APMIS 112: 605–11, 2004
Printed in Denmark . All rights reserved

APMIS
ISSN 0903-4641

Treatment of the common cold with troxerutin

RONALD B. TURNER,[1] SANDRA L. FOWLER[2] and KURT BERG[3]

[1]Department of Pediatrics, University of Virginia School of Medicine,
[2]Department of Pediatrics, Medical University of South Carolina, Charleston, SC and
[3]The Panum Institute, University of Copenhagen, Copenhagen, Denmark

Turner RB, Fowler SL, Berg K. Treatment of the common cold with troxerutin. APMIS 2004;112:605–11.

The rutosides are naturally occurring flavonoids that have documented effects on capillary permeability and edema. The purpose of this study was to assess the effect of troxerutin, one of the rutosides, on the symptoms of the common cold. Ninety-four volunteers with common cold symptoms were recruited for participation in the study. Volunteers were randomized to either active treatment (n=49) with troxerutin (50 mg) and Zn gluconate (25 mg) or control treatment (n=45) with 10 mg Zn gluconate. Symptoms were assessed by subjective symptom score prior to treatment and then daily for the next 4 days. The total symptom score over the 4 days of study treatment was 27.7±2.0 (mean±SEM) and 33.0±2.6 in the active and control groups, respectively (p=0.10, unpaired *t*-test). The total daily symptom score on day 1 was reduced by 11% compared to baseline in the active group and by 1% in the control group (p=0.03). Evaluation of the effect of treatment on individual symptoms revealed a significant effect on rhinorrhea. The total rhinorrhea score over the course of the study was 3.7±0.4 in the active group compared to 5.1±0.5 in the control group (p=0.025, unpaired *t*-test). Daily rhinorrhea scores were significantly lower in the active group on study days 1 and 3. Based on this preliminary study, the possibility that the rutosides might provide a safe and effective treatment for rhinorrhea in the common cold deserves systematic evaluation.

Key words: Common cold; treatment; troxerutin; rhinitis; anti-edema:

Ronald B. Turner, Department of Pediatrics, P.O. Box 800386, University of Virginia Health System, Charlottesville, VA 22908, USA. e-mail: rbt2n@virginia.edu

The common cold is a ubiquitous illness that is associated with significant medical and socioeconomic consequences. Rhinorrhea and nasal obstruction are among the most frequent symptoms reported during the common cold and are identified as the "most bothersome" symptoms by a majority of individuals (1–3). A major contributor to the development of rhinorrhea is increased vascular permeability with leakage of serum into the nasal secretions (4, 5). Current treatments for the common cold that have proven efficacy are limited to agents that are directed at specific symptoms. These treatments – antihistamines for rhinorrhea, nasal decongestants for nasal obstruction and analgesics for relief of pain – have limited effectiveness, generally relieving the target symptom by 15–25% at the peak of activity, and may be associated with bothersome side effects.

The rutosides (also known as rutin) are naturally occurring flavonoids that are found in many different plants. Various formulations of rutosides for systemic use have been commercially available for over 25 years and are used primarily as treatment for edema related to venous insufficiency (6–12). Troxerutin (3′,4′,7′-tri-O-(beta-hydroxyethyl)-rutoside) is one of the rutosides that has been used as a treatment for this syndrome. The proposed mechanism of action of the rutosides in venous insufficiency includes a reduction in capillary permeability

Received March 15, 2004.
Accepted August 25, 2004.

with a decrease in capillary filtration rate (13–15). Given the role of serum transudation and nasal edema in the symptoms of the common cold, this study was designed to assess the effect of a lozenge formulation containing troxerutin for treatment of the common cold.

