

A randomized, double-blind, placebo-controlled, clinical dose–response trial of an extract of *Baptisia*, *Echinacea* and *Thuja* for the treatment of patients with common cold

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Abstract

The aim of this study was to verify the efficacy and safety of an herbal medication containing an extract of a mixture of *Baptisiae tinctoriae* radix, *Echinaceae pallidae/purpureae* radix and *Thujae occidentalis* herba (SB-TOX) in the treatment of upper respiratory tract infections (URIs), and to test whether SB-TOX's clinical efficacy is dose dependent. A total of 91 adults (mean age 42.1 ± 13.0 years) were randomised to receive 19.2 mg of SB-TOX ($n = 31$), 9.6 mg SB-TOX ($n = 29$) or placebo ($n = 31$) three times daily for 3–12 days. Since a “running nose” is the main symptom of a common cold, the total number of facial tissues used throughout the clinical duration of their cold was the primary efficacy parameter. In the intention-to-treat analysis, this total number of tissues decreased with increasing extract dose. The slope across groups according to the Jonckheere test was significant ($p = 0.0259$). In the high-dose group, the standardised effect size Δ/SD was 0.46 compared with placebo. Time to relevant improvement in cold symptoms (measured as the time until less than 30 tissues per day were used) was 1.1 days (95% CI 0.52; 1.67), 0.76 days (95% CI 0.28; 1.24) and 0.52 days (95% CI 0.22; 0.82) in the placebo, low-dose and high-dose groups, respectively ($p_{\text{LogRank}} = 0.0175$). No adverse events were reported. This study demonstrates the efficacy and safety of SB-TOX in the treatment of URIs, and that its efficacy is dose dependent.

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Introduction

Upper respiratory tract infections (URIs), conventionally called the common cold, pose a significant health burden on western populations in terms of human suffering and economic losses. Every year, about 25 million people in the USA visit their doctors because

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of this illness which results in about 20 million days of lost work and 22 million days of school absences (Adams et al., 1999). Usually, antibiotic therapy is not helpful since most infections are virally induced. New antiviral agents for the treatment of the common cold have been developed, but their optimum use requires rapid detection of the specific causative virus. According to a recent Cochrane review (Arroll and Kenealy, 2004), the evidence on the benefits of antibiotics in the treatment of URIs does not warrant their use. Moreover, antibiotics treatment is associated with a significant increase in adverse events. Consequently, a universally effective treatment for the condition has not become available to date (Heikkinen and Jarvinen, 2003). Therefore, treatment of the common cold remains within the domain of over-the-counter drugs, mainly involving phytotherapeutics.

Echinacea is one of the most extensively used plants for the prevention and treatment of URIs. Melchart et al. (2004) concluded from their systematic review that the majority of available studies report positive results. However, there has not been enough evidence thus far to recommend a specific Echinacea product or preparation for treatment. Consistent with this statement, Barrett (2003) observed that a great deal of moderately good quality scientific data is available on Echinacea, yet many gaps still exist in the knowledge base. In a recent study, Taylor et al. (2003) found no evidence on *Echinacea purpurea* treatment in children suffering from URIs. However, the authors concluded from their study that their findings are not transferable to Echinacea use in adults or to other brands of Echinacea. Another randomised double-blind placebo-controlled study on adults with colds arrived at similar results (Barrett et al., 2002).

Notwithstanding, wild indigo and arbor vitae among other immunostimulating plants have also been found to stimulate the immune system (Bodinet et al., 2002a, b). For example, both *in vitro* and *in vivo* investigations have shown that these plants enhance macrophage activity (Bodinet et al., 2002a, b), activate CD4-positive cells (Gohla et al., 1986), stimulate the proliferation of the spleen cells (Bodinet et al., 2002a, b), induce the production of cytokines like IL-1, IL-2, IFN alpha and gamma, increase the NO production of alveolar macrophages and the differentiation of B lymphocytes and raise antibody production (Bodinet and Freudenstein, 1999). Moreover, these plants have been found to inhibit directly viral replication and growth (Gohla et al., 1990).

