CLINICAL REPORT

Effects of echinacea on electrocardiographic and blood pressure measurements

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Purpose. The effects of *Echinacea purpurea* on electrocardiographic and blood pressure measurements in healthy volunteers were evaluated.

Methods. Healthy volunteers were randomized to receive a single 350-mg dose of *E. purpurea* or placebo in a crossover fashion with a seven-day washout period between treatment phases. Twelve-lead electrocardiograms were acquired, and systolic and diastolic blood pressure measurements were taken immediately before (baseline) and at one, three, five, and eight hours after ingestion of the study drug. Electrocardiographic variables (P wave and QRS complex duration and PR, Q-T, Q-Tc, and RR intervals) were measured in lead II by one blinded study investigator. Duplicate blood pressure determinations were taken manually at each time point and then averaged. The maximum posttreatment values, irrespective of time point, for each electrocardiographic and blood pressure measurement were compared between groups.

Results. Of the 17 healthy adults initially screened for this study, 16 completed both phases. There was no difference in maximum posttreatment electrocardiographic or blood pressure (systolic or diastolic) variables noted between groups. Mild headache was reported by one patient receiving echinacea and one receiving placebo. One participant receiving echinacea experienced shortness of breath five hours posttreatment and mild flu-like symptoms after eight hours; symptoms completely resolved over the next several days.

Conclusion. A single 350-mg dose of *E. purpurea* had no effect on electrocardiographic and blood pressure measurements of healthy volunteers.

Index terms: Blood pressure; *Echinacea purpurea;* Electrocardiography; Toxicity

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Americans suffer 1 billion colds annually, with adults averaging 2–4 colds and children 6–10 colds each year.[1] About 40% of lost work time and 30% of time off from school are attributed to symptoms from the common cold.[2] The common cold is associated with a large financial burden on society, with about $1.5 billion spent annually on physician's visits and another $2 billion spent on nonprescription treatments.[3]

The German Commission E, World Health Organization, and Canadian Natural Health Products Directorate have advocated the use of echinacea to treat the common cold.[4-8] This recommendation is supported by three recent meta-analyses suggesting that echinacea can both prevent and treat the common cold.[9-11] In the United States, echinacea-containing products are the most common nutraceuticals used by consumers and are taken by over 40% of individuals who use nutraceuticals.[12,13]

Echinacea angustifolia, *E. pallidae*, and *E. purpurea* are the most common species used for their purported medicinal value.[14] The mechanism of the proposed immunostimulatory effects of echinacea remains unclear. Some evidence suggests that up-regulation of tumor necrosis factor-α

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messenger RNA, which is stimulated by agonistic activity of the cannabinoid receptor 2 by alkamides present in echinacea, plays a role.[15]

Though adverse events with echinacea have not been commonly reported in clinical trials, gastrointestinal upset and rash have been noted most often.[14] In a recent compilation of adverse-event reports involving echinacea submitted to the spontaneous reporting programs of the Food and Drug Administration, World Health Organization, and regulatory bodies in Australia, England, and Germany, a total of 907 adverse events were reported, with 23 classified as affecting heart rate and rhythm and 18 affecting the vascular system.[14]

To our knowledge, no studies have evaluated the cardiac safety of echinacea-containing products. With dietary supplements such as those containing ephedra being removed from the U.S. market due, in part, to ephedra's effect on the corrected Q-T (Q-Tc) interval and blood pressure, evaluations of commonly used natural supplements are important. The objective of this study was to evaluate the electrocardiographic and blood pressure effects of *E. purpurea* in healthy volunteers.

Methods

Study design. This was a randomized, double-blind, placebo-controlled trial approved by the University of Connecticut institutional review board. Written informed consent was required, and all study procedures were conducted in accordance with ethical standards for research in human subjects. Healthy adults at least 18 years of age and in general good health who expressed interest in participating in the study were evaluated. Individuals who had any of the following were excluded from study participation: cardiac rhythm other than normal sinus rhythm, history of atrial or ventricular arrhythmia, family history of premature sudden cardiac death, left ventricular hypertrophy, atherosclerosis, hypertension, palpitations, T-wave abnormalities, baseline Q-Tc interval over 440 milliseconds, thyroid disease, type 1 or 2 diabetes mellitus, recurrent headaches, depression, any psychiatric or neurologic disorder, history of alcohol or drug abuse, renal or hepatic dysfunction, concurrent use of drugs that may interact with echinacea or affect electrocardiographic or blood pressure measurements (i.e., anticoagulants, monoamine oxidase inhibitors, cytochrome P-450 [CYP] 3A4 substrates or inhibitors, nonprescription medications containing pseudoephedrine, or any dietary supplements), and unwillingness to sign the informed-consent form. Pregnant or lactating women were excluded from study participation, with urine dipstick tests used to confirm the absence of pregnancy.