METHODS

Subjects

Volunteers between the ages of 18 and 75 years old with recent onset of common cold symptoms were recruited from the community of Charleston, South Carolina in the months of February through April. Individuals interested in participating in the study were recruited by advertisement and were evaluated by a single study coordinator at one site. Subjects were required to have at least two different common cold symptoms and a total symptom score of at least 3 based on the symptom scoring method described below. No symptom could be present for more than 36 hour prior to beginning study treatment. Volunteers who had had any respiratory illness or had used an antihistamine or decongestant in the 7 days prior to onset of common cold symptoms, had used corticosteroids in the last 2 weeks or non-steroidal analgesics in the last 3 days, had fever $>38.3^{\circ}C$ at the time of presentation, had a daily sleep pattern that was not compatible with the dosing requirement for the study or were pregnant or lactating were excluded. Participants were asked to refrain from using other medications for the duration of the study, although continued use of hormonal contraception, selective serotonin reuptake inhibitors, other anti-depressants, and long-term antibiotics (e.g., indicated for acne, urinary tract infection prophylaxis) was permitted. The study was reviewed and approved by the Institutional Review Board for Human Subjects at the Medical University of South Carolina. All participants gave written informed consent and were compensated for their participation.

Study procedures

Interested individuals presented to the study site before noon on day 0. At this visit, the eligibility of the volunteer to participate in the study was determined and eligible subjects were given the first two doses of study medication and a study diary. Careful instructions for drug administration and for recording symptoms, the time the study medications were taken, the blinding assessment and adverse events were given at this visit. Volunteers were discharged from the study site with instructions to return for a final visit within 48 h of completing the study medication. At the final visit diaries were collected and all entries reviewed and clarified, adverse events were reviewed and excess study medication was collected.

Study medication

Participants in the study were randomized to receive either troxerutin 50 mg with Zn gluconate 25 mg ("active") or Zn gluconate 10 mg ("control"). Both treatments were given as lozenges that also contained sorbitol, peppermint oil, and magnesium stearate. The study was double blinded. Individual bottles, labeled with a subject number, contained either active or control medication based on a randomization code matched to the subject number. The randomization code was generated using a single block of 100 and a 1:1 ratio of active to control treatment. The randomization and preparation of study medications was done by the research pharmacy of the Medical University of South Carolina and the randomization code was supplied to the investigators only after all study data were recorded and verified. Subject numbers were assigned to participants sequentially as they were enrolled in the study. Volunteers were enrolled in the study before noon on day 0. The study staff administered two lozenges at the time of enrollment (one lozenge followed immediately by the second). Volunteers were then instructed to take a single lozenge at four regularly spaced intervals throughout the remainder of the day with the last dose at bedtime. On study days 1–3 volunteers took one lozenge at approximately 3 h intervals with the last dose at bedtime (total of five lozenges per day). Blinding was assessed by asking volunteers to record in the study diary on the morning of day 1 whether they believed they were receiving active or control medication (or "don't know"). Volunteers were asked to record in the study diary the time when each dose of study medication was taken and to return unused study medications to the study site. Compliance was assessed by review of the study diary and by counting returned doses of medication. For purposes of the per protocol analyses, the subject was assessed as compliant with the protocol if at least 80% of the planned doses were taken.

Symptom assessment

Symptoms were scored before the first dose of study medication on day 0, and once each day between 8 AM and 10 AM. The symptoms of nasal obstruction, rhinorrhea, sore throat, cough, sneezing, headache, malaise, and chilliness were assessed as either absent (0), mild (1, present but barely noticeable), moderate (2, definitely present and bothersome), severe (3, symptom is hard to tolerate and interferes with normal daily activities), and very severe (4, symptom prevents normal daily activity). The sum of all symptom scores on study days 1, 2, 3 and 4 was the total symptom score. The sum of the scores on each day comprised the total daily symptom score.

In addition to the evaluation of specific symptoms, an assessment was also made of the effect of symptoms on daily function. For this assessment, the volunteers rated how bothersome their illness was on

a 5-point scale (0=absent, 1=barely noticeable, 2=bothersome but does not interfere with normal activity, 3=interferes with normal activity, 4=prevents normal activity) to assess the impact of common cold symptoms on daily functioning. The effect of the cold on sleep was determined by asking the volunteer whether their symptoms interfered with sleep (yes/no). These assessments were done daily on study days 0–4.

Symptoms were recorded in a symptom diary provided forto the volunteer. The day 0 (baseline) symptoms were recorded by the study staff in an interactive interview during which instruction in the proper assessment of symptoms was provided.

Statistical analysis

Using the assumptions that the control-treated subjects would have a total symptom score of 32.8 with a standard deviation of 16 (assumptions based on a previous unpublished pilot study) a sample size of 47 subjects per treatment arm was needed to detect a difference in total symptom score of approximately 25% between active and control arms with $p_\alpha=0.05$ (two-sided) and $p_\beta=0.2$ (one-sided).

