Phytomedicine
International Journal of Phytotherapy and Phytopharmacology

Reprint

Echinaforce® and other *Echinacea* fresh plant preparations in the treatment of the common cold

A randomized, placebo controlled, double-blind clinical trial

R. M. Brinkeborn, D. V. Shah and F. H. Degenring

URBAN & FISCHER

Phytomedicine · Volume 6(1) · pp. 1-6 · 1999 · ISSN 0944-7113

Phytomedicine, Vol. 6(1), pp. 1–6

http://www.urbanfischer.de/journals/phytomed

Phytomedicine

Echinaforce® and other *Echinacea* fresh plant preparations in the treatment of the common cold

A randomized, placebo controlled, double-blind clinical trial

R. M. Brinkeborn[1], D. V. Shah[2] and F. H. Degenring[2]

[1]Elisabeth Hospital, Wallingatan, Uppsala, Sweden
[2]Medical Department, Bioforce AG, Roggwil, Switzerland

Summary

The aim of this randomized, double-blind, placebo controlled study was to investigate the efficacy and safety of different doses and preparations of *Echinacea purpurea* in the treatment of common cold. 246 of 559 recruited healthy, adult volunteers caught a common cold and took 3 times daily 2 tablets of either Echinaforce® (*Echinacea purpurea*-preparation from 95% herba and 5% radix), *Echinacea purpurea* concentrate (same preparation at 7 times higher concentration), special *Echinacea purpurea* radix preparation (totally different from that of Echinaforce®) or placebo until they felt healthy again but not longer than 7 days. The primary endpoint was the relative reduction of the complaint index defined by 12 symptoms during common cold according to the doctor's record. Echinaforce® and its concentrated preparation were significantly more effective than the special *Echinacea* extract or placebo. All treatments were well tolerated. Among the *Echinacea* groups the frequency of adverse events was not significantly higher than in the placebo group. Therefore, Echinacea concentrate as well as Echinaforce® represent a low-risk and effective alternative to the standard symptomatic medicines in the acute treatment of common cold.

Key words: *Echinacea purpurea,* common cold, immuno-stimulation, randomized, double-blind, placebo controlled clinical trial.

Introduction

Common cold is the most frequent acute form of illness throughout the industrialized world. Although this illness is temporary, it causes high costs for medical care and accounts for 40% of all time lost from jobs among employed people. Thus, it plays an important socioeconomic role (Kirkpatrick, 1996).

Among the large variety of viruses which can cause common cold, the Rhinoviruses are the most frequent (Spector, 1995) and include more than 100 serotypes (Kirkpatrick, 1996). This great variety makes it very difficult to produce vaccines or medicaments active against any kind of viruses responsible for common cold.

Standard treatment of the common cold consists of symptomatic therapy including antihistamines, decongestants, expectorants, antitussives, antipyretics and analgesics. Many of the most popular remedies, however, are thought to be either ineffective or counterproductive (Spector, 1995). For instance, both aspirin and acetaminophen may have a detrimental effect on cold treatment, neutralizing antibodies and increasing nasal symptoms (Graham, 1995). Some antihistamines do not seem to be very effective, whereas others may provide mild benefit (Berkowitz and Tinkleman, 1995).

Because people with weak immune response are more prone to common cold (Wagner, 1996) treatment with an immunostimulant represents an alternative to the symptomatic treatment.

Echinacea is the most popular phytotherapeutical

0944-7113/99/06/01-001 $ 12.00/0

immunostimulant. Several pharmacological (Bauer et al. 1988; 1989) and 26 controlled clinical trials indicate that preparations containing extracts of *Echinacea* can be effective. However, evidence is still insufficient to support unequivocal therapeutic recommendations as to which preparation to use and which dose to employ for a specific indication (Melchart et al. 1994). Since our study design contained not only two different preparations of *Echinacea*, but also two different doses, the results could pave the way for an answer to these questions about the treatment of the common cold.

Methods

Healthy volunteers were recruited by means of newspaper advertisements. This study was performed between November 1996 and May 1997 according to the EU regulations of GCP for trials on medicinal products and took place at a center for infectious diseases in Uppsala, Sweden.

