The Effect of Echinacea on the Duration of Upper Respiratory Tract Infections

Melanie L. Jackson

A. Study Purpose and Background

Upper respiratory tract infections (URI) have the highest incidence of acute illness in the developing world. According to estimates, the average adult in the United States has 2 to 4 colds per year.[1] URI are the most frequent cause of time spent away from work and school.[2] More than 200 viruses are responsible for URI and treatment is directed towards the relief of symptoms. An important approach in treating URI is to strengthen the immune system to decrease the incidence, duration and severity of cold symptoms.

Now various preparations from plants of the genus Echinacea are among the most widely used herbal medicines throughout Europe and North America for the prevention and treatment of URI. Herbal medicine has grown faster than any other alternative treatment in the United States. The use of herbal medicines in the United States has increased by 385% between 1990 and 1997.[3] Echinacea is the fifth top selling herbal medicine in the United States grossing $70 million in 1998.[4] A gallop poll in 1997 showed that 32% of Americans use herbal medicines.[1] Due to this widespread use of herbal medicines, unknown adverse reactions and interactions with prescription medications. It is important that physicians acquire sufficient knowledge in this area to advise our patients responsibly.

Echinacea has been used for centuries and was first used by Native Americans. Native Americans used Echinacea species extensively for the treatment of colds and variety of other illnesses.[5] There are nine species found in the genus Echinacea, which are members of the Compositae/Asteracae family. The three primary species of E. angustifolia, E. pallida, and E. purpurea are used as herbal medications. The use of Echinacea into homeopathic medicine gained popularity in Europe in the 1920's.[6] Echinacea purpurea has been the species most often used for treatment of URI and studied in clinical trials.

Multiple treatment and prevention trials using various preparations of Echinacea have been done to determine its efficacy and safety. Barrett et al reviewed 13 treatment trials and 4 prevention trials (randomized and double blind). Eight of the nine treatment trials reported benefit. Two of the prevention trials reported marginal benefit. The third prevention trial reported benefit in a subgroup analysis, but later reported it as largely negative. The fourth prevention trial found no benefit. Currently, the German Commission E has approved the oral use of Echinacea purpurea herb for URI and urinary tract infections, and it's topical use for poorly healing wounds.[7]

Echinacea contains at least six chemical constituents with pharmacologic activity: polysaccharides, flavonoids, chicoric acid glycosides, essential oils, polyacetylenes, and alkylamides.[8] The polysaccharide, alkylamide, and chicoric acid glycoside components are believed to provide most of Echinacea's nonspecific immunostimulatory activity. These immunostimulating properties have been shown to stimulate phagocytosis in vitro and in vivo and enhance the production of oxygen radicals by macrophages.[6] An increase in serum levels of properdin, a member of the complement system, IL-1, IL-6, IL-10, TNF alpha and several other cytokines have been observed after administration of Echinacea.[1] Anti-inflammatory effects have also been reported.

Previous trials have used various preparations of Echinacea with and without other immunostimulating herbal medicines. The purpose of this study is to determine the effect dried extract of Echinacea purpurea herb has on the duration of symptoms of URI when taken within 24 hours of developing cold symptoms and continued for 14 days.

B. Study Design and Statistical Analysis

This study will be a randomized, double blind, placebo-controlled clinical trial to determine the efficacy of Echinacea to decrease the duration of symptoms in upper respiratory tract infections. Using the unpaired t-test, a total of 130 subjects (65 in each arm) will be needed to achieve a power of 80% at a $p<0.05$. The subjects will be randomized to the placebo group or treatment group (Echinacea) at the earliest sign of one of seven cold symptoms (headache, sneezing, rhinorrhea, nasal congestion, sore throat, cough, and malaise). The duration of treatment will last for 14 days, which have been previously studied by Turner et al.[9]

A blinded primary care physician will follow the subjects for 28 days with follow-up visits at day 7, 15 and 28. Subjects will be asked to fill out a questionnaire at visit 2 (day 15) that has been used in previous studies.[6] Subjects will be contacted by a blinded nurse practioner on day 4 and 10 as a reminder to take the medication. The primary outcome will be to determine the efficacy of Echinacea to decrease the total duration of symptoms for upper respiratory tract infections. The results will be analyzed using the unpaired t-test.

C. Study Procedure

All potential subjects will be initially assessed by a blinded primary care physician by history and physical exam within 24 hours of developing one of seven cold symptoms. During the initial visit, all potential subjects will be evaluated for influenza by a rapid influenza test and strep throat by a rapid strep test. Potential subjects will also be evaluated to determine if symptoms require more aggressive medical management. All eligible subjects will be instructed not take any over the counter medications during the study.

Recruited subjects will be given one bottle containing 42 pills and instructed to take one pill three times a day for 14 days. Subjects will receive a phone call by a blinded nurse practioner as a reminder to take the medication on day 4 and 10, and return for three follow up visits on day 7, 15, 28. Subjects should keep a log of symptoms and will be required to fill out a questionnaire on visit 2 (day 15). During each follow up visit, the blinded primary care physician will assess each subject for severity of illness to determine if more aggressive medical management is needed, compliance, and question the use of other medications. Subjects will be asked to bring bottles to visit 1 and 2. During visit 3 (day 28), subjects will be asked about any adverse reactions and questioned about if they thought they were receiving treatment.