All subjects who recorded their symptom scores according to the study protocol were included in the primary efficacy analysis. The primary endpoint for the study was the comparison of total symptom score in the control treated subjects with the total symptom score in the subjects who received active medication. These treatment groups were compared using the unpaired *t*-test with p=0.05 considered statistically significant. Planned secondary endpoints included comparison between the treatment groups with regard to total symptom scores by day, symptom scores for individual symptoms, how bothersome the cold symptoms were by day, and effects of the illness on sleep. The adequacy of blinding was assessed by comparison of the proportion of subjects who believed they received active medication in the active and control treatment groups.

RESULTS

Ninety-five volunteers were enrolled in the study and randomized to study medication. One volunteer voluntarily withdrew from the study and provided no study records or data. The remaining 94 subjects completed the study as planned. Forty-nine subjects were randomized to the active treatment and 45 subjects were randomized to the control treatment. The average ages of the subjects were 28.3±9.8 and 27.6±9.2 (mean±SD) in the active and control groups, respectively, and the male: female ratios in the groups were 24:25 and 20:25.

Blinding

Of the 49 subjects randomized to active treatment, 19 believed they had received the active, 16 believed they had received the control, and 13 didn't know. Of the 45 subjects randomized to the control treatment, 11 believed they had received the active, 20 believed they had received the control, and 11 didn't know. The proportion of subjects who believed they were receiving active drug did not differ significantly between the groups (p=0.18, Fisher's exact test). Four subjects (1 active, 3 control) did not provide data.

Compliance

Compliance was assessed by review of the study diary and lozenge count. Two subjects, one in each treatment group, had missed doses based on diary review. Five subjects, two in the active and three in the control group, had missed doses based on lozenge count. All subjects were assessed as "compliant" based on the protocol definition of compliance (80% of intended lozenges used).

Effect of treatment on symptoms

The total symptom score over the 4 days of study treatment was 27.7±2.0 (mean±SEM) and 33.0±2.6 in the active and control groups, respectively (p=0.10, unpaired *t*-test). The total daily symptom score on day 1 was reduced by 11% compared to baseline in the active group and by 1% in the control group (p=0.03) (Fig. 1).

Evaluation of the effect of treatment on individual symptoms revealed a significant effect on rhinorrhea. The total rhinorrhea score over the

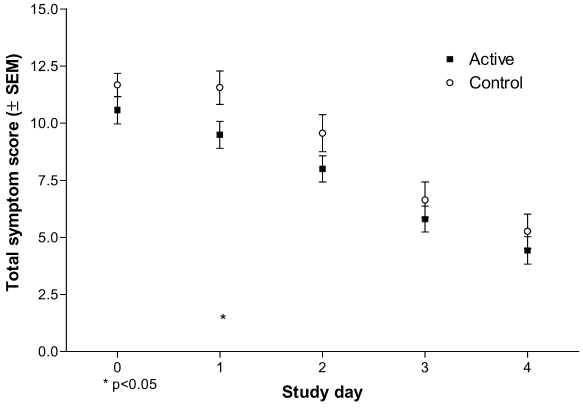

Fig. 1. Effect of troxerutin on total symptom score by treatment day. Volunteers were started on study medication on treatment day 0.

course of the study was 3.7±0.4 in the active group compared to 5.1±0.5 in the control group (p=0.025, unpaired *t*-test). Daily rhinorrhea scores were significantly lower in the active group on study days 1 and 3 (Fig. 2), and also had a greater reduction from baseline compared to the controls. The rhinorrhea symptom scores were reduced by 25%, 33% and 58% from the baseline in the active group and by 0%, 9% and 34% in the control group on days 1, 2, and 3, respectively. There was no significant effect of treatment over the course of the cold on the other symptoms assessed, although comparison of daily symptom scores revealed occasional differences (Fig. 2). There were also no significant differences in the assessment of the bothersome score or sleep disturbance between the active and control groups.