One of the world's mostly widely used herbal preparations for the treatment of URIs is Esberitox[®] (SB-TOX), an immunomodulator that enhances the body's own immunoresistance. This herbal mixture contains an extract of two species of *Echinacea* roots (*pallida/purpurea*) and the two immunostimulating plants (wild indigo roots and arbor vitae tips). It is

licensed for sale in many countries as an over-the-counter product.

Recently, Teuscher et al. (2004) analysed the most relevant pharmacological studies demonstrating the immunostimulating properties of the single active plants in this preparation as well as of the drug mixture extract itself. In addition, the clinical efficacy of this medication in the treatment of URIs has been demonstrated in three randomized, placebo-controlled studies (Vorberg, 1984; Reitz and Hergarten, 1990). Henneicke-von Zepelin et al. (1999) confirmed the efficacy of this herbal mixture in the treatment of patients with common colds in a double-blind placebo-controlled study conducted according to good clinical practice (GCP) standards. Köhler et al. (1998) conducted a survey in children who presented in the practices of 1000 general practitioners in Germany. They confirmed the dose recommendations for children and stratified them according to children's age groups. In a yet unpublished user survey, an unexpectedly high proportion of physicians and pharmacists reported greater efficacy when the higher dosage of the herbal remedy was given in the early treatment of URIs. However, a clinical dose–response study in adults has not been done to date. The objective of the current study was to confirm the efficacy and safety of SB-TOX in the treatment of URIs in adults and to find out whether there is a dose–response relationship. For this purpose, two different dosages of this herbal remedy were compared to placebo.

Methods

Study design

The monocentre study was conducted as a prospective randomised double-blind placebo-controlled clinical dose–response trial with parallel groups in patients suffering from URIs, i.e. the common cold. At visit 1 (day 1), patients who had given written informed consent to study enrolment were screened for eligibility. Demographic details, medical history, concomitant medication and cold symptoms were recorded.

The primary efficacy parameter was the total number of facial tissues used throughout the clinical duration of their cold. For this purpose, the sum of the number of facial tissues used from day 2 until the end of observations was calculated (the number of tissues used on day 1 was used for stratification; therefore the value on day 1 could not be included to the primary variable).

Secondary objectives of this study included exploratory observations of the following: The overall safety of the study medication, onset of improvement (estimated by days until number of tissues used daily was less than at baseline), time to marked improvement, duration of

the treatment, number of tissues used on single days. The study was conducted according to GCP; the study of protocol was approved by the independent ethics committee of the local regulatory authority (Melegnano, Italy).

Patients

Patients were recruited at one centre in Milan, Italy. The inclusion criteria were adults aged 18 years or older who were suffering from a common cold for not more than 1 day and required to use facial tissues during the cold. Patients with any of the following characteristics were not eligible for enrolment in this study: underlying diseases (such as AIDS or end stage liver disease), patients in a chronic vegetative state, patients receiving any investigational agent or antineoplastic chemotherapy, patients with hypersensitivity to the study medication or any of its ingredients and patients vaccinated for influenza. Pregnant or nursing women were excluded as well as patients receiving disallowed concomitant therapies and patients with granulocyte counts <1000 per mm^3 due to malignancy or chemotherapy.

Treatment

Patients were randomised to receive 19.2 or 9.6 mg of the dry extract of SB-TOX or placebo three times daily. The treatment was commenced as soon as possible after symptom onset and was to last until the end of rhinitis symptoms. It actually lasted for 3–12 days. One tablet of the active study medication SB-TOX (Esberitox[®] Tablets, Schaper & Brümmer GmbH & Co. KG, Salzgitte, Germany) contained 3.2 mg of a native dry extract (DER 4–9:1) from *Baptisia tinctoria* root/*Echinacea purpurea* root/*Echinacea pallida* root and *Thuja occidentalis* herba at a ratio of 4.92:1.85:1.85:1. The extraction medium was ethanol 30% (V/V). The placebo contained the same inactive ingredients only and was similar in appearance, taste and smell to the active drug tablets. One box of the study medication was supplied to each patient for the entire treatment, which was anticipated to last no longer than 12 days. Tablets were blistered and packaged by blister card technology. The patients were asked to take the tablets like lozenges.

