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REVIEW

A randomised, double-blind, placebo-controlled trial of a herbal medicinal product containing *Tropaeoli majoris* herba (Nasturtium) and *Armoraciae rusticanae* radix (Horseradish) for the prophylactic treatment of patients with chronically recurrent lower urinary tract infections

Uwe Albrecht [a], Karl-Heinz Goos [b] and Berthold Schneider [c]

[a] *Mediconomics GmbH, Hannover, Germany*

[b] *Repha GmbH, Biologische Arzneimittel, Langenhagen, Germany*

[c] *Institut für Biometrie, Medizinische Hochschule Hannover, Germany*

Address for correspondence: **Dr. Uwe W. Albrecht, Mediconomics GmbH, Hannover, Germany. Tel.: +49 (0) 511 560 998 0; Fax: +49 (0) 511 560 998 20; albrecht@mediconomics.com**

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ABSTRACT

Objectives: The aim of this study was to verify the efficacy and safety of a herbal medicinal product containing *Tropaeoli majoris* herba and *Armoraciae rusticanae* radix in the prophylactic treatment of chronically recurrent urinary tract infections (UTIs), and to test whether the medicinal product decreases the incidence of relapses over the study period.

Methods: A total of 219 adults aged between 18 and 75 years were screened and 174 patients enrolled. Of these 174 patients, a group of 45 patients were screening failures. Patients were randomised to receive either the study drug or placebo twice daily for 90 days. A UTI is confirmed by defined symptoms together with a laboratory result. The diagnosis of a new episode of a recurrent UTI included urine analysis from a central laboratory. The primary efficacy criterion – the number of recurrent UTIs over the study period – was tested between the treatment groups.

Results: For the per-protocol population, the mean number of recurrent UTIs in the study period was 0.43 versus 0.77 for the placebo group. This result is statistically significant ($p = 0.035$). A total of 36 patients in the test group and 37 patients in the placebo group reported adverse events. Two serious adverse events were reported in the placebo group and one serious adverse event in the treatment group (not associated with the study medication).

Conclusion: This randomised, double-blind, placebo-controlled trial demonstrates the efficacy and safety of the herbal medicinal product Angocin Anti-Infekt N* in the prophylactic treatment of chronically recurrent UTIs.

* Angocin Anti-Infekt N is a registered trade name of Repha GmbH, Langenhagen, Germany

Introduction

A urinary tract infection (UTI) is a condition where one or more structures in the urinary tract become infected after bacteria overcome the structures' strong natural defences. Despite these defences, UTIs are the most common of all infections and can occur at any time in the life of an individual. Almost 95% of UTI cases are caused by bacteria that typically multiply at the opening of the urethra and travel up to the bladder (the ascending route). Much less often, bacteria spread to the kidney from the bloodstream. Chronically recurrent UTIs, in particular, are a significant challenge in daily clinical practice. The common symptoms are dysuria, pollakisuria, suprapubic pain and urine anomalies. Most patients with recurrent UTIs are females. The reason for the predominance of this disease in women is the anatomical structure of the urethra, which is approximately 2–4 cm long in females – compared with 20–25 cm in males. Consequently, bacteria can easily access the bladder. Recurrence is common after both complicated and uncomplicated UTIs. After a single uncomplicated acute urinary tract infection, 27–48% of women will have a recurrence.

Recurrent infections are mostly due to underlying pathological circumstances (for instance, anomalies of the urinary tract) and, also caused by concomitant diseases (for instance diabetes mellitus), chronic trauma to the urinary tract (UTIs due to catheters), reflux of urine (for instance prostate hyperplasia), certain physiological circumstances (such as pregnancy), neurogenic damage, high sexual activity and, most importantly, insufficient hygiene.

Most infections are normally found in the lower urinary tract, the urethra and the bladder. However, such UTIs bear the problem that, in given circumstances, bacteria ascend to the kidney and cause an acute pyelonephritis. The worst possible outcome of such an event is a transition to the blood with resulting urisepsis, which may end in death. Therefore, infections of the lower urinary tract need to be treated carefully in order to avoid potential severe medical problems and also to relieve the uncomfortable symptoms.