D. Study Drug

Echinacea purpurea is herbal supplement that is not FDA-approved, but has been used over the last century for the prevention and treatment of upper respiratory tract infections. Various chemical constituents, including alkamides, caffeic acid derivatives (cicchoric acid), flavonoids, glycoprotiens, isobutylamides, polyenes, and polysaccharides, have been identified and implicated as active constituents.[1]

Multiple studies especially in Europe using different preparations of Echinacea purpurea showed a decrease in the duration and severity of symptoms for upper respiratory tract infections when taken at the onset of symptoms.[1-2,6] Turner et al determined that Echinacea was ineffective for the prevention of experimental rhinovirus colds.[9] Two recent studies showed that Echinacea purpurea given as a fluid extract did not significantly decrease the incidence, duration or severity of upper respiratory tract infections.[10-11]

Overall, multiple studies and the German Commission E monographs have documented the safety of Echinacea in humans and animals with rare side effects.[8] Adverse events include mild and transient central nervous system and gastrointestinal effects such as headache or nausea. There has been only one documented case of anaphylaxis in a patient with multiple food and drug allergies.[4] There have been no

reported deaths secondary to Echinacea use. One prospective study suggests that use of Echinacea during the first trimester of pregnancy is not associated with an increased risk for major malformations.[3]

Subjects in the treatment group will take a 400 mg capsule of dried extract Echinacea purpurea herb orally three times a day for 14 days based on the German Commission E monographs' recommendation. The exact amount of extract for a range of 350-450 mg will be determined by HPLC at an outside lab. The usage of Echinacea should not exceed 8 weeks and subjects will be cautioned on possible rebound of immune system after discontinuation.[4]

E. Medical device

None

F. Study Questionnaire

See attached

G. Study Subjects and Recruitment

Subjects will be recruited from the pediatric department in Babies and Children Hospital of New York Presbyterian Hospital from October to March. All potential subjects will be first informed of the study in September and given information sheets on Echinacea. Potential subjects will be informed to volunteer and report to our blinded primary care physician at the earliest sign of cold symptoms and be randomized to the placebo or treatment group.

Eligibility criteria: men; women on birth control; ages 18-40 that are free from any acute illness; subjective sensation of having a cold and at least one of the following symptoms: headache, sneezing, rhinorrhea, nasal congestion, sore throat, cough, malaise

Exclusion criteria: acute respiratory tract infection within the last week; chronic diseases such as asthma and cancer; serious progressive diseases such as tuberculosis, multiple sclerosis, HIV, AIDS, autoimmune diseases, collagen vascular diseases; systemic intake of steroids, antibiotics, immunosupressants, or immunostimulants in the previous 2 weeks; allergy to the Compositae family; pregnant or nursing women; organ transplantation

H. Confidentiality of Study Data

All study data will be coded and secured in a locked cabinet in the AIM clinic administration office.

I. Potential Conflict of Interest

None

J. Location of the Study

All subjects will evaluated in the AIM clinic, VC-2, at the time of enrollment and each follow up visit.

K. Potential Risks and Benefits

There are very few potential risks and side effects in using Echinacea, which are mild and transient CNS and gastrointestinal symptoms. The potential benefits of Echinacea are to decrease the duration of URI symptoms.

L. Alternative Therapies

None

M. Compensation to Subjects

All study subjects will be compensated $20 for participation, and reimbursed for travel costs to each follow up visit, if necessary. Checks will be given to subjects at the final visit on day 28.

N. Cost to Subjects

None

O. Minors as Research Subjects

None

P. Radiation or Radioactive Substances

None

Q. References

1. Barrett B, Vohmann M, Calabrese C. Echinacea for upper respiratory infection. J Fam Pract 1999; 48(8): 628-35.

2. Schulten B, Bulitta M, et al. Efficacy of Echinacea purpurea in Patients with a Common Cold: A placebo-controlled, randomized, double-blind clinical trial. Arzneimittel-Forschung 2001; 51(7): 563-8.

3. Gallo M, Sarkar M, Waisze A, et al. Pregnancy Outcome Following Gestational Exposure to Echinacea: A prospective controlled study. Arch Intern Med 2000; 160(20): 3141-3.

4. Ernst E. The Risk-Benefit Profile of Commonly Used Herbal Therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava. Ann of Intern Med 2002; 136(1): 42-53.

5. Borchers A, Keen C, Stern J, and Gershwin M. Inflammation and Native American medicine: the role of botanicals. Am J Clin Nutr 2000; 72: 339-347.

6. Lindenmuth, G. and Lindenmuth E. The Efficacy of Echinacea Compound Herbal Tea Preparation on the Severity and Duration of Upper Respiratory and Flu Symptoms: A Randomized, Double-Blind Placebo-Controlled Study. J Altern and Comp Med 2000; 6(4): 327-34.

7. Percival SS. Use of Echinacea in Medicine. Biochem Pharm 2000; 60(2): 155-8.

8. Gunning K. Echinacea in the treatment and prevention of upper respiratory tract infections. WJM 1999; 171(3): 198-200.

9. Turner R, Riker D, Gangemi D. Ineffectiveness of Echinacea for Prevention of Experimental Rhinovirus Colds. Antimicrobial Agents & Chemotherapy 2000; 44(6): 1708-9.

10. Grimm W. and Muller H. A Randomized Controlled Trial of the Effect of Fluid Extract of Echinacea Purpurea on the Incidence and Severity of Colds and Respiratory Infections. Am J Med 1999; 106(2): 259-60.

11. Melchart D, Walther E, Linde K, et al. Echinacea Root Extracts for the Prevention of Upper Respiratory Tract Infections: A Double-blind, Placebo-Controlled Randomized Trial. Arch Fam Med 1999; 7: 541-45.

Questionnaire

Please rate on the following scale the effectiveness of the medication at relieving your cold

1	2	3	4	5
(not effective)	(fair)	(medium)	(good)	(excellent)

Please circle the number of days your cold symptoms lasted:

Less than 4 5 6 7 8 More than 10

Please circle the number of days it took before you began to notice a difference in your symptoms:

Immediately 2 3 4 More than 5 Not at All