Randomisation and blinding

The patients' allocation to one of the three different treatment groups was performed by randomisation into permuted blocks generated by the validated RanCode Plus software (idv, Gauting). The patients received the study drugs in boxes pre-numbered in consecutive order according to the time of their enrolment into the study always using the lowest number available.

Both patient and physician remained blinded as to which preparation was being administered. The blind could be broken for an individual patient in the event of an emergency. However, no emergencies occurred. Moreover, all other study participants including monitor, auditor, biometrician, principal investigator and sponsor remained blinded throughout the study. The blind was maintained during review of the complete database for patients' validity and allocation to the populations of analyses. Thereafter, the database was closed and the code broken for statistical evaluation.

Safety

Safety variables were weight, vital signs, and adverse event reporting and detailed clinical laboratory tests including differential haematology, microscopic urinalysis, and fourteen key biochemical parameters.

Statistical analysis and sample size

The biometrical evaluation and table generation were done with SPSS 7.5. The primary objective of the study was to show a significant upward slope in the dose–response function of the three treatment groups according to ICH guideline, E4, “Dose Response Information to Support Drug Registration”. This was tested using the Jonckheere test (Jonckheere, 1954) stratified for the quartiles of the day 1 value of the primary parameter. Accordingly, the null hypothesis “ $F_1 = F_2 = F_3$ ” was tested against the alternative “ $F_1 \geq F_2 \geq F_3$; where at least one of the inequalities is strict” at the 5%-level expecting a negative slope for the numbers of tissues used with increasing dosage.

In accordance with the principle of ordered hypotheses, the Mann–Whitney test was subsequently used to compare the pairs of the dosage groups. If the first step resulted in significance (Jonckheere test across all groups as overall test), the three subsequent steps were also tested simultaneously using the same $\alpha = 0.05$ (Shaffer, 1986).

A total of 90 patients (30 per treatment arm) evaluable for efficacy were planned for enrolment in the trial. This sample size was deemed sufficient to provide a 90% power for detecting a mean difference in number of tissues per patient of $\Delta = 20$ between the placebo group and the high-dose group, assuming a standard deviation of $SD = 25$ at $\alpha = 0.05$. The power of the Jonckheere test may be better than that of the Wilcoxon test for two treatment groups. Since no standardised software was available to calculate a reasonable sample size for the Jonckheere test, the sample size was conservatively estimated based on the Wilcoxon U test including a 7% dropout rate.

Both an intention-to-treat (ITT) and a per-protocol-analysis (PP) were performed. Only patients whose reason for dropping out of the study was conclusively not related to the study medication were excluded from all PP analyses. Patients without any documentation of the number of tissues used were omitted from the ITT analysis and included in the safety analysis only.

For patients who dropped out of the study, missing values in facial tissue use were replaced using the following pre-planned strategy: 50% of the last observed (and documented) number of tissues used were extrapolated to the subsequent day until the limit of less than 10 was reached (e.g. 14→7; 13→7; 12→6; 22→11→6; 20→10→5). In these patients, the duration of their cold was extrapolated by adding the number of days of missing values in facial tissue use that had been imputed.

Results

A total of 94 patients were randomised (Fig. 1). Three of them did not report the primary efficacy variable. Therefore, 91 patients remained for the ITT analysis. Another six patients stopped taking the study medication before the use of facial tissues had returned to normal (≥ 10 per day). The major reason for dropout in all six patients was “patient’s wish”. Eighty-five patients completed the study per protocol (PP population). Major violations of inclusion or exclusion criteria did not occur. Only two patients seemed to have had their

cold longer than 1 day at baseline. But their cold had started in the night. Hence, this was judged as only “minor protocol violation” during the blinded review, and the patients remained in the PP population.

All the demographic parameters age, height, weight and ethnic origin were similar in the three treatment groups. The mean age was 42.1 years (range: 20–74 years; SD = 13.0 years). In total, 44% of the patients were male, 56% were female. The mean height of the male patients was 176 ± 6 cm and of the female 163 ± 5 cm. The mean weight was 71 ± 9 kg in male and 59 ± 7 kg in female. All patients except for one were Caucasians. More details are presented in Table 1.