Amongst the bacteria causing infections of the lower urinary tract, gram-negative bacteria are predominant. The most important bacterial strain involved is *Escherichia coli*. Other bacteria concerned are *Proteus* spp, *Klebsiella* spp, *Staphylococcus saprophyticus* and *Enterobacter* spp. Gram-positive bacteria play a less important role. This fact is important in the choice of adequate antibiotic therapy which is normally carried out with fluoroquinolones or cotrimoxazole.

At present, the prophylaxis of chronically recurrent UTIs in patients is problematic. In daily practice, low-dose administration of antibiotics is frequently chosen (cotrimoxazole, trimethoprime, nitrofurantoin, fluoroquinolones). These have proven to be efficacious to a certain degree. However, long-term administration of classical antibiotics is associated with the development of resistance of certain bacterial strains. In addition, potential side-effects of long-term treatment, such as neuropathies, may occur. Due to these safety factors, many physicians do not carry out long-term prophylaxis with classical antibiotics.

Angocin Anti-Infekt N is a herbal medicinal product (film-coated tablets) containing two active ingredients: horseradish root (*Armoraciae rusticanae* radix) 80 mg and nasturtium (*Tropaeoli majoris* herba) 200 mg. For these two active ingredients an antimicrobial efficacy has been proven *in vitro*[1–12], which is based on the isothiocyanates (mustard oils). The herbs contain different isothiocyanates – in horseradish root, alylisothiocyanate and phenylethylisothiocyanate are the relevant mustard oils; in nasturtium, benzylisothiocyanate is the corresponding mustard oil. In a recent *in vitro* study[13], the investigators confirmed previous reports of the antibacterial properties of mustard oils. The antimicrobial testing of a combination of nasturtium and horseradish revealed broad antibacterial activities against clinically relevant pathogens covering both gram-positive and gram-negative organisms. The study demonstrated that the combination of the two active ingredients leads to an additive activity. The results prove that there is a rational basis for treatment of both UTIs and upper respiratory tract infections with this medicinal product. It is important to emphasize that no bacterial resistance against the isothiocyanates has been observed.

The inactive prodrugs of the mustard oils, glucosinolates, are activated by myrosinase. The routes of excretion for isothiocyanates are the kidneys. Therefore an even higher local concentration can be achieved in the urinary tract and utilized for the treatment of UTIs. Most isothiocyanates are eliminated unchanged and some are metabolized. Pharmacokinetic investigations have shown that a high amount of the administered dose is recovered in the urine[3]. With regard to the daily dose for prophylactic treatment of chronically recurrent UTIs, a regimen has been chosen based on clinical experience with the medicinal product in the identical composition over decades of use in the daily practice.

There is a vast clinical experience published in the scientific literature for the treatment of bacterial infections with Angocin Anti-Infekt N[14–20]. However, this trial is the first randomised controlled clinical trial carried out in accordance with the relevant guidelines of the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use – Guideline for Good Clinical Practice (ICH-GCP).

Patients and methods

Study design

This multicentre study was conducted as a prospective randomised, double-blind, placebo-controlled trial with parallel groups in patients suffering from chronically recurrent UTIs. The goal of the study was to investigate the efficacy and safety of Angocin Anti-Infekt N versus placebo in the prophylactic treatment of chronically recurrent UTIs.

During a screening visit (visit 1, day 1) the inclusion and exclusion criteria were checked and informed consent was obtained. Medical history and demographic data were recorded. The status of an acute UTI was confirmed by urine analysis (stix, investigation of the midstream urine specimen in the central laboratory). Treatment with either cotrimoxazole or ciprofloxacin was initiated. Seven days after visit 1 the patient attended the study site for visit 2. The result of the antibiotic treatment was checked and investigated to establish whether the acute exacerbation of the UTI was cured. If healing was confirmed positively, patients were further randomised to receive either the study medication or placebo. Study medication for the first 30 days was handed out. Further visits to the study site were conducted at intervals of 30 days (visits 3, 4 and 5). At each visit blood pressure, pulse and body temperature were recorded as well as the potential occurrence of adverse events. It was confirmed that no new acute UTI existed (stix and investigation of midstream urine specimen in the central laboratory). Patient satisfaction (satisfaction with the treatment) was recorded on a visual analogue scale ranging from 0 to 10. Study medication was given to the patient at each visit and compliance was recorded in a drug accountability sheet.

In cases where a patient visited the study site between scheduled visits with an acute exacerbation of a UTI, an extra visit was carried out. The patient was then treated according to the decision of the physician and returned to receive study medication after confirmation of healing of the acute exacerbation.

