ALTERNATIVE MEDICINE

AN EVIDENCE-BASED APPROACH

Echinacea Update

—This column reviewed the available data on echinacea for the common cold in December 2002, at which time a Cochrane systematic review determined that "variations in preparations and methodologic inadequacies precluded a quantitative metaanalysis." Despite this lack of evidence of efficacy, echinacea remains a popular herbal remedy.

—A new randomized study that tested laboratory-formulated preparations of Echinacea angustifolia *root found no benefit for the herb.*

The Trial

The study, sponsored by the National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (NIH), included a 7-day prophylaxis phase prior to challenge with rhinovirus type 39, followed by a 5-day treatment phase.

A total of 437 healthy, college-aged volunteers participated in the trial, receiving either one of three different extracts of echinacea or placebo.

The participants took the medications on an outpatient basis during the prophylaxis phase, then were isolated in individual hotel rooms for the remainder of the study.

Symptoms (including sneezing, sore throat, rhinorrhea, and malaise) were rated on a scale of 0-4 twice each day following viral challenge; the higher score each day was recorded. Participants whose total symptom score was 6 or more for 5 days and who reported at least 3 days of rhinorrhea or the subjective impression of having a cold were classified as having a clinical cold.

The study found:

► No significant effect for any of three echinacea preparations as prophylaxis against rhinovirus infection.

► No effect on infection rate among patients who received echinacea in the treatment phase only.

► No effect on viral titers.

► No significant effect on symptoms or in number of patients with clinical colds.

► No effect on the course of illness.

► No benefit in severity as measured by weight of nasal secretions.

► No significant effect on interleukin-8 or polymorphonuclear-leukocyte concentrations.

The authors, led by Ronald B. Turner, M.D., professor of pediatrics at the University of Virginia School of Medicine, Charlottesville, concluded that, "as tested, the putative active constituents of *E. angustifolia* do not have clinically significant effects on rhinovirus infection or illness." They noted, however, that the generalizability of their findings might be affected by the wide variety of echinacea preparations available, which contain different plant species and plant parts, and which may be cultivated and extracted in different ways (N. Engl. J. Med. 2005;353:341-8).

The Commentary

The study was accompanied by a commentary by Wallace Sampson, M.D., emeritus clinical professor of medicine, Stanford (Calif.) University, in which he called for an end of funding for research on echinacea.

"As long as research sponsored by NCCAM and private foundations continues, advocates of alternative treatments can claim that a state of equipoise exists when, in fact, the issues should have been settled on the basis of previous knowledge," Dr. Sampson wrote.

He pointed out that the NIH has spent almost $1.5 billion on alternative medicine research since 1999, and NCCAM has spent almost half that in evaluating "folkway uses of herbs and sectarian remedies." It is time for reassessment, he continued. "What is needed is knowledge-based medicine, with randomized clinical trials of treatments with histories that indicate some reasonable chance of efficacy" (N. Engl. J. Med. 2005;353:337-9).

"NCCAM, if it is to justify its existence, must consider halting its search for active remedies through clinical trials of treatments of low plausibility," he said. "A wealth of information also awaits discovery in the psychology of personal beliefs in irrational proposals, in the study of erroneous thinking, and in the study of the mechanisms behind errant social-medical trends such as the alternative-medicine movement."

Other Views

The day before the study was published the American Botanical Council issued a statement challenging certain aspects of the study and its conclusions. A particular concern was the dosage used in the trial. Although the 900-mg/day dose chosen was that recommended by the German Commission E, both the World Health Organization and the recently drafted monograph on echinacea by the Canadian Natural Health Products Directorate recommend a much higher dosage of 3 g/day.

"This is not a definitive trial on the efficacy of echinacea, nor should the results be generalized to echinacea preparations widely available," said Mark Blumenthal, executive director of the American Botanical Council. *E. angustifolia* today is less commonly used in commercial preparations in North America, where *E. pallida* and *E. purpurea* are more commonly cultivated and used in such products.

In a statement that the NCCAM posted on its Web site, director Stephen E. Straus, M.D., said that "the common cold is a major burden on society, and there is not much that conventional medicine can do to prevent it or ease its symptoms. Thus, there is a lot of appeal in the idea of a readily available remedy that might prevent us from getting a cold or make us feel better if we do get one. However, it's important to ask whether science has proven that echinacea really does work for these purposes."