The volunteers were included if they signed the consent sheet and met the following criteria: age older then 18 years and prone to common cold, otherwise healthy. Patients were excluded if they met one of the following criteria: a) participation in another clinical trial during the last 4 weeks, b) suffering from chronic diseases which influence the test variables (diabetes mellitus, bronchial asthma, allergy or autoimmune deficiency), c) suffering from serious non-related illnesses, especially progressive systemic diseases (tuberculosis, leukemia, collagenous diseases and multiple sclerosis) and/or d) taking other medicines which may affect the immune system like immunostimulants and antibiotics or may influence the symptoms like nose-drops or anticoughs.

Eligible patients were double blindly assigned at random to Echinaforce® (6.78 mg *Echinacea purpurea* crude extract based on 95% herb and 5% root), *Echinacea* concentrate preparation (48.27 mg of the same crude extract), special *Echinacea purpurea* extract preparation (29,60 mg crude extract based on root only) or placebo. The treatments were allocated by a computer-generated randomization list in blocks of four, and the randomization was concealed by consecutively numbered drug bottles.

The trial doses of the four treatments were presented in identical vials with identical labels and could almost not be distinguished from one other by their smell or taste. The recorded treatment randomly allotted to each patient number was put into an envelope not to be opened except in case of emergency.

At their first visit patients were instructed to take 3 times daily 2 tablets of the trial medicine immediately after the onset of the first symptoms of common cold and were advised to see the investigator at the same time or at the second day at the latest. They received a diary in order to record the progress of the illness day-by-day and and were instructed to take the medicine until they felt healthy or otherwise not longer than 7 days. The same day they were instructed to visit the investigator for the final examination.

The following 12 symptoms were assessed using a 4-point score (absent = 0, mild = 1, moderate = 2, severe = 3) by the investigator at visit 2 and 3 and daily by the patient: severity of illness (general impression), runny nose and sneezing, tearing/burning eyes, sore throat, headache and dizziness, weakness and drowsiness, muscle pains and pains in the limbs, fever, coughing, blocked nose, earache or any other complaint most probably related to the cold. The chosen primary endpoint was the relative reduction of the complaint index (= sum score) based on all 12 symptoms according to the doctor's record. Secondary endpoints were: a) the relative reduction of the complaint index according to the patient's diary; b) the assessments of efficacy and tolerance by the investigator and the patients; and c) the frequency and severity of adverse events (AE).

Statistical analysis

Based on the results of a study of resistance against common cold with use of an *Echinacea purpurea* root preparation (Bräunig et al. 1992) a difference in the complaint index between verum and placebo was assumed at 3.8 ± 5.5. α was taken as equal to 0.05 and β as equal to 0.1. The rate of dropouts and protocol violations were estimated to be 41%.

The null hypothesis presumed that the average reduction of the complaint index in all verum groups was not greater than in the placebo group. The alternative hypothesis was assumed when the average reduction of the complaint index in at least one of the verum groups should be significantly greater than in the placebo group. A treatment was valued as successful when the reduction of the complaint index in at least one of the treatment groups with *Echinacea* was significantly higher than in the placebo group.

Since the success criterion should include all verum groups we decided to perform Kruskal-Wallis one way ANOVA on ranks-test including Dunn's multiple comparison-test versus the control group for the confirmatory analysis. For the exploratory analysis different treatment groups were to be compared with the placebo group using the one tailed U-test.

Per protocol analysis (PP) was performed to evaluate efficacy in a confirmatory manner by the chosen primary endpoint. Data are presented together with the results of the intent-to-treat analysis (ITT) in Table 2–5.

Table 1: Demographic data, comedication, concomitant diagnosis, CRP blood level, tablet intake (n = 246).

Treatment	n	women	age mean ± SD	not illicit comed.	illicit comed.	concomitant diagnosis	CRP <10 mg/l	tablet intake mean ± SD
Echinaforce	55	42	41 ± 12	9	13	1	42	5.1 ± 1.4
Echinacea conc.	64	49	42 ± 16	8	15	1	54	5.1 ± 1.2
Echinacea special	63	48	40 ± 14	7	19	5	55	4.9 ± 1.6
Placebo	64	42	42 ± 14	11	18	1	48	5.0 ± 1.2
total	246	181		35	66	8	199	

Table 2. Complaint index (CI) of all 12 symptoms according to the doctor's record.