Efficacy

For the ITT patients, the mean number of facial tissues used at baseline (day 1) was 29 ± 8 in the placebo group, 27 ± 6 in the “9.6 mg SB-TOX group” and 27 ± 5 in the “19.2 mg SB-TOX” group. Similar values were found for the PP patients. Statistical comparison of these baseline values did not reveal any significance in the ITT population ($p = 0.522$) or in the PP population ($p = 0.795$).

The total number of facial tissues used throughout the observational period decreased with increasing dose of extract administered. The slope across groups according to the Jonckheere test was significant for the primary efficacy parameter in both the ITT ($p = 0.0259$) and PP analyses ($p = 0.0146$). A statistically significant slope

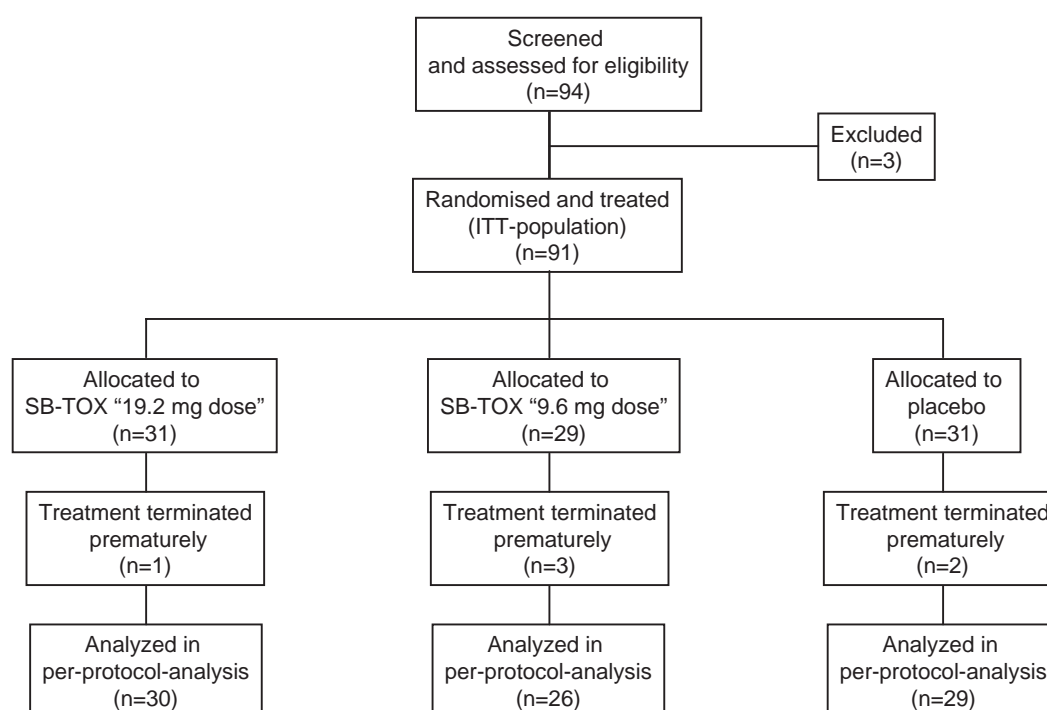
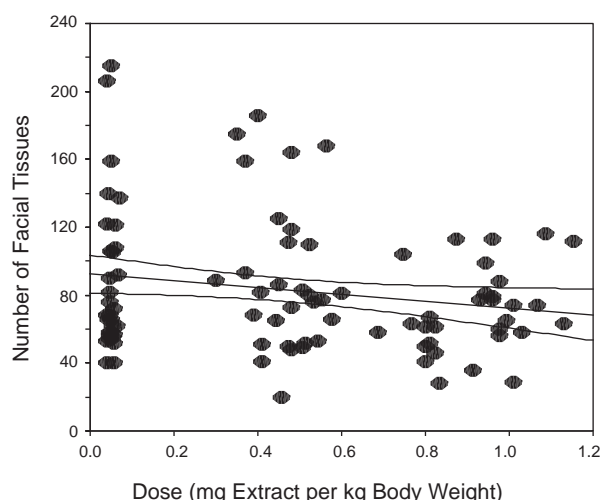


Fig. 1. Flow chart of the clinical trial.

