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Acute Otitis Externa: Efficacy and Tolerability of N-Chlorotaurine, a Novel Endogenous Antiseptic Agent

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Objective: **The study's objective was to test the tolerability and efficacy of the endogenous antiseptic N-chlorotaurine (NCT) in comparison with a standard clinical treatment according to a phase IIb clinical trial protocol.** ***Study Design:*** **The antimicrobial agent NCT was compared with the antibiotic component drops Otosporin (containing neomycin, polymyxin B, and hydrocortisone) for topical treatment of acute otitis externa in a randomized and rater-blinded clinical study.** ***Methods:*** **Fifty patients suffering from acute otitis externa were divided into two groups according to a randomized list. The test group was treated with 1 mL of 1% aqueous NCT solution, the reference group with 1 mL of Otosporin. The substances were applied to the external ear canal at one daily session until the signs of infection disappeared. Efficacy and tolerability were evaluated daily by visual analogue scale and a six-step infection score. In addition, smears were analyzed to identify the causative pathogens.** ***Results:*** **Both medications were equally well tolerated by the patients. The treatment was successful for all patients of the NCT group, whereas in one patient from the reference group, the infection did not disappear. The inflammation score improved more rapidly in the NCT group, which resulted in an earlier termination of the therapy. This difference became highly significant on days 4 to 7 ($P < .01$ each). Time needed for disappearance of inflammation (score 0) was 5.6 ± 1.6 (mean ± SD, range 3–9) days in the NCT group and 7.4 ± 1.6 (range 4–10) days in the Otosporin group ($P < .001$). As expected, microbiologic cultures from ear swabs revealed *Pseudomonas aeruginosa* (58%) followed by *Staphylococcus aureus* (18%) as the main causative pathogens.** ***Conclusions:*** **NCT appears to be well tolerated and more effective than the therapy using antibiotic component drops. Because of its endogenous nature and its higher efficacy, NCT appears to be a good choice for topical treatment of acute otitis externa.** ***Key Words:*** **N-chlorotaurine, Otosporin, otitis externa, swimmers ear.**

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INTRODUCTION

Acute otitis externa is a frequent disease mostly caused by bacteria and triggered by moisture ("swimmer's ear").[1] The dominating pathogens are *Pseudomonas aeruginosa* and *Staphylococcus aureus*; in about 10% of cases, fungi (mostly *Aspergillus spp.*) are detected.[2] Pseudomonas infections sometimes also spread to osteomyelitis, a life-threatening complication that has to be treated systemically (malignant otitis externa).[3] Apart from theses cases, application of ear drops is generally the treatment of choice because a high concentration of active agents can be delivered to the site of infection with a minimum of adverse effects. Drugs applied range from single compounds such as acetic acid solution and antibiotics like neomycin, polymyxin B, quinolones, and aminoglycosides to various combinations of antibiotics, some including additional steroids.[1,2] Generally, it takes 5 to 7 days of treatment until the infection completely disappears.[1] The standard therapy that has proven successful for many years in our department is the application of Otosporin (containing neomycin, polymyxin B, and hydrocortisone) (Glaxo Wellcome Pharma, Vienna, Austria) delivered by a cotton-wool swab.

Nevertheless, antiseptics should generally be preferred to antibiotics for topical applications because they provide a broad spectrum against pathogens without development of resistance. However, local irritative effects and the potential ototoxicity limit their use in the outer

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ear canal, in particular if swelling is severe and perforation of the tympanic membrane may occur.[4]

An efficient treatment of otitis externa could be achieved using N-chlorotaurine (NCT), an endogenous antimicrobial agent that is currently under investigation for topical application of various infections at our university.[5–9] The substance is an endogenous, long-lived oxidant normally generated by leukocytes during inflammation,[10–13] and it has microbicidal activity against gram-positive and gram-negative bacteria and fungi including the above-mentioned pathogens.[14–17]

In addition to its microbicidal activity, NCT exhibits a good tolerability of tissue without signs of allergic reactions. The possible risk of ototoxicity was already tested in two previous studies. On instillation of 0.1% to 10% solution to the middle ear in a mouse model, no damage of the inner ear could be detected. The only side effect was a delay of healing of an artificial perforation of the tympanic membrane, which was used for the application of the agent.[9]

The aim of the present study was to test the efficacy and tolerability of NCT in acute otitis externa compared with Otosporin (the standard medication used in our hospital) on the basis of a phase IIb clinical trial protocol. Special emphasis was given to quantify the effect of treatment using the visual analogue scale and an infection score.