The prophylactic treatment with study medication or placebo ended after 90 days and a physical examination, including physical signs (blood pressure, pulse, body temperature), was carried out.

Subsequent to the end of the prophylactic treatment, two further visits were conducted (visit 6 at 120 days and visit 7 at 180 days after visit 2). During these visits the occurrence of a recurrent UTI and potential adverse events were recorded. At study end a physical examination was performed.

The physician recorded all confirmed recurrent UTIs prior to study start. During the course of the study an additional record was completed in which the physician recorded all recurrent UTIs, the treatment administered and the status of the patient.

This study was conducted according to ICH-GCP. The study protocol was approved by the independent ethics committees responsible for the respective study site.

Patients

A total of 219 patients were recruited in 35 active centres in Germany. The inclusion criteria were adults of both genders aged from 18 to 75 years with a medical history of at least three recurrent UTIs according to the records of the physician: two of the recurrent UTIs had to have been recorded during the past 6 months prior to study start. The patient had to present to the study site with an acute exacerbation of a UTI. For safety reasons, females of childbearing potential needed to employ an adequate contraception. The patient was asked to sign an informed consent form as approved by the independent ethics committee. Those non-eligible were patients with progression of the infection from the proximal end of the bladder with systemic involvement (pyelonephritis, urisepsis), irritable bladder syndrome, abnormalities or obstruction of the urinary tract, medical history of surgery of the urinary tract, chronic organic dysfunction (for instance, chronic renal insufficiency), acute infection except the UTI, pyelonephritis, acute ulcers of the stomach or duodenum, known hypersensitivity to one of the ingredients, concurrent participation in a clinical trial or participation in a clinical trial in the past 14 days prior to study entry.

Treatment

Patients were randomised to receive either Angocin Anti-Infekt N film-coated tablets in a dosage of 2 tablets twice daily or placebo tablets in the identical dosage. Treatment was initiated at visit 2 after confirmation of successful healing of the acute UTI and was to last until day 90 of the study period. One tablet of the active study medication (Angocin Anti-Infekt N, Repha GmbH, Langenhagen, Germany) contained horseradish root 80 mg and nasturtium 200 mg. The placebo contained inactive ingredients (celluloses, iron oxides and hydroxides E 172, hypromellosis, macrogol, potato starch, sodium carboxy methyl starch, highly dispersed silicon dioxide, stearine acid, talcum, titanium dioxide E 171) only.

Placebo tablets were similar in appearance to the active drug tablets. One box of the study medication was supplied to each patient at the start of treatment and thereafter at visits 3, 4 and 5 for the respective intervals of 30 days each. Tablets were produced in

accordance with GMP standards and, for the herbal components, standardised tests for the content were employed. Tablets were packaged into plastic containers according to GMP. The patients were asked to take the tablets after a meal with some fluid.

Randomisation and blinding

Patients were distributed to one of the two treatment groups and allocated randomly generated treatment numbers provided by the independent statistician. Packaging according to the randomisation list was carried out by the contract manufacturer.

Treatment boxes were then transported to the study sites. No interference by the manufacturer was therefore possible. Only the 'master of the graduated plan' held a sealed randomisation list for emergencies, but blinding was maintained and the code remained unbroken. Allocation of the treatment numbers to the medication was carried out by the manufacturer according to the randomisation list. 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 blinding was maintained during review of the complete database for patients' validity and allocation to the populations of statistical analysis. Thereafter, the database was frozen and the code broken for statistical evaluation.

Safety

Safety variables were clinical signs, frequency and severity of reported adverse events, together with clinical laboratory tests (blood count, AST, ALT γ-GT) as well as body weight, body temperature, blood pressure and pulse rate recorded at each visit.

Statistical analysis and sample size

It was assumed that the two treatment groups showed identical standard deviations regarding the number of recurrent UTIs during the study period. Should the mean number of recurrences in the test group (μ-test) be half of the standard deviation lower as the mean number of recurrences in the placebo group (μ placebo) $(\mu \text{ test} - \mu \text{ placebo})/\sigma = -½$), then a significant result with a probability (power) of 0.8 on the one-tailed level $\alpha = 0.05$ could be expected. In order to achieve this, a sample size of 51 patients per group (total 102 patients) was required. In a clinical trial performed by Tammen[21] which include 150 subjects, a standard deviation of approximately one UTI recurrence within 6 months was reported. Assuming the identical standard deviation for this study, a significant result with a power of 0.8 and a sample size of 100 patients was expected to be achieved, if the mean frequency of recurrences in the test group would be ½ lower than the mean in the placebo group.