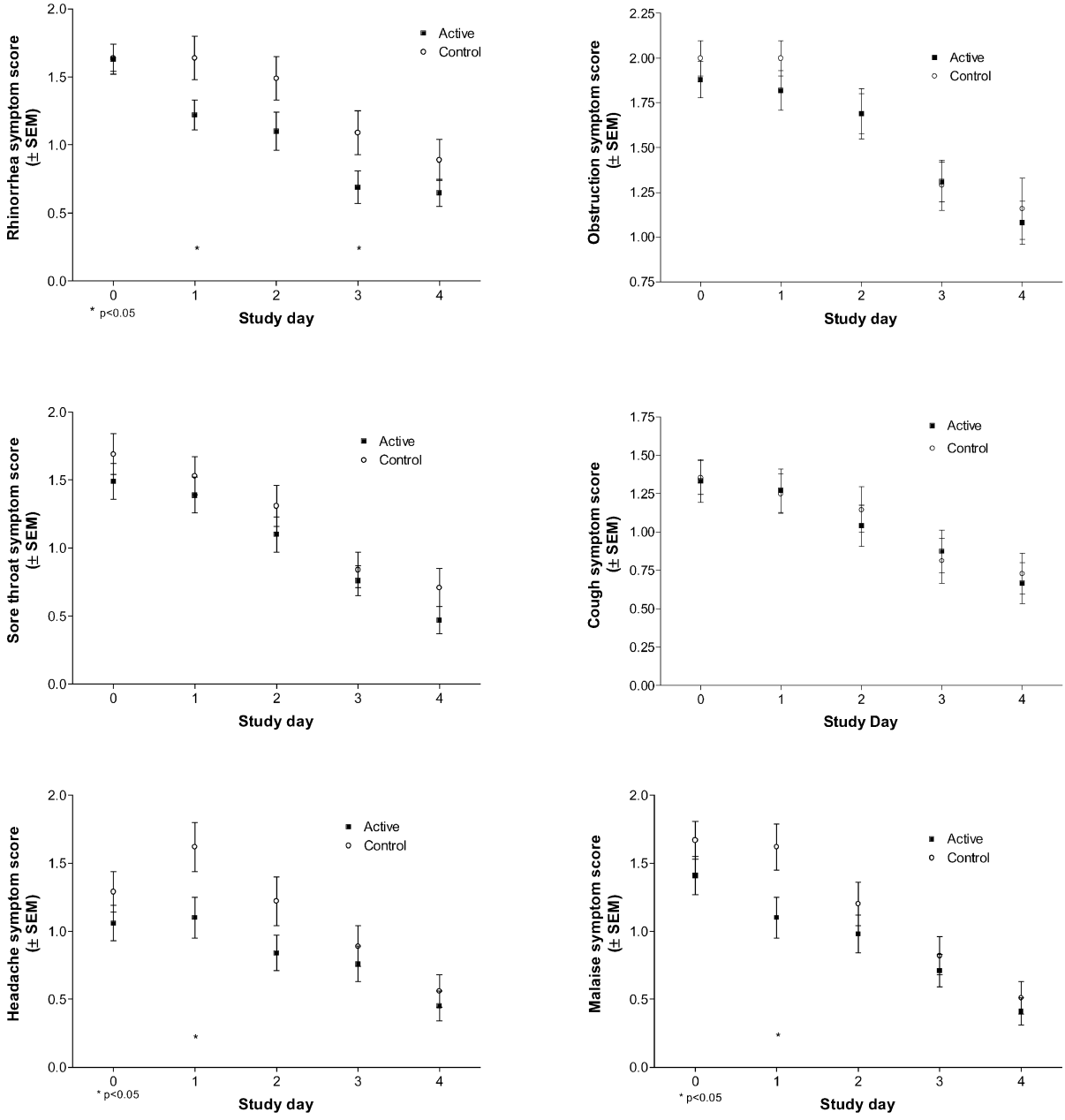

Fig. 2. Effect of troxerutin on symptom severity for individual symptoms by treatment day. Volunteers were started on study medication on treatment day 0.

Adverse events

There were no serious adverse events reported in the study. Fifteen (31%) of the 49 subjects randomized to active treatment reported adverse events compared to 6 (13%) of the 45 subjects randomized to control treatment ($p=0.05$, Fisher's exact test). The most common adverse events reported by the subjects in the active treatment group were sore mouth (4%), nausea (8%), bad taste (8%), and dry mouth (8%). These same adverse events were each reported by one (2%) of the subjects in the control group.