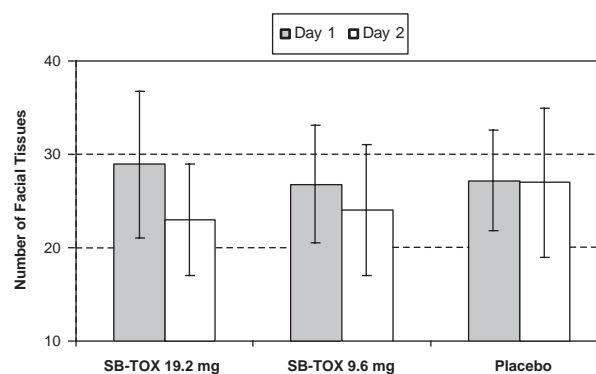
Table 1. Demographic data at baseline

Parameter	SB-TOX 19.2 mg	SB-TOX 9.6 mg	Placebo
No. of patients	31	32	31
Age (mean \pm SD) (years)	41.8 \pm 13.0	41.9 \pm 14.1	42.3 \pm 12.3
Sex (M: F)	12: 19	10: 22	19: 12
Height (mean \pm SD) (cm)			
Male	174.8 \pm 5.1	177.9 \pm 7.9	175.3 \pm 5.3
Female	163.2 \pm 4.3	164.0 \pm 4.8	159.3 \pm 4.7
Weight (mean \pm SD) (kg)			
Male	71.2 \pm 11.1	71.9 \pm 11.4	70.6 \pm 6.9
Female	60.6 \pm 6.9	60.1 \pm 7.1	55.0 \pm 5.7
No. of common colds during the last 3 years (mean \pm SD)	2.6 \pm 1.0	2.8 \pm 1.0	3.1 \pm 1.4
Smoking history (<i>n</i>) (ex-smokers /current smokers)	9	5	11

**Fig. 2.** Scatter plot of the total number of facial tissues used throughout the cold episode in relation to SB-TOX dose in mg/kg body weight. Individual patients' data (dots), linear regression and the corresponding 90% CI.

was found for both the dose–response function and the dose/kg response function (Fig. 2). The standardised effect size Δ /SD was 0.46 in the high-dose group compared to placebo. Subsequent analyses of the pairwise group comparisons in the ITT population confirmed a statistically significant superiority of the “19.2 mg dose” as compared with placebo ($p = 0.0323$) or as compared with the “9.6 mg group” ($p = 0.0101$). Differences between the “9.6 mg group” and placebo could not be demonstrated ($p = 0.284$). Similar to slightly better differences in favour of the herbal remedy were found in the PP population.

The efficacy of SB-TOX was also demonstrated by the secondary efficacy parameters. The number of tissues used differed significantly between groups as early as day 2 ($p = 0.0112$) (Fig. 3). A significant decrease in the number of facial tissues used on distinct days was also found in the succeeding days (Table 2; ITT). Similar results were shown in the PP analysis (Table 3). The average time to relevant improvement of the cold (as

**Fig. 3.** The total number of facial tissues used after 2 days of therapy compared with baseline (day 1).

measured by time until number of tissues used was less than 30 per day) was 1.1 days (95% CI 0.52; 1.67), 0.76 days (95% CI 0.28; 1.24) and 0.52 days (95% CI 0.22; 0.82) in the placebo group, “9.6 mg group” and the “19.2 mg group”, respectively. The log rank trend test revealed $p = 0.0175$.

Safety

No adverse events were reported. Clinically relevant changes in laboratory parameters were not seen in any of the active drug groups with two exceptions. In two patients, their white blood cell count showed a decrease from baseline to the end of observation period probably because their cold was cured. Interestingly, the numbers of patients with at least trace amounts of white blood cells in their urinary sediment decreased over time proportionate with the increasing dose of SB-TOX. No other differences were detected between the groups. Vital signs were not affected either.