Describing the trial as "well-designed" and "led by a team with expertise in the preparation and study of herbal medicines and the treatment and prevention of respiratory virus infections," Dr. Straus concurred that the study showed no evidence for efficacy. He also noted that the echinacea used was chemically consistent throughout the study, that "internationally recognized" doses were used, and that the testing approach used was the currently most powerful one.

He also said that NCCAM continues to support studies on echinacea and other biologically based complementary and alternative therapies, investigating them in the laboratory as well as in patients, "building on promising and compelling earlier evidence."

—Nancy Walsh

In AOM, Combo Curbs Resistant Pathogens

BY HEIDI SPLETE
Senior Writer

An amoxicillin/clavulanate combination was significantly more effective than azithromycin in eliminating bacterial acute otitis media, including penicillin-resistant strains, reported Alejandro Hoberman, M.D., of the Children's Hospital of Pittsburgh, and his colleagues.

In a randomized, investigator-blinded study sponsored in part by GlaxoSmithKline, 730 children aged 6-30 months were randomized to receive either a 90-mg amoxicillin and a 6.4-mg clavulanate/kg combination daily in 2 divided doses for 10 days, or a 10-mg/kg dose of azithromycin once daily for 1 day, followed by 5 mg/kg once daily for 4 days.

H. influenzae was the more common pathogen, found in 49% of patients treated with amoxicillin/clavulanate and in 51% of those treated with azithromycin.

The study was conducted at 34 centers worldwide, including ones in Bulgaria, Chile, the Dominican Republic, Guatemala, Israel, Peru, Romania, Latvia, Mexico, and the United States from April 2001 to November 2002.

The evolution of antimicrobial resistance among pathogens that cause acute otitis media (AOM) and the approval of a large-dose pediatric formulation of amoxicillin/clavulanate prompted the study.

At baseline, 494 (68%) of the children had at least one protocol-defined pathogen. Of those, 249 were in the amoxicillin/clavulanate group and 245 were in the azithromycin group.

Of these, 19 (8%) children in the amoxicillin/clavulanate group and 38 (16%) in the azithromycin group had more than one pathogen at baseline (Pediatr. Infect. Dis. J. 2005:24:525-32).

The children without discernible pathogens at baseline (118 in each group) were included in the safety analysis.

In addition, of the 229 total *Streptococcus pneumoniae* isolates (111 children in the amoxicillin/clavulanate group and 118 children in the azithromycin group), 49%, 11%, and 21% were not susceptible to penicillin, amoxicillin, and azithromycin, respectively.

Overall, clinical success rates among children with baseline AOM pathogens were significantly greater in the amoxicillin/clavulanate group (91%), compared with the azithromycin group (81%).

Clinical success was defined as the lessening or complete resolution of acute ear infection and inflammation, with or without middle-ear effusion, to the extent that no additional antibiotics were needed.

Clinical response at 12-14 days after the start of therapy served as the primary end point of the study.

Bacteriologic success was defined as the eradication of the initial AOM pathogen with or without a new pathogen, based on a lack of middle-ear fluid.

Bacteriologic success at an "on-therapy" visit 4-6 days after the start of treatment was associated with clinical success at the end of the therapy in 96 of 105 children (91%) in the group treated with the amoxicillin/clavulanate combo and in 80 of 89 (90%) children in the azithromycin group.

The distribution of pathogens was similar between the two groups.

H. influenzae was the more common. It was found in 49% of the group that was treated with amoxicillin/clavulanate and in 51% of the azithromycin group.

In the subset of 101 amoxicillin/clavulanate patients and 82 azithromycin patients who demonstrated bacteriologic responses after 4-6 days, amoxicillin/clavulanate was significantly more effective than azithromycin against penicillin-resistant *S. pneumoniae*, with eradication in 23 of 25 cases (92%) vs. 12 of 22 cases (55%), respectively.

Although significantly more children in the amoxicillin/clavulanate group withdrew from the study due to an adverse event, compared with the azithromycin group (21 vs. 7), the total number of adverse events was not significantly different between the two groups (139 vs. 128).

Fever was the most common adverse event reported, and it occurred in approximately 10% of the patients in each group.

Diarrhea occurred in 6% of patients taking amoxicillin/clavulanate and 4% of those taking azithromycin.

Overall, the compliance rates were high in both groups: 86% in the amoxicillin/clavulanate group and 91% in the azithromycin group. ■