DISCUSSION

Symptomatic therapies directed at specific symptoms are the only effective treatments that are currently available for the common cold. None of these treatments has demonstrated an impact on the overall symptom burden of the cold. Similarly, troxerutin did not significantly reduce total symptom burden as measured by the total symptom score in this study. The reduction in total symptom score from 33 to 27.7, a 16% decrease compared to control, did not meet the goal of a 25% reduction judged prior to the study to be a clinically meaningful reduction in overall symptom severity. Pleconaril, an antiviral agent with activity against the rhinoviruses, reduced the total symptom score by 19% compared to placebo in a large study of rhinovirus colds (16).

The troxerutin treatment in this study did have an apparent effect on rhinorrhea. This observed effect is consistent with the known effect of the rutosides on capillary permeability and the role of serum transudation in common cold pathogenesis. Rhinorrhea scores were reduced by 27% by treatment compared to the control group over the 4 days of the study. The magnitude of the effect on rhinorrhea compares favorably with the effect of other treatments directed at this symptom. Clemastine, a first-generation antihistamine, reduced rhinorrhea symptom scores 9% and 26% more than placebo on the first 2 days of treatment in a natural cold study (17). Similar results were seen for clemastine and brompheniramine in studies of volunteers with experimental rhinovirus colds (18, 19). Ipratropium bromide, an anticholinergic agent used intranasally, reduced rhinorrhea 22%–31% in a series of natural colds studies (20–22).

The flavonoids have been found to have a variety of biologic effects. The apparent effect of troxerutin on rhinorrhea is consistent with the previously observed effects of the flavonoids on capillary filtration in venous insufficiency. Other activities of the flavonoids include antioxidant effects and inhibition of NFkB-dependent gene expression (23, 24). Oxidant stress and NFkB-dependent expression of proinflammatory cytokines have been proposed as a potential contributor to common cold pathogenesis (reviewed in (25)), but the observation that the effect of troxerutin in this study was limited to a reduction in rhinorrhea seems incompatible with a general reduction in the host response as the mechanism of action. Our study was not designed to determine the mechanism of the treatment effect and future studies of troxerutin treatment of common cold symptoms should address this issue directly.

Assessment of the effect of troxerutin on the common cold in this study may have been confounded by the addition of zinc gluconate, in different concentrations, to the troxerutin formulation and to the control treatment. Since 1984 there have been at least 12 clinical trials conducted to assess the role of zinc in the treatment of the common cold (26–36). Although these studies have produced disparate results, a reasonable and widely accepted interpretation of these studies is that zinc gluconate, given alone, has little if any benefit as a common cold treatment. In none of the studies was a specific effect of treatment seen on rhinorrhea. The formulation of troxerutin that was available for this study contained troxerutin plus 25 mg zinc gluconate. The taste of the zinc would potentially unblind the active study material and, for this reason, the control arm in this study used an oral lozenge containing 10 mg zinc gluconate. Although the zinc would not be expected to affect the efficacy of the treatment, the side effects of sore mouth, nausea and bad taste reported in this study are similar to the side effects that have been reported in previous studies of zinc gluconate.

In summary, in this preliminary study, troxerutin appeared to have an effect on rhinorrhea comparable to that reported for currently available common cold therapies. Current treat-

ments are associated with undesirable side effects of drowsiness and nasal drying for the antihistamines and nasal irritation for ipratropium bromide. The possibility that the rutosides might provide a safer and equally effective treatment for rhinorrhea deserves systematic evaluation.

Funding and study medications for this study were provided by Nordic Phytopharma Ltd., Brøndby, Denmark. Genny Connelly, BSN, was the study coordinator for the study.

