1-g capsules (360 mg eicosapentaenoic acid, 240 mg docosahexaenoic acid), six capsules twice daily, was started. Proteinuria was 3299 mg/d before fish oil therapy and 458 mg/d (normal value, <165 mg/d) with therapy. Over the ensuing 5 years to the present, 10 years after the second transplantation, the patient’s proteinuria has remained at this level and kidney function is well preserved. The patient began taking an angiotensin-receptor blocker in 1999, but his proteinuria did not improve further. The Figure summarizes the patient’s clinical course.

Discussion: This case illustrates the progressive nature of IgA nephropathy in transplanted kidneys. Although recurrent IgA nephropathy was initially thought to be benign, longer follow-up has shown that it results in significant loss of transplanted kidneys in 30% to 60% of cases (2–4). Clinical recurrence usually occurs within 6 years (2–5), and proteinuria of more than 1 g/d portends future graft loss (6). Recurrence in a second transplanted kidney is not unique. In one series, three patients with second transplanted kidneys lost the kidneys because of progressive recurrent disease (4). In our case, addition of fish oil therapy to the treatment regimen reduced proteinuria and extended the life of the patient’s second transplant to 10 years, compared with 6 years for the first transplant.

The largest study to date of patients with primary IgA nephropathy treated with fish oil therapy showed that the treatment was effective (7). The putative role of omega-3 polyunsaturated fats is to limit production of vasoconstrictive and proinflammatory eicosanoids and to decrease the production of cytokines (8). In a case report with 1-year follow-up, Butani and Palmer also described the effectiveness of fish oil therapy in recurrent IgA nephropathy after initial treatment with high-dose alternate-day corticosteroids (9). Since high-dose corticosteroids have been effective in at least one trial (10), fish oil therapy given concomitantly with low-dose corticosteroids may be more effective than fish oil therapy alone. This could explain the dramatic effect in Butani and Palmer’s case. Doses of corticosteroids or other immunosuppressive drugs can be increased, but this confers additional risk. Fish oil therapy has no such risk and may even be beneficial from a cardiovascular standpoint.

Conclusion: The current case clearly demonstrates a beneficial effect of fish oil therapy on post-transplantation IgA nephropathy. Trials with larger numbers of patients are warranted.

Roland Ng, MD
University of Hawaii John A. Burns School of Medicine
Honolulu, HI 96817

References
**Correction:** The Relative Safety of Ephedra Compared with Other Herbal Products

An article on adverse effects of ephedra (1) has been revised. The authors, Bent and colleagues, originally estimated that ephedra had a 0.82% share of sales of the herbal product market in the United States in 2001. The estimate was based on product sales data provided by a natural products information company (SPINS, Inc., San Francisco, California). The authors requested sales data for all herbal products containing ephedra and seven other key herbs. The company provided these data. After Bent and colleagues’ article was published, the company realized that data on some products, which contain ephedra and other herbs but which the company classifies as “vitamins/supplements” or “grocery” items rather than “herbal products,” had not been provided to the authors.

When sales data on products from these additional categories were included, ephedra made up 4.3% of herbal sales rather than 0.82% (the figure originally published), and the relative risk for an adverse reaction from ephedra compared with all other herbs was 40 (95% CI, 37 to 44) rather than 220 (CI, 200 to 240). Changes in estimates of relative risk for other herb comparisons are given in the Table. The natural products company has stated that all of its ephedra and other herb sales data are captured within the three categories mentioned here. Of note, the revised 4.3% figure for ephedra sales is within the range that was used in Bent and colleagues’ sensitivity analysis (0.82% to 13.5%), and the conclusions of the article, that the risk for adverse reactions with ephedra is elevated compared with other herbs, are not changed.

Reference

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

<table>
<thead>
<tr>
<th>Herb</th>
<th>Adverse Reactions, n</th>
<th>Herbal Product Sales in United States, %*</th>
<th>Relative Risk (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedra</td>
<td>1178</td>
<td>4.29</td>
<td>1.0</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>28</td>
<td>4.94</td>
<td>49 (35-77)</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>31</td>
<td>1.55</td>
<td>14 (10-21)</td>
</tr>
<tr>
<td>Echinacea</td>
<td>69</td>
<td>5.99</td>
<td>24 (19-31)</td>
</tr>
<tr>
<td>Ginseng</td>
<td>46</td>
<td>15.33</td>
<td>92 (71-130)</td>
</tr>
<tr>
<td>Valerian</td>
<td>44</td>
<td>0.91</td>
<td>5.7 (4.3-8.1)</td>
</tr>
<tr>
<td>Kava</td>
<td>59</td>
<td>2.99</td>
<td>14 (11-19)</td>
</tr>
<tr>
<td>Yohimbe</td>
<td>10</td>
<td>0.14</td>
<td>3.8 (2.4-10)</td>
</tr>
<tr>
<td>All herbal products (excluding ephedra)</td>
<td>654</td>
<td>95.71</td>
<td>40 (37-44)</td>
</tr>
</tbody>
</table>

* Sales percentage is calculated on the basis of units of the herbal product sold (SPINS, Inc., San Francisco, California).
† Relative risk is defined as number of adverse reactions per unit sales of ephedra divided by number of adverse reactions per unit sales of comparison herb.
‡ Includes all herbal products (single and combinations with other herbs and substances).
TO THE EDITOR: Simvastatin is an antilipemic agent that decreases low-density lipoprotein cholesterol levels by inhibiting hydroxymethylglutaryl coenzyme A reductase. Statins have an excellent safety profile (1). However, reports have described a lupus-like hypersensitivity reaction with late, insidious onset (2–4). Symptoms include polymyalgia, elevated erythrocyte sedimentation rate (ESR), positivity for antinuclear antibodies, and potentially life-threatening pneumonia. To highlight the diversity of this drug-induced hypersensitivity, we report a case in which the patient presented with dysphasia.

A 74-year-old man with coronary artery disease and hypertension presented with sudden onset of dysphasia. He was initially thought to have a viral illness, but symptoms progressed over weeks to the point where he was able to swallow only liquids. His hematocrit decreased from an initial value of 0.44 to 0.28 with no reticulocyte response or evidence of hemolysis. Eosinophilia (eosinophils, 38%), ESR of 100 mm/h, and lactate dehydrogenase level of 320 U/L were noted. Results of endoscopy and esophageal peristalsis studies were normal. Computed tomography showed borderline splenomegaly with mediastinal and retroperitoneal adenopathy. Bone marrow biopsy revealed only increased eosinophils. The rheumatoid factor level was normal, and the patient was strongly positive for antinuclear antibodies.

Medications included simvastatin, fosinopril, aspirin, colchicine, ranitidine, gemfibrozil, digoxin, and atenolol. The patient had tolerated all medications well for more than 2 years. Simvastatin was the only drug discontinued, and afterward, the patient’s dysphasia resolved in a few days. Lactate dehydrogenase level and ESR normalized, and hematocrit subsequently improved.

Statins are commonly used, well-tolerated drugs. A few cases of lupus-like hypersensitivity to statins have been described. Although these reactions are rare, they are difficult to diagnose because they can occur after several years of treatment. This report highlights the diverse symptoms of this reaction. For prescribing clinicians, it is very important to bear these unusual, potentially life-threatening adverse effects in mind.

Katarina LeBlanc, MD, PhD
Mary T. Brophy, MD, MPH
Boston Veterans Affairs Healthcare System
Boston, MA 02130

References