The de-blinding was planned subsequent to a blinded data review and freeze of the database. For the analysis of all data between the treatment groups descriptive statistical methods (calculation of the means, standard deviations for quantitative variables, frequency of the contingency tables for categorical variables) were employed. The baseline values between the groups were compared by applicable statistical methods (*t*-distribution test, χ^2-adoption test etc.).

The primary efficacy criterion was chosen to be the difference of the means between the groups regarding the number of clinically confirmed recurrences during the study period tested by the *t*-distribution test. The nil hypothesis, that the number of recurrences in the test group was not lower than in the placebo group ($\mu \text{ test} \geq \mu \text{ placebo}$), was to be tested against the alternative hypothesis that this was not lower ($\mu \text{ test} < \mu \text{ placebo}$). The error probability to reject the nil hypothesis in error, was determined to be $\alpha = 0.05$.

It was laid down to carry out the statistical analysis for the intent-to-treat data set (ITT) as well as for the per-protocol data set (PP). It was determined that into the ITT data set, all patients would be subsumed, who were randomised and were available at least at visit 3. For patients participating in the clinical trial for < 6 months, it was planned to extrapolate the number of recurrences for the 6-month period based on a linear model. Furthermore it was laid down that only those patients would be part of the PP data set, which participated regularly for 6 months, attended the scheduled visits according to the protocol and did not show major protocol violations (for instance non-compliance).

The patients' satisfaction – measured with a visual analogue scale – had to be analysed statistically as secondary efficacy criterion and be compared between the treatment groups by the *t*-distribution test. For the visual analogue scale, 'very bad' was applicable for the worst and 'excellent' for the best judgement, whereas this was related to the general well-being and the satisfaction with the treatment. Satisfaction with the treatment was not a measure for efficacy and safety of the therapy.

Each AE had to be recorded in conjunction with supplementary information (severity, duration, relationship to study drug, action taken, results). The frequency of adverse events had to be compared between the treatment groups.

Results

In 35 active study sites a total of 219 patients were enrolled. One study site (the site of the principal investigator) was the outpatient department of a hospital. All other study sites were private practice. The flow of the patients through the study is shown in Table 1.

A total of 45 patients were not randomised and did not receive study medication. The remaining 174 patients were attributed to the ITT population. Out of these, 84 patients (48.3%) were treated with the active study medication and 90 patients (51.7%) with placebo. According to the protocol, the study was completed by 131 patients. For 28 patients, the acute UTI was not cured at visit 2.

Two patients in the test group (2.4%) and two patients in the placebo group were males (2.2%). All other patients were female. The mean age in the test group was 56.52 years (s = 18.83 years) and in the placebo group 52.32 years (s = 21.56 years). The difference is statistically not significant (p = 0.174, t-test). Means and standard deviations are displayed for height, weight, blood pressure, pulse and body temperature for visit 1 in Table 2. There are no statistical significant differences between the groups.

All patients were attributed to the PP population which did not have a UTI at visit 2 (start of prophylactic treatment) and who finished the study according to the protocol. This group comprises a total number of 103 patients. A total of 51 patients (49.5%) were treated with the active medication and 52 (50.5%) received placebo.

Efficacy

Intention-to-treat

In the ITT population, the mean number of UTI relapses from start of prophylaxis until end of the study, was for the test group 0.65 and for the placebo group 0.64. The difference is not statistically significant (p (one-sided) = 0.476, t-test). For the period of 180 days (180 × number/time of observation), the mean number of UTI relapses was 0.74 for the test group and 0.63 for the placebo group (p (one-sided) = 0.260, t-test). For the period of prophylactic treatment (maximum 90 days) the mean number of UTI relapses was 0.44 for the test group and 0.39 for the placebo group (p (one-