REFERENCES

1. Gwaltney JM Jr, Hendley JO, Simon G, Jordan WS Jr. Rhinovirus infections in an industrial population. II. Characteristics of illness and antibody response. J Am Med Assoc 1967;202:494–500.
2. Rao SS, Hendley JO, Hayden FG, Gwaltney JM Jr. Symptom expression in natural and experimental rhinovirus colds. Am J Rhinol 1995;9:49–52.
3. Turner RB, Witek TJ Jr, Riker DK. Comparison of symptom severity in natural and experimentally induced colds. Am J Rhinol 1996;10:167–172.
4. Igarashi Y, Skoner DP, Doyle WJ, White MV, Fireman P, Kaliner MA. Analysis of nasal secretions during experimental rhinovirus upper respiratory infections. J Allergy Clin Immunol 1993;92:722–31.
5. Douglas RG Jr. Pathogenesis of rhinovirus common colds in human volunteers. Ann Otol Rhinol Laryngol 1970;79:563–71.
6. Vanscheidt W, Rabe E, Naser-Hijazi B, Ramelet AA, Partsch H, Diehm C, et al. The efficacy and safety of a coumarin-/troxerutin-combination (SB-LOT) in patients with chronic venous insufficiency: a double blind placebo-controlled randomised study. Vasa 2002;31:185–90.
7. Petruzzellis V, Troccoli T, Candiani C, Guarisco R, Lospalluti M, Belcaro G, et al. Oxerutins (Venoruton): efficacy in chronic venous insufficiency – a double-blind, randomized, controlled study. Angiology 2002;53:257–63.
8. Incandela L, Cesarone MR, DeSanctis MT, Belcaro G, Dugall M, Acerbi G. Treatment of diabetic microangiopathy and edema with HR (Paroven, Venoruton; 0-(beta-hydroxyethyl)-rutosides): a prospective, placebo-controlled, randomized study. J Cardiovasc Pharmacol Ther 2002;7 Suppl 1:S11–5.
9. Incandela L, Belcaro G, Renton S, DeSanctis MT, Cesarone MR, Bavera P, et al. HR (Paroven, Venoruton; 0-(beta-hydroxyethyl)-rutosides) in venous hypertensive microangiopathy: a prospective, placebo-controlled, randomized trial. J Cardiovasc Pharmacol Ther 2002;7 Suppl 1:S7–10.
10. Cesarone MR, Incandela L, DeSanctis MT, Belcaro G, Griffin M, Ippolito E, et al. Treatment of edema and increased capillary filtration in venous hypertension with HR (Paroven, Venoruton; 0-(beta-hydroxyethyl)-rutosides): a clinical, prospective, placebo-controlled, randomized, dose-ranging trial. J Cardiovasc Pharmacol Ther 2002;7 Suppl 1:S21–4.
11. Cesarone MR, Belcaro G, Incandela L, Geroulakos G, Griffin M, Lennox A, et al. Flight microangiopathy in medium-to-long distance flights: prevention of edema and microcirculation alterations with HR (Paroven, Venoruton; 0-(beta-hydroxyethyl)-rutosides): a prospective, randomized, controlled trial. J Cardiovasc Pharmacol Ther 2002;7 Suppl 1:S17–20.
12. Clement DL. Management of venous edema: insights from an international task force. Angiology 2000;51:13–7.
13. Rehn D, Hennings G, Nocker W, Diebschlag W. Time course of the anti-oedematous effect of O-(beta-hydroxyethyl)-rutosides in healthy volunteers. Eur J Clin Pharmacol 1991;40:625–7.
14. Renton S, Leon M, Belcaro G, Nicolaides AN. The effect of hydroxyethylrutosides on capillary filtration in moderate venous hypertension: a double blind study. Int Angiol 1994;13:259–62.
15. Cesarone MR, Laurora G, Ricci A, Belcaro G, Pomante P, Candiani C, et al. Acute effects of hydroxyethylrutosides on capillary filtration in normal volunteers, patients with venous hypertension and in patients with diabetic microangiopathy (a dose comparison study). Vasa 1992; 21:76–80.
16. Hayden FG, Herrington DT, Coats TL, Kim K, Cooper EC, Villano SA, et al. Efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses in adults: results of 2 double-blind, randomized, placebo-controlled trials. Clin Infect Dis 2003;36:1523–32.
17. Turner RB, Sperber SJ, Sorrentino JV, O'Connor RR, Rogers J, Batouli AR, et al. Effectiveness of clemastine fumarate for treatment of rhinorrhea and sneezing associated with the common cold. Clin Infect Dis 1997;25:824–30.
18. Gwaltney JM Jr, Druce HM. Efficacy of brompheniramine maleate for the treatment of rhinovirus colds. Clin Infect Dis 1997;25:1188–94.
19. Gwaltney JM Jr, Park J, Paul RA, Edelman DA, O'Connor RR, Turner RB. Randomized controlled trial of clemastine fumarate for treatment of experimental rhinovirus colds. Clin Infect Dis 1996;22:656–62.
20. Dockhorn R, Grossman J, Posner M, Zinny M, Tinkleman D. A double-blind, placebo-con-