	Treatment	n	visit 2 mean ± 95%-CI	visit 3 mean ± 95%-CI	rel. reduction mean ± 95%-CI	one tailed U-test versus placebo
PP	Echinaforce	41	8.8 ± 1.1	3.5 ± 1.2	62.7% ± 11%	p = 0.020
	Echinacea conc.	49	8.0 ± 1.1	2.6 ± 0.9	64.3% ± 12%	p = 0.003
	Echinacea special	44	7.7 ± 1.1	3.6 ± 1.1	44.8% ± 20%	p = 0.060
	Placebo	46	8.3 ± 1.0	5.6 ± 1.4	29.3% ± 18%	
ITT	Echinaforce	55	9.0 ± 1.1	4.1 ± 1.2	58.7% ± 10%	p = 0.045
	Echinacea conc.	64	8.7 ± 1.0	3.4 ± 0.9	58.1% ± 11%	p = 0.027
	Echinacea special	63	8.4 ± 1.0	4.0 ± 1.1	46.1% ± 16%	p = 0.133
	Placebo	64	8.8 ± 0.9	5.3 ± 1.3	33.6% ± 17%	

Table 3. Complaint index (CI) of all 12 symptoms according to the patient's record.

	Treatment	n	mean day 1–2 mean ± 95%-CI	visit 3 mean ± 95%-CI	rel. reduction mean ± 95%-CI	one tailed U-test versus placebo
PP	Echinaforce	41	10.6 ± 1.4	5.2 ± 1.2	50.6% ± 11%	p = 0.032
	Echinacea conc.	49	9.8 ± 1.3	4.3 ± 1.0	55.9% ± 9%	p = 0.010*
	Echinacea special	44	9.5 ± 1.5	5.5 ± 1.3	35.2% ± 17%	p = 0.271
	Placebo	46	10.0 ± 1.0	6.1 ± 1.2	37.0% ± 13%	
ITT	Echinaforce	55	10.9 ± 1.3	6.1 ± 1.2	43.6% ± 11%	p = 0.085
	Echinacea conc.	64	10.5 ± 1.2	5.1 ± 1.0	52.0% ± 8%	p = 0.012
	Echinacea special	63	10.0 ± 1.3	5.9 ± 1.1	35.8% ± 13%	p = 0.225
	Placebo	64	10.8 ± 1.2	6.6 ± 1.1	33.2% ± 13%	

* one tailed Dunn's multiple comparison test.

Table 4. Efficacy, doctor's judgement.

Treatment		n	effective	ineffective or not discernible	CHi^2-test
PP	Echinaforce	41	28	13	p = 0.035
	Echinacea conc.	49	38	11	p = 0.001
	Echinacea special	44	22	22	p = 0.683
	Placebo	46	20	26	
ITT	Echinaforce	55	34	21	p = 0.034
	Echinacea conc.	64	44	20	p = 0.003
	Echinacea special	63	30	33	p = 0.539
	Placebo	64	26	38	

Table 5. Efficacy, patient's judgement.

Treatment		n	effective	ineffective or not discernible	CHi^2-test
PP	Echinaforce	41	32	9	p = 0.022
	Echinacea conc.	49	41	8	p = 0.002
	Echinacea special	44	31	13	p = 0.118
	Placebo	46	24	22	
ITT	Echinaforce	55	39	16	p = 0.022
	Echinacea conc.	64	48	16	p = 0.004
	Echinacea special	63	42	21	p = 0.058
	Placebo	64	31	33	

Table 6. Body systems affected by adverse events, severity and causality (n = 246).

Body system	Severity and causality									Total
	mild			moderate			total			
	d/l	p/t	n/n	d/l	p/t	n/n	d/l	p/t	n/n	
gastrointestinal tract	1	16	8		2		1	18	8	27
whole body			2						2	2
nervous system		2						2		2
skin			1						1	1
urinary system		1						1		1
total	1	19	11		2		1	21	11	33

Table 7. Adverse events, treatment and causality (n = 246); d/l = definitive or likely; p/t = possible or tentatively possible, n/n = not related or not known.

Treatment	d/l	p/t	n/n	total	z-test versus placebo
Echinaforce	1	4	2	7	p = 0.772
Echinacea conc.	0	6	2	8	p = 0.777
Echinacea special	0	7	5	12	p = 0.191
Placebo	0	4	2	6	
total	1	21	11	33	

Results

At the first visit 559 patients were recruited for the study and received their medication for the immediate treatment of the common cold (Figure 1). The intention-to-treat analysis tock account of 246 patients (181 women and 65 men) who fell ill, used the medication and returned for the second visit. The four treatment groups were comparable in sex, age, comedication, concomitant diagnosis, CRP-blood level and tablet intake (Table 1). 65 of 246 cases (27%) were excluded from the PP because of drop-outs; protocol violations with illicit comedication and late start or comedications affecting symptoms of the common cold (Figure 1). With regard to these factors the four treatment groups did not differ significantly from each other in the number of excluded patients.