Table 1. *Patient flow*

Action	Visit 1 Screening day –7	Visit 2 Starting prophylaxis day 1	Visit 3 day 30	Visit 4 day 60	Visit 5 day 90	Visit 6 Follow-Up day 120	Visit 7 Follow-up day 180
Written informed consent	X						
Inclusion/exclusion criteria	X	X*					
Medical history	X						
Vital parameters	X	X	X	X	X	X	X
Treatment with standard antibiotic	X						
Randomisation (hand-over of the randomised study medication)		X					
Reconciliation of the study medication		X	X	X			
Treatment with 2 × 2 tab./day		X	X	X	X		
Return of the study medication			X	X	X		
Blood sample	X				X		
Urine test	X	X	X	X	X	X	X
Patient satisfaction		X	X	X	X	X	X
Concomitant medication, starting from visit 2	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X

*No infection by urine sticks proven (if required analysis of the sediment)

Table 2. Data for the ITT population at visit 1

	Angocin			Placebo			Total		
	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*N*
Age	56.52	18.83	84	52.32	21.56	90	54.35	20.34	174
Height (cm)	166.18	8.00	84	165.50	6.14	90	165.83	7.08	174
Weight (kg)	71.46	13.96	84	68.64	13.43	90	70.00	13.72	174
Blood pressure systolic	128.83	17.12	84	124.51	18.05	90	126.60	17.69	174
Blood pressure diastolic	77.26	9.78	84	75.08	10.49	90	76.13	10.18	174
Pulse	74.06	8.56	84	73.24	7.99	90	73.64	8.25	174
Body temperature	36.90	0.66	84	36.78	0.53	90	36.84	0.60	174

sided) = 0.260, *t*-test). For 90 days the mean number of UTI relapses for the test group was 0.43 and for the placebo group 0.37 (p (one-sided) = 0.280).

Per protocol

In the PP population, the mean number of UTI relapses during the entire study period was 0.43 for the test group and 0.77 for the placebo group. This difference is statistically significant (p (one-sided) = 0.035, *t*-test). For 180 days, the mean number of UTI relapses for the test group was 0.43 and for the placebo group 0.75 (p (one-sided) = 0.039, t-test). For the period of prophylactic treatment (maximum 90 days) the mean number of UTI relapses for the test group was 0.29 and for the placebo group 0.42 (p (one-sided) = 0.175, t-test). For 90 days the mean number of UTI relapses was 0.28 for the test group and 0.41 for the placebo group (p (one-sided) = 0.167).

Means and standard deviations for UTI relapses for the period of prophylactic treatment (between visits 2 and 5), subsequent to prophylactic treatment (between visit 5 and 7) and in total (between visits 2 and 7) are displayed in Table 3. For all periods the mean number of UTI relapses is lower in the test group compared with the placebo group. On the one-sided level α = 0.05 the differences for the period subsequent to prophylactic treatment (visits 5–7) and for the entire period between visit 2 and 7 are statistically significant (p (one-sided = 0.019 respectively 0.035). The nil hypotheses has therefore to be rejected and it has to be assumed that for the treatment with the test medication a lower number of UTI relapses is proven.

Means and standard deviations of days with prophylactic treatment and the entire study duration are displayed in Table 4, those of UTI relapses related to 90 days and 180 days are displayed in Table 5. The difference of the mean duration for the two groups is not statistically significant. The difference in the number of UTI relapses for 180 days is statistically significant on the one-sided level 0.05 significant (p = 0.039).

Patient satisfaction

Patient satisfaction with the therapy was recorded by the patient on a visual analogue scale. In both groups, at all visits, satisfaction with the therapy was judged with a mean score of 0.7. There is no statistical significant difference between the groups.

Safety

In all, 36 patients in the test group and 37 patients in the placebo group reported adverse events. One patient in the test group and two patients in the placebo group recorded serious adverse events (SAEs), none of which were associated with the study medication. One patient in the test group presented with a head wound and commotio cerebri. One patient from the placebo group was diagnosed with cancer of the duodenum. The second SAE in the placebo group was attributed to an episode of arterial hypertension and tachycardia, which made hospitalisation necessary. The adverse events observed were: nausea, flatulence, dysuria, vertigo, edema, hyperhidrosis, elevation of liver enzymes, allergy against test medication, nutritional allergy and laryngitis. There are no statistically significant differences between the treatment groups. The analysis of blood parameters (day –7, day 90), analysed in a central laboratory, did not reveal any adverse events.

Discussion

The data of this clinical study suggest the clinical efficacy and safety of Angocin Anti-Infekt N as a prophylactic treatment for chronically recurrent UTI.