MATERIALS AND METHODS

Reagents

Pure NCT as a crystalline sodium salt[18] was dissolved in sterile distilled water to a concentration of 1% (55 mmol/L). Purity was verified by iodometric titration and spectrophotometry. Because aqueous solutions of NCT exhibit a pH of 8 and a broad spectrum activity against pathogens, no preservatives and buffers were added. Solutions were stored at 2°C to 4°C and allowed to reach room temperature before application to the patients.

The agent applied in the reference group, Otosporin (Glaxo Wellcome Pharma, Vienna, Austria), is a solution containing 1.27 mg of polymyxin B sulfate, 5 mg of neomycin sulfate, and 10 mg of hydrocortisone per milliliter. It was stored at room temperature and protected from light.

Study Design

A randomized, controlled, clinical study was performed in 50 outpatients, 25 who were treated with NCT (test group) and 25 with Otosporin (control group). Patients were numbered consecutively and assigned to the groups according to a randomization code. Because of the markedly different viscosity of the substances (higher viscosity of the antibiotic solution), the application of the substances could be only blinded for the patient.

The evaluation of the symptoms was performed by an independent ear, nose, and throat (ENT) specialist according to a double-blinded protocol. The complete study was performed in accordance with the Declaration of Helsinki and was approved by the ethical committee of the University of Innsbruck. All patients contributing to the study gave their written informed consent to the protocol.

Subjects

The population under study comprised 22 female and 28 male outpatients, ranging from 8 to 89 years of age, median 34 years (Table I). Inclusion criterion was the presence of acute otitis externa, which was diagnosed by an ENT doctor at the outpatient department. Exclusion criteria were malignant otitis externa, topical treatment with other agents, systemic application of antibiotics or corticoids, pregnancy, and participation in another study at the same time.

Evaluation of Symptoms

Medical status was determined on the basis of the individual medical patient history including medication and detailed otorhinolaryngologic examination. Primary criterion for the judgment of the inflammation was a six-scale score (0–5) based on the visually observed extent of inflammation (0 = outer ear canal without signs of inflammation, 5 = serious inflammation with ear canal completely obstructed by swelling).

As a secondary criterion, the intensity of pain before every application procedure was quantified by visual analogue scale (0 = no pain, 10 = intolerable pain). Assessment of symptoms was performed daily by clinical examination. The time in days required until complete healing (score 0) was considered as the endpoint criterion for the termination of the study.

The bacterial origin of the disease was verified by qualitative cultural and biochemical characterization of pathogens gained from smears from the external ear canal before the beginning of each treatment. Susceptibility to neomycin and polymyxin B was tested by standard disk diffusion test.

Treatment and Time Course

For both groups, the substances were applied once daily to the outer ear canal using a rolled cotton "wick" soaked with the agent. This ear wick was left in place and was changed daily at the outpatient department until the inflammatory symptoms disappeared (i.e., corresponding to an inflammation score of 0). In the test group, an additional dose of 1 mL of NCT solution was instilled immediately before application of the next wick, as soon as the diameter of the ear canal had increased. This procedure was performed to avoid rapid drying of NCT because of its low viscosity.

Statistical Analyses

Baseline characteristics, inflammation scores, days until healing, and pain were compared between both treatment groups using the Mann-Whitney U test. The scores of all premature drop-outs were evaluated on an intention-to-treat basis. For microbiologic results and for categorical baseline characteristics such as sex, a chi-square test was applied. $P < 0.05$ was consid-

TABLE I.
Patient Profile.