Primary endpoint

With respect to the relative reduction of the complaint index according to the doctor's record the four treatment groups differed significantly (p = 0.015). In the *Echinacea* concentrate group and the Echinaforce group the relative reductions of the complaint index were significantly higher than in the placebo group (p = 0.003 and p = 0.020, Figure 2 and Table 2).

Secondary endpoints

The four treatment groups also differed with respect to the relative reduction of the complaint index according to the patient's diary (p = 0.036). The Echinacea conc. group was significantly better than the placebo group

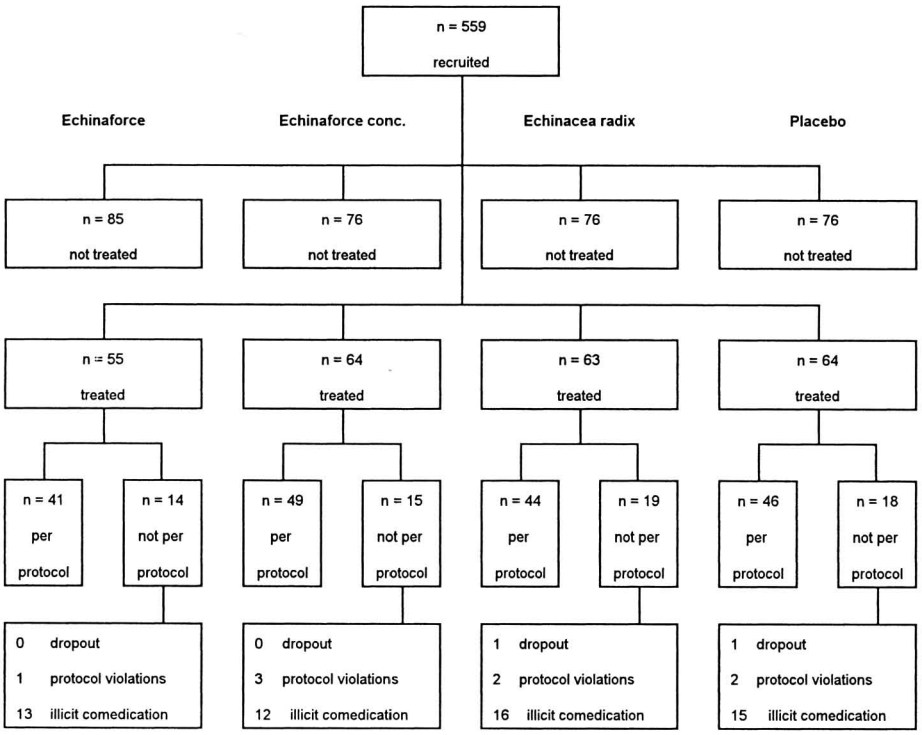

Fig. 1. Disposition of the patients recruited for the treatment of common cold.

(p = 0.010, one tailed Dunn's multiple comparison-test). The Echinaforce group was also better than the placebo group (p = 0.032, one tailed U-test, Table 3). According to the doctor's as well as the patient's judgement *Echinacea* concentrate as well as Echinaforce were frequently more effective than placebo (p = 0.001 and p = 0.002 for *Echinacea* concentrate; p = 0.035 and p = 0.022 for Echinaforce, Chi^2-test, Table 4, 5). The PP-results were slightly better than those of the ITT, but they show the same tendency (Tables 2 to 5). According to the doctor's and the patient's judgements the trial medicine was well tolerated by more than 95% of the persons studied (Table 6).

In 33 of 246 cases (13%) adverse events (AE) were observed (Table 7). The majority of AE involved the gastrointestinal tract. In addition, some AE affected the body as a whole, the nervous system, the skin and the urinary system. In only one case was causality of the study medication likely (transient nausea of mild severity). Causality of the trial medicine was probable or tentatively probable in 21 cases and unrelated or unknown in 11 cases. Insignificantly more AE occurred in the group treated with special *Echinacea* extract than in the other groups (Table 8). However, this difference was mainly due to AE with unrelated or unknown causality of the trial medicine. Furthermore, this group did not differ statistically significant from the placebo group to the number of AE (p = 0.191, Z-test).