Volunteers included in the study were randomized to receive a 350-mg capsule of *E. purpurea* (Nature's Resource, Mission Hills, CA) or an identical placebo as their first treatment using a random permuted block method, with a block size of four subjects per group. The echinacea and placebo were packaged in identical opaque capsules using lactose (Fisher Scientific, Leicestershire, United Kingdom). Volunteers were instructed to refrain from consuming caffeinated products 12 hours before and during study phases. During the first phase of the study, participants received one capsule of either *E. purpurea* or placebo. After a seven-day washout period, study participants returned for the second phase of the trial and received the treatment not received during the first phase. During each phase, electrocardiographic variables (P wave and QRS complex duration and P-R, Q-T, Q-Tc, and RR intervals) and systolic and diastolic blood pressures were evaluated at baseline (pretreatment) and one, three, five, and eight hours posttreatment.

To minimize circadian variations of the Q-Tc interval and blood pressure measurements, participants received the study drug and were evaluated at approximately the same time of day and rested 15 minutes before electrocardiographic or blood pressure measurements were taken.

Electrocardiographic measurements. Electrocardiographic deflections and patterns were measured using a 12-lead electrocardiograph (Welch-Allyn, Skaneateles Falls, NY) obtained while participants were in the recumbent position, breathing freely, and recorded with 1-mV/cm standardization at a paper speed of 25 mm/sec. Electrocardiographic variables were manually derived by a single, blinded study investigator using a precision ruler of 0.5-mm scale (Schadler-Quinzel, Parsippany, NJ).

The primary endpoint was the maximum posttreatment Q-Tc interval occurring over eight hours in both groups. The Q-Tc interval was calculated using the Framingham linear correction formula (Q-Tc = Q-T + 0.154 [1–RR]) since Bazett's formula may overcorrect at heart rates below 60 beats/min. In each study phase, the Q-Tc interval was determined at each time period by taking the average of three readings from lead II of the same electrocardiogram. The maximum Q-Tc interval for each patient in each study phase was determined by selecting the electrocardiogram with the greatest average Q-Tc interval among posttreatment hours 1, 3, 5, and 8. The maximum P-R, QRS, Q-T, and RR intervals were measured similarly.

Blood pressure measurements. A standard mercury sphygmomanometer was used in accordance with published recommendations for obtaining manual blood pressures.[16] Systolic blood pressure was measured as the point of appearance (phase 1) of Korotkoff sounds and diastolic blood pressure at the point of disappearance (phase 5).

The primary endpoint was the maximum systolic blood pressure over the eight-hour study period in the two groups; diastolic blood pressures were compared similarly. At each time period, blood pressure was measured in duplicate more than two minutes apart and then averaged.[17] The maximum systolic and diastolic blood pressures were determined by selecting the highest average among the four posttreatment time points in each study phase.

Adverse effects. Adverse events were evaluated at all posttreatment time points and daily thereafter by asking participants if they had experienced any unpleasant feelings or symptoms since taking the experiment medication. Any symptoms reported were monitored for degree (mild, moderate, or severe), progression (same, worse, or improved), and resolution.

Statistical analysis. For an alpha of 0.05 and a power of 0.8, the sample size needed to detect an intergroup Q-Tc interval difference of 6 ± 3 milliseconds or systolic blood pressure difference of 4 ± 4 mm Hg was 4 and 10, respectively. We selected a between-group Q-Tc interval difference of 6 milliseconds and systolic blood pressure difference of 4 mm Hg based on previous published studies suggesting maximum normal variability.[18,19] The standard deviation for both variables was based on our previous work in this area.[20]

Intergroup comparisons for continuous variables were performed using a paired *t* test, with a *p* value of less than 0.05 considered significant.

Results

Of the 17 healthy adults initially screened for this study, 16 completed both phases. One was excluded because he or she was not available to participate in the second phase of the study. There were equal numbers of men and women, and the average age of study participants was 24 years. There were 12 Caucasians, 2 Asians, and 2 African Americans. Four participants were taking daily multivitamins, and 3 were taking oral contraceptives.

No differences were noted between the placebo and echinacea groups for any maximum posttreatment electrocardiographic variables evaluated (Table 1). Similarly, no differences were noted between groups for maximum posttreatment systolic or diastolic blood pressure measurements.