Discussion

Our data confirm that the clinical efficacy of SB-TOX is statistically significant and clinically relevant in the

Table 2. Number of facial tissue used (mean \pm SD; min–max) with increasing dose (ITT analysis)

	Day			
	2	3	4	5
Placebo	27 \pm 8 [16–50]	21 \pm 10 [10–42]	17 \pm 8 [8–40]	13 \pm 8 [4–32]
SB-TOX 9.6 mg	24 \pm 7 [10–40]	21 \pm 8 [7–40]	17 \pm 8 [3–37]	13 \pm 7 [0–25]
SB-TOX 19.2 mg	23 \pm 6 [10–40]	19 \pm 6 [8–30]	13 \pm 6 [4–28]	9 \pm 5 [0–16]
<i>p</i> -Value	0.0112	0.3509	0.0071	0.0495

Table 3. Number of facial tissue used (mean \pm SD; min–max) with increasing dose (PP analysis).

	Day			
	2	3	4	5
Placebo	26 \pm 8 [16–50]	20 \pm 10 [10–42]	17 \pm 8 [8–40]	13 \pm 8 [4–32]
SB-TOX 9.6 mg	25 \pm 7 [10–40]	22 \pm 9 [7–40]	17 \pm 9 [3–37]	13 \pm 7 [0–25]
SB-TOX 19.2 mg	23 \pm 6 [10–40]	19 \pm 6 [8–30]	13 \pm 6 [4–28]	8 \pm 5 [0–16]
<i>p</i> -Value	0.0093	0.3376	0.0060	0.0191

treatment of URIs. This fact was demonstrated by both the ITT analysis ($p = 0.0259$) and the PP analysis ($p = 0.0146$). Subsequent pairwise-group comparisons confirmatorily showed a statistically significant superiority of the higher SB-TOX dose over placebo and over the lower SB-TOX dose ($p = 0.0323$ or even lower).

The primary aim of this clinical study was not powered for the statistical confirmation of the recommended dosage but focused on (i) the efficacy of SB-TOX in general and (ii) the question as to whether efficacy can be enhanced by elevating the dose and (iii) confirmation of recent proof of efficacy of SB-TOX using an independent clinical method. These three objectives were achieved and confirmed to be statistically significant. Moreover, the standardised effect size in the ITT population of $d \cong 0.5$ or even less can be interpreted as clinically relevant.

According to Henneicke-von Zepelin et al. (1999), the multiple symptoms of a cold that are effectively improved by this herbal remedy can be factorised to three dimensions: rhinitis score, bronchitis score and general well-being. Nasal stuffiness and discharge are the main clinical symptoms in common colds and the number of facial tissues used per day (number of paper handkerchiefs) can serve as surrogate measure of the total symptom complex and is easily measured by counting. Therefore, the total number of facial tissues was employed as the primary efficacy measure in this study. This tool for measuring a drug's efficacy in URIs has been used and validated in several preliminary investigations (Weidner et al., 1998; Scaglione and Lund, 1995; Walker et al., 1967). To our knowledge,

the current study is the first time that this method was applied in a double-blinded manner and according to GCP standards.

One limitation of our study is the fact that subjective symptoms were not investigated. However, in another GCP-compliant, double-blind, placebo-controlled clinical trial, Henneicke-von Zepelin et al. (1999) verified the efficacy and safety of SB-TOX for treatment of the common cold. They studied the intensity of 18 cold symptoms and an overall assessment of the cold on a 10-point scale and the general well-being. This study also demonstrated the therapeutic benefit of SB-TOX with respect to subjective symptoms.

In contrast to a recent study (Taylor et al., 2003), which did not support the use of *E. purpurea* for the treatment of URI symptoms in children, our results were indeed able to show that the Echinacea-containing drug SB-TOX yields benefits in the management of these URI symptoms manifest as the common cold. Besides the limitations of the study by Taylor et al. (2003) just discussed, the different results between our study and theirs might be explained by variations in drug composition. The SB-TOX used in our study contains a native dry extract of two Echinacea species along with two other immunomodulating plants (wild indigo roots and arbor vitae leaves).