For the PP data set, the mean number of UTI relapses for the entire study period for the test group was 0.43 versus 0.77 for the placebo group. This difference is statistically significant (p (one-sided) = 0.035, *t*-test). Therefore the clinical efficacy of the prophylactic

Table 3. *Confirmed UTI per patient during, following prophylaxis and total (PP)*

	Angocin			Placebo			Total		
	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*N*
No. UTI relapses between visit 2 and visit 5	0.29	0.50	51	0.42	0.85	52	0.36	0.70	103
No. UTI relapses between vist 5 and visit 7	0.14	0.45	51	0.35	0.56	52	0.24	0.51	103
No. UTI relapses between visit 2 and visit 7	0.43	0.78	51	0.77	1.06	52	0.60	0.94	103

Table 4. *Duration of prophylactic treatment and entire study duration (PP)*

	Angocin			Placebo			Total		
	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*N*
Duration prophylactic treatment (days)	93.59	7.10	51	93.27	8.36	52	93.43	7.73	103
Entire study period (days)	188.57	31.58	51	183.29	11.37	52	185.90	23.68	103

Table 5. *Number of UTIs during prophylactic treatment and total per 90 and 180 days (PP)*

	Angocin			Placebo			Total		
	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*N*
No. UTIs per 90 days	0.28	0.49	51	0.41	0.84	52	0.35	0.69	103
No. UTIs per 180 days	0.43	0.77	51	0.75	1.04	52	0.59	0.93	103

treatment with Angocin Anti-Infekt N versus placebo is suggested to be proven.

The primary efficacy criterion – the comparison of the number of relapses over the study period – was chosen in order to prove the efficacy of the medicinal product in a specific patient population. During enrolment of patients it was observed that the number of patients meeting the stringent inclusive and exclusive criteria was limited. This is due to the fact that after diagnosis, treatment with a standard antibiotic was started by the physician and healing was not confirmed as patients did not return for a follow-up visit. Therefore, there is a degree of uncertainty whether patients suffered from reinfections or from a relapse. Approximately 80% of recurring UTIs are reinfections occuring several weeks after antibiotic treatment has cleared up the initial episode. A different bacterial strain from the one that caused the original episode then needs to be treated. In certain circumstances, a long-term treatment with antibiotics is the preferred treatment option. However, this might lead to unwanted medical complications. Moreover, the resistance of bacteria against standard antibiotics is a substantial problem. This is also reflected in the study results, for instance in the ITT data set. The results are different from the analysis of the PP data set. This is due to the fact that for 28 patients at the start of prophylactic treatment (visit 2) the UTI was not completely cured with the standard antibiotics utilised in this study.

As the efficacy of Angocin Anti-Infekt N has been observed over decades in daily practice, it was the goal to verify former clinical investigations in an ICH-GCP clinical study. The sample size calculation for the study was based on published scientific data. The rationale for the assumption of a successful outcome of the trial was supported by recent *in vitro* studies. These confirmed the excellent antibacterial efficacy of the active ingredients of Angocin Anti-Infekt N. The mustard oils from horseradish root (alylisothiocyanate and phenylethylisothiocyanate) and the corresponding mustard oil contained in nasturtium (benzylisothiocyanate) revealed broad antibacterial activities against clinically relevant pathogens. The *in vitro* study demonstrated that the combination of the two active ingredients leads to a synergistic activity. Therefore it was important to verify the results in a clinical study.

A potential weakness of the study is that although the study was finalised with a PP data set according to the target sample size, a number of patients failed to enter the treatment phase with active treatment.

This was due to the fact that 28 patients were not cured with standard antibiotic treatment at the start of prophylaxis. In total, 219 adults were screened and 174 patients enrolled. Out of these 174 patients, a group of 45 patients were screening failures. The study design to enrol patients who are only present with complete healing after an initial treatment with standard antibiotics is a potential strength of the study as this potentially gave evidence of treatment failures with standard antibiotic treatment.

Conclusion

The results of this prospective randomised placebo-controlled study suggest the efficacy and safety of Angocin Anti-Infekt N as a herbal medicinal product in the prophylactic treatment of chronically recurrent UTIs. The treatment can be regarded as a benefit for this special patient population, mostly women. A dose of 2 tablets twice daily of Angocin Anti-Infekt N is recommended. Based on these results, Angocin Anti-Infekt N may provide physicians with an alternative to long-term treatment with standard antibiotics. This study suggests efficacy and safety for a treatment period of 90 days.