A mild headache was reported by one participant who received echinacea and one who received placebo during the eight-hour study period, both of which resolved within a couple hours. One participant receiving echinacea experienced shortness of breath five hours posttreatment and mild flu-like symptoms at eight hours. The following day, the participant still had flu-like symptoms, but the symptoms completely resolved over the next several days.

Discussion

Recent meta-analyses have shown the benefit of echinacea for both the prevention and treatment of the common cold. Schoop et al.[10] conducted a meta-analysis of three randomized, double-blind, placebo-controlled, inoculation trials (i.e., cold induced by investigator) in which subjects receiving placebo had a 55% greater risk of developing a cold compared with those taking echinacea. In another meta-analysis of 14 randomized, double-blind, placebo-controlled studies, echinacea reduced the odds of developing a cold by 58% and decreased the duration of a cold by 1.9 days.[11] As such, it is possible that echinacea-containing products do provide some measure of protection against the common cold, but they cannot be recommended to patients until the safety of the products is known.

There are no clinical trials that fully evaluate the safety profile of echinacea. Gastrointestinal upset and rash are the more frequently noted adverse events with echinacea use. In rare instances, severe allergic reactions and asthma exacerbations have also been noted.[21] Other adverse events reported in patients taking echinacea have included heart rate, heart rhythm, and vascular-related disturbances; however, because of the lack of pertinent information in these reports (e.g., dosage, comorbidities), causality was difficult to ascertain.[14] In our study, echinacea use did not appear to have any discernible effects

Table 1.
Maximum Electrocardiographic and Blood Pressure Measurements after Treatment with *Echinacea purpurea*

Variable	Mean ± S.D. Value			*p*[a]
	Baseline	Placebo	Echinacea	
Q-T interval, sec	0.371 ± 0.03	0.385 ± 0.03	0.385 ± 0.02	0.882
Q-Tc interval, sec	0.395 ± 0.02	0.410 ± 0.02	0.405 ± 0.02	0.118
P-wave duration, sec	0.094 ± 0.02	0.101 ± 0.02	0.101 ± 0.02	0.793
RR interval, sec	0.843 ± 0.15	0.933 ± 0.01	0.962 ± 0.13	0.176
P-R interval, sec	0.151 ± 0.02	0.159 ± 0.02	0.161 ± 0.02	0.549
QRS interval, sec	0.085 ± 0.01	0.089 ± 0.01	0.089 ± 0.01	1.000
Systolic blood pressure, mm Hg	112 ± 9	116 ± 8	118 ± 8	0.150
Diastolic blood pressure, mm Hg	75 ± 7	79 ± 8	77 ± 6	0.081

[a]Comparison between values for patients receiving *E. purpurea* vs. placebo.

on electrocardiographic or blood pressure measurements.

This study had several limitations. While the manufacturer of the product used in this study recommends *E. purpurea* 350 mg four times a day and the Canadian Natural Health Products Directorate recommends a dosage of 1 g three times a day, we evaluated the effect of a single 350-mg daily dose on electrocardiographic and blood pressure variables. Thus, we cannot be certain that higher dosages or chronic therapy is not associated with different effects. However, institutional review boards would be unlikely to approve more intensive studies without data from this initial safety study. As it was, study participants had to be directly observed for safety reasons at all times during each study phase. If an active metabolite of the echinacea product used needed to accumulate for electrocardiographic or hemodynamic alterations to be observed, we would have missed the alterations in our single-dose study. With multiple doses, the echinacea or metabolite concentrations achieved would rise until steady state was achieved. We did not achieve steady state with our single-dose methodology. While *E. purpurea* may be safe in healthy volunteers, it might not be safe in hypertensive or obese patients, in whom baroreceptor buffering capacity is diminished and blood pressure changes can be accentuated. Studies in a population with cardiac disease should be conducted before recommending the use of echinacea in that patient population. Since women tend to have a higher baseline Q-Tc interval than do men, the effect of gender should also be evaluated in future studies.[22]

We did not perform an independent quality assessment of the contents of the *E. purpurea* capsules. However, we used a USP-verified echinacea product that met the integrity, purity, and potency standards set by USP.[23] Some echinacea-containing products contain other ingredients, and our study results should not be extrapolated to such products. We studied *E. purpurea* and not other species of echinacea, so our study results cannot be extrapolated to these other formulations. Echinacea is a CYP 3A4 enzyme inhibitor, so the potential for drug interactions must be assessed.[24]

Further studies need to be conducted in larger patient populations with higher doses over longer treatment periods to confirm the cardiac safety of echinacea.

Conclusion

A single 350-mg dose of *E. purpurea* had no effect on electrocardiographic and blood pressure measurements of healthy volunteers.

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