The immunopharmacological potential of SB-TOX has been established by various *in vitro* and *in vivo* test models (Teuscher et al., 2004; Bodinet et al., 2004). The immunostimulating and antiviral activities have been proven for the single drugs themselves as well as for the extract of the drug mixture. The single drugs were

effective on different parameters but differed in their main activities, while SB-TOX showed a stronger activity in the majority of systems tested. In a direct comparison, SB-TOX mostly was superior to the single drugs and had the broadest spectrum of effectiveness. In addition, Teuscher et al. (2004) concluded from their investigations that the extract of the mixture, especially the macromolecular components polysaccharides and glycoproteins contained therein, can put the immunocompetent cells of the upper respiratory tract and gut mucosa on the alert. The immune response itself, however, is only triggered by a specific infection. As the body's first contact with immunocompetent cells takes place in the anterior nasal and throat mucosa, the local effect of the drug appears crucial. From this observation, it can be assumed that lozenge-like tablets as used in our study might be more effective than other medicinal forms. This hypothesis might additionally explain why some preparations containing Echinacea have not worked effectively.

It should also be emphasised that the drug in our study showed superior efficacy after just 2 days. This is clinically relevant because patients suffering from common colds usually self-medicate with over-the-counter drugs bought without consulting their physicians. On the one hand, they want to get well as early as possible. When the symptoms improve quickly, there is no need to consult a doctor and the patients have additional savings. On the other hand, their doctors do not need to try other treatments like antibiotics whose benefit is the subject of controversy and whose use in the treatment of the common cold is associated with significant risks (Arroll and Kenealy, 2004). Our results are also in accordance with those of Hauke et al. (2002) who found that co-medication with antibiotics and a liquid formulation of SB-TOX is superior to antibiotics alone in the treatment of an acute exacerbation of chronic obstructive pulmonary disease. The time to half-maximal improvement of lung function was significantly reduced from 12.8 days in the placebo group to 5.7 days in the SB-TOX group.

Conclusions

The results of this prospective randomised placebo-controlled study confirm – using an objective parameter – the efficacy and safety of the herbal remedy Esberitox® in the treatment of the common cold. Patients recover more rapidly, within just a few days, and the effect was dose-dependent, i.e., the higher the dosage the better the efficacy. Even the highest dosage did not produce any safety concerns. Based on these results and overall, it is recommended that treatment is initiated as soon as possible after symptom onset and with a high dose.