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References

1. Gruia F.S. Möglichkeiten der Infektionsbehandlung in der Praxis. Eine klinische Studie. Erfahrungsheilkunde Acta Medica Empirica 1986;7:486-490
2. Halbeisen T. Untersuchungen über die antibiotischen Wirkstoffe von Tropaeolum majus. Naturwissenschaften 1954;41:378
3. Halbeisen T. Untersuchung des antibiotischen Wirkstoffes einer höheren Pflanze (Tropaeolum maius – Kapuzinerkresse). Medizinische 1954;36:1212
4. Halbeisen T. Eine antibiotisch wirksame Substanz aus Cochlearia Armoracia L. Arzneim Forsch Drug Res 1957;7:321
5. Kienholz M. Die antibakterielle Wirkung ätherischer Öle aus Meerrettichwurzel. Arzneim Forsch Drug Res 1960;10:917
6. Orzechowski G. Antimikrobiotika in höheren Pflanzen und die Problematik der Therapie mit Antibiotika. Pharm Rundsch 1961;3:41
7. Rudat KDLJM. Über die bakterienhemmende Wirkung der in der Kapuzinerkresse enthaltenen antibiotischen Stoffe, insbesondere gegen aerobe Sporenbildner. Pharmazie 1955;10:729
8. Schmidramsl H. Angocin® Kresse und Meerrettich bei Atemwegsinfekten. Ergeb Therapiestudie 1998:1-5
9. Thiel H. Erfahrungen mit Angocin in der Praxis. Hippokrates 1958;18:1-7
10. Winter AGWL. Über Antibiotika. in höheren Pflanzen: Vl. Mitteilung Gasförmige Hemmstoffe aus Tropaeolum majus und ihr Verhalten im menschlichen Körper bei Aufnahme von Tropaeolum-Salat per os. Naturwissenschaften 1952;39:236
11. Winter AG. Antibiotische Therapie mit Arzneipflanzen. Planta Med 1955;3:1
12. Gaase A. Bakteriologische Empfindlichkeitstestung eines Antibiotikums. Ärztl Prax 1968;20:667
13. Conrad et al. In-vitro-Untersuchungen zur antibakteriellen Wirksamkeit einer Kombination aus Kapuzinerkressenkraut (Tropaeoli majoris herba) und Meerrettichwurzel (Armoracia rusticanae radix). Arzneim Forsch Drug Res 2006;56(12): 842-9
14. Goos KH, Albrecht U, Schneider B. Efficacy and safety profile of a herbal drug containing nasturtium herb and horseradish root in acute sinusitis, acute bronchitis and acute urinary tract infection in comparison with other treatments in the daily practice/results of a prospective cohort study. Arzneim Forsch Drug Res 2006;56:249
15. Göres EKU. Ermittlung der Senfölkonzentration im Probandenharn nach. Gabe von Angocin Anti-Infekt N. Berlin: Prüfbericht Biopharm, 1997
16. Schaffer R.J. Untersuchungen zur in vitro-Wirksamkeit von Benzylsenföl gegen pathogene Bakterien und Sprosspilze. Dissertation, Köln. 1980.
17. Winter AGHM. Untersuchungen über Antibiotika in höheren Pflanzen: IX. Mitteilung: Gasförmige Hemmstoffe aus Cochlearia armoracia (Meerrettich) und ihr Verhalten im menschlichen Körper bei Aufnahme per os. Naturwissenschaften 1953;40:489
18. Germer WD. Ein neues Präparat für die antibiotische Therapie auf pflanzlicher Grundlage. Dtsch.Med.Wochenschr 1954;79:1445
19. Klesse PLR. Untersuchungen über die bakteriostatische Wirksamkeit einiger Senföle. Arzneim.-Forsch./ Drug Res 1955;5:505
20. Stickl H. Über eine antibiotisch wirksame Pflanzensubstanz. Dtsch.Med.Wochenschr. 1954;79:1722
21. Tammen H. Immunobiotherapy with Uro-Vaxom in recurrent urinary tract infections: The German Urinary Tract Infection Study Group. Br J Urol. 1990;65(1):6-9

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