trolled study of the safety and efficacy of ipratropium bromide nasal spray versus placebo in patients with the common cold. J Allergy Clin Immunol 1992;90:1076–82.
21. Diamond L, Dockhorn RJ, Grossman J, Kisicki JC, Posner M, Zinny MA, et al. A dose-response study of the efficacy and safety of ipratropium bromide nasal spray in the treatment of the common cold. J Allergy Clin Immunol 1995;95:1139–46.
22. Hayden FG, Diamond L, Wood PB, Korts DC, Wecker MT. Effectiveness and safety of intranasal ipratropium bromide in common colds: aA randomized, double-blind, placebo-controlled trial. Annals Intern Med 1996;125:89–97.
23. Park YC, Rimbach G, Saliou C, Valacchi G, Packer L, Son JK. Activity of monomeric, dimeric, and trimeric flavonoids on NO production, TNF-alpha secretion, and NF-kappaB-dependent gene expression in RAW 264.7 macrophages. FEBS Lett 2000;465:93–7.
24. Di Carlo A, Passi S, Ippolito F, Candiani C. Free radical scavenger activity of rutosides. Minerva Cardioangiol 2002;50:701–7.
25. Turner RB. The treatment of rhinovirus infections: progress and potential. Antiviral Res 2001; 49:1–14.
26. Macknin ML, Piedmonte M, Calendine C, Janosky J, Wald E. Zinc gluconate lozenges for treating the common cold in children. J Am Med Assoc 1998;279:1962–7.
27. Eby GA, Davis DR, Halcomb WW. Reduction in duration of common colds by zinc gluconate lozenges in a double-blind study. Antimicrob Agents Chemother 1984;25:20–4.
28. Al-Nakib W, Higgins PG, Barrow I, Batstone G, Tyrrell DA. Prophylaxis and treatment of rhinovirus colds with zinc gluconate lozenges. J Antimicrob Chemother 1987;20:893–901.
29. Farr BM, Conner EM, Betts RF, Oleske J, Minnefor A, Gwaltney JM Jr. Two randomized controlled trials of zinc gluconate lozenge therapy of experimentally induced rhinovirus colds. Antimicrob Agents Chemother 1987;31:1183–7.
30. Godfrey JC, Conant Sloane B, Smith DS, Turco JH, Mercer N, Godfrey NJ. Zinc gluconate and the common cold: a controlled clinical study. J Int Med Res 1992;20:234–46.
31. Mossad SB, Macknin ML, Medendorp SV, Mason P. Zinc gluconate lozenges for treating the common cold: a randomized, double-blind, placebo-controlled study. Ann Intern Med 1996; 125:81–8.
32. Smith DS, Helzner EC, Nuttall CE Jr, Collins M, Rofman BA, Ginsberg D, et al. Failure of zinc gluconate in treatment of acute upper respiratory tract infections. Antimicrob Agents Chemother 1989;33:646–8.
33. Weismann K, Jakobsen JP, Weismann JE, Hammer UM, Nyholm SM, Hansen B, et al. Zinc gluconate lozenges for common cold. A double-blind clinical trial. Dan Med Bull 1990;37:279–81.
34. Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. Clin Infect Dis 2000;31: 1202–8.
35. Turner RB. Ineffectiveness of intranasal zinc gluconate for prevention of experimental rhinovirus colds. Clin Infect Dis 2001;33:1865–70.
36. Hirt M, Nobel S, Barron E. Zinc nasal gel for the treatment of common cold symptoms: a double-blind, placebo-controlled trial. Ear Nose Throat J 2000;79:778–80, 782.