References

- Adams, P.F., Hendershot, G.E., Marano, M.A., 1999. Current estimates from the National Health Interview Survey. *Vital Health Stat* 10, 1996.
- Arroll, B., Kenealy, T., 2004. Antibiotics for the common cold and acute purulent rhinitis (Cochrane Review). The Cochrane Library, (1). Wiley, Chichester, UK.
- Barrett, B., Brown, R., Locken, K., Maberry, R., Bobula, J.A., D'Alessio, D., 2002. Treatment of the common cold with unrefined Echinacea. *Ann. Intern. Med.* 137, 939–946.
- Barrett, B., 2003. Medicinal properties of Echinacea: a critical review. *Phytomedicine* 10, 66–86.
- Bodinet, C., Freudenstein, J., 1999. Effects of an orally applied aqueous-ethanolic extract of a mixture of *Thuja occidentalis* herba, *Baptisia tinctoriae* radix, *Echinaceae purpureae* radix and *Echinaceae pallidae* radix on antibody response against sheep red blood cells in mice. *Planta Med.* 65, 695–699.
- Bodinet, C., Lindequist, U., Teuscher, E., Freudenstein, J., 2002a. Effect of an orally applied herbal immunomodulator on cytokine induction and antibody response in normal and immunosuppressed mice. *Phytomedicine* 9, 606–613.
- Bodinet, C., Mental, R., Wegner, U., Lindequist, U., Teuscher, E., Freudenstein, J., 2002b. Effect of oral application of an immunomodulating plant extract on influenza virus type A infection in mice. *Planta Med.* 68, 896–900.
- Bodinet, C., Lindequist, U., Teuscher, E., Freudenstein, J., 2004. Influence of peroral application of a herbal immunomodulator on the antibody production of Peyer's patches cells. *Arzneim.-Forsch./Drugs Res.* 54, 114–118.
- Gohla, S.H., Haubeck, H.-D., Schrum, S., Soltan, H., Neth, R.D., 1986. Activation of CD4-positive T cells by polysaccharide fractions isolated from the Cupressaceae *Thuja occidentalis* L. (Arborvitae). *J. Allergy Klin. Immunol.* 77, 268–272.
- Gohla, S.H., Zeman, R.A., Gartner, S., Popovic, M., Jurkiewicz, E., Haubeck, H.D., Schrum, S., Gallo, R.C., Neth, R.D., Hunsmann, G., 1990. Inhibition of the replication of HIV-1 by TPSg, a polysaccharide-fraction isolated from the Cupressaceae "*Thuja occidentalis* L.". *AIDS Res. Hum. Retroviruses* 6, 131.
- Hauke, W., Köhler, G., Henneicke-von Zepelin, H.-H., Freudenstein, J., 2002. Esberitox® N as supportive therapy when providing standard antibiotic treatment in subjects with a severe bacterial infection (acute exacerbation of chronic bronchitis). *Chemotherapy* 48, 259–266.
- Heikkinen, T., Jarvinen, A., 2003. The common cold. *Lancet* 361 (9351), 51–59.
- Henneicke-von Zepelin, H.-H., Hentschel, C., Schnitker, J., Kohnen, R., Köhler, G., Wüstenberg, P., 1999. Efficacy and safety of a fixed combination phytomedicine in the treatment of the common cold (acute viral respiratory tract infection): results of a randomised, double-blind, placebo controlled, multicentre study. *Curr. Med. Res. Opin.* 15, 214–227.
- Jonckheere, A.R., 1954. A distribution-free k-sample test against ordered alternatives. *Biometrika* 41, 133–145.

- Köhler, G., Elosge, M., Hasenfuss, I., Wüstenberg, P., 1998. Kinderdosierung von Phytopharmaka: repräsentative exemplarische altersstratifizierte Dosierungspraxis für die pflanzliche Wirkstoffkombination Esberitox[®]. *N. Z. Phytother.* 19, 318–322.
- Melchart, D., Linde, K., Fischer, P., Kaesmayr, J., 2004. Echinacea for preventing and treating the common cold (Cochrane Review). *The Cochrane Library*, (1). Wiley, Chichester, UK.
- Reitz, H.-D., Hergarten, H., 1990. Immunmodulatoren mit pflanzlichen Wirkstoffen 2. Teil: eine wissenschaftliche Studie am Beispiel Esberitox[®]. *N. notabene medici* 20, 304–306, 362–366.
- Scaglione, F., Lund, B., 1995. Efficacy in the treatment of the common cold of a preparation containing an Echinacea extract. *Int. J. Immunother.* 11, 163–166.
- Shaffer, J., 1986. Modified sequentially rejective multiple test problems. *JASA* 81, 826–831.
- Taylor, J.A., Weber, W., Standish, L., 2003. Efficacy and safety of Echinacea in treating upper respiratory tract infections in children. *JAMA* 290, 2824–2830.
- Teuscher, E., Bodinet, C., Lindequist, U., Freudenstein, J., 2004. Untersuchungen zu Wirksubstanzen pflanzlicher Immunstimulanzien und ihrer Wirkungsweise bei peroraler Applikation. *Zeitschrift f. Phytother.* 25, 11–20.
- Vorberg, G., 1984. Bei Erkältung unspezifische Immunabwehr stimulieren. *Ärzt. Praxis* 36, 97–98.
- Walker, G.H., Bynoe, M.L., Tyrrell, D.A., 1967. Trial of ascorbic acid in prevention of colds. *Br. Med. J.* 1, 603–606.
- Weidner, T.G., Cranston, T., Schurr, T., Kaminsky, L.A., 1998. The effect of exercise training on the severity and duration of a viral upper respiratory illness. *Med. Sci. Sports Exerc.* 30, 1578–1583.