Discussion

With respect to the relative reduction of the complaint index according to the doctor's record *Echinacea* concentrate and Echinaforce proved significantly more effective in the treatment of the common cold than the placebo. These results were confirmed by recordings in the patient's diary. Forthermore, *Echinacea* concentrate and Echinaforce were effective in many more cases than placebo according to the doctor's and the patient's judgement. The results revealed that *Echinacea* concentrate was slightly superior to Echinaforce, but the special *Echinacea extract* preparation was not significant-

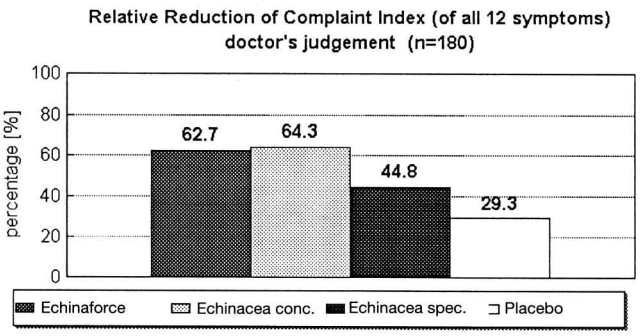

Fig. 2. Percent reduction of the Complaint Index from day 1/2 to day 5/7 of the common cold according to the doctor's record.

ly more effective than placebo. From these results it can be concluded that Echinaforce is more effective in the treatment of common cold than the concentrated root preparation alone. Furthermore, a seven-fold higher dosage of Echinaforce was only slightly more effective than the standard dosage.

All three *Echinacea* preparations studied were well tolerated. The frequency of AE was small and the *Echinacea* preparations did not differ considerably from the placebo group in this respect. Causality of the trial medicine was rated as possible in most of the cases and as likely in only one patient for the occurence of mild transient nausea.

A reduction of the complaint index by more than 60% according to the doctor's judgement and more than 50% according to the patient's diary as well as an assessed effectivity of approximately 70% by the doctor and of around 80% by the patients, respectively, indicate that the therapeutic success of *Echinacea* concentrate and Echinaforce can be assumed as clinically relevant. This is in contrast to many of the most popular standard medicines which are considered to be ineffective or even counterproductive in treatment of the common cold (Spector 1995).

To determine whether the duration of illness can be reduced by Echinafore, a further clinical study is necessary. In this trial the treatment for each patient is thought to be continued until his or her complaint index has fallen below 2 points.

In summary, we can conclude that *Echinacea* concentrate as well as Echinaforce represent low-risk and effective alternatives to standard medicines for symptomatic treatment of the common cold.

References

Bauer, R., Jurcic, K., Puhlmann, J., Wagner, H.: Immunologische In-vivo- und In-vitro-Untersuchungen mit Echinacea-Extrakten. Arzneim.-Forsch. *Drug Res. 38:* 276–281, 1988.

Bauer, R., Remiger, P., Jurcic, K., Wagner, H.: Beeinflussung der Phagozytose-Aktivität durch Echinacea-Extrakte. *Z. für Phytotherapie, 10:* 43–48, 1989.

Berkowitz, R. B., Tinkleman, D. G.: Evaluation of oral terfenadine for treatment of the common cold. *Ann. Allergy 67:* 593–597, 1991.

Bräunig, B., Dorn, M., Knick, E.: Echinaceae pupureae radix: zur Stärkung der körpereigenen Abwehr bei grippalen Infekten. *Z. für Phytotherapie 13:* 7–13, 1992.

Graham, N. M., Burrell, C. J., Douglas, R. M., et al.: Adverse effects of aspirin, acetaminophen and ibuprofen on immune function, viral shedding, and clinical status in rhinovirusinfected volunteers. *J. Infect. Dis. 162:* 1277–1282, 1990.

Kirkpatrick, G. L.: The common cold. *Primary Care 23 (4):* 657–675, 1996.

Spector, S. L.: The common cold: current therapy and natural history. *J. Clin. Immunol. 95:* 1133–1138, 1995.

Wagner, H.: Pflanzliche Immunstimulänzin. Zur Prophylaxe und Therapie von Erkältungskrankheiten. *Z. für Phytotherapie 17:* 79–99, 1996.

Address

F. H. Degenring, Medical Department, Bioforce AG, CH-9325 Roggwil, Switzerland

84698.00/0799