	NCT	Otosporin	*P* Value
Age	34 (13–89)*	34 (8–89)*	>0.05
Sex	13 female	9 female	>0.05
	12 male	16 male	>0.05
Positive cultures†			
P. aeruginosa	14	15	>0.05
S. aureus	5	4	>0.05
Other pathogens	2	4	>0.05
Duration of study therapy (days)	5 (3–9)*	8 (4–9)*	<0.001

*Values are shown as median (minimum to maximum).
†Number of patients out of 25 showing positive cultures from swabs.
NCT, N-chlorotansine.

ered to indicate statistical significance. Bonferroni's correction was applied to account for multiple comparison because of the daily calculation of the scores.

RESULTS

The evaluation of pathogens causing otitis externa showed *Pseudomonas aeruginosa* (29 cases, 58% of patients) and *Staphylococcus aureus* (9 cases, 18% of patients) as the dominating pathogens (Table I). *Proteus mirabilis* was found in two (4%) cases, *Streptococcus pyogenes*, *Escherichia coli*, *Enterococcus sp.*, and *Aspergillus sp.* in one (2%) case each. All bacteria detected were susceptible to either neomycin or polymyxin B. There was no baseline difference between the study groups regarding demographic values and severity of inflammation (Tables I and II).

Tolerability of Treatment

Both kinds of therapy were completely performed according to the study protocol and were tolerated very well by the patients. All subjects contributing completed the study. As expected, during application of the ear wicks, increased pain was noted by the patients, which lasted less than 10 minutes (maximum) independent of agent applied. There were no signs of allergic reactions and no increase of inflammation symptoms during the whole period of treatment. No dizziness and no nystagmus occurred.

Efficacy of Treatment

In both groups except in one patient of the control group, the treatment of acute otitis externa was successful. The average score of inflammation decreased gradually from day to day, but the improvement appeared more rapidly in the test group as compared with the control group (Fig. 1) (Table II). The difference became significant on day 3 ($P = .02$) and highly significant on days 4 to 7 ($P < .01$ each) (Table II). This was still true for days 4 to 7 according to Bonferroni's correction for multiple comparisons. Accordingly, the time needed to achieve complete disappearance of inflammation (score 0) was shorter in the NCT group (i.e., 5.6 ± 1.6 [mean ± SD, range 3–9] days compared with 7.4 ± 1.6 days in the Otosporin group [mean ± SD, range 4–10 days, $P < .001$]. For instance, on day 5, 13 (52%) of 25 subjects treated with NCT and 4 (16%) treated with the standard medication did not show further symptoms (Table II).

In 1 patient of 25, an 89-year-old woman, Otosporin was not effective, although the causative *P. aeruginosa* was susceptible in vitro. In this particular case, the therapy was changed at a score of 4 after 9 days. After changing to the treatment with NCT, the score improved to 3 within 1 day and to 2 within 4 days; after 8 days, the signs of inflammation disappeared completely.

In the patients who received NCT, the pain before instillation evaluated by visual analogue scale decreased

TABLE II.
Scores of Inflammation.

	Day No.								
	1	2	3	4	5	6	7	8	9
NCT	No. Out of 25 patients								
Score									
0	0	0	1	6	13	20	22	24	25
1	0	1	2	7	6	4	3	1	0
2	0	3	11	8	5	1	0	0	0
3	4	12	8	4	1	0	0	0	0
4	10	6	3	0	0	0	0	0	0
5	11	3	0	0	0	0	0	0	0
Median score	4	3	2	1	0	0	0	0	0
Range	3–5	2–5	0–4	0–3	0–3	0–2	0–1	0–1	0–0
Otosporin									
Score									
0	0	0	0	1	4	7	10	21	23
1	0	0	3	5	6	7	13	2	1
2	0	2	3	7	6	8	0	1	0
3	6	7	10	6	7	1	1	0	0
4	10	11	7	6	2	2	1	1	1
5	9	5	2	0	0	0	0	0	0
Median score	4	4	3	2	2	1	1	0	0
Range	3–5	2–5	1–5	0–4	0–4	0–4	0–4	0–4	0–4
P value	0,47	0,07	0,022	0,004	0,001	<0,001	<0,001	0,15	0,15

NCT, N-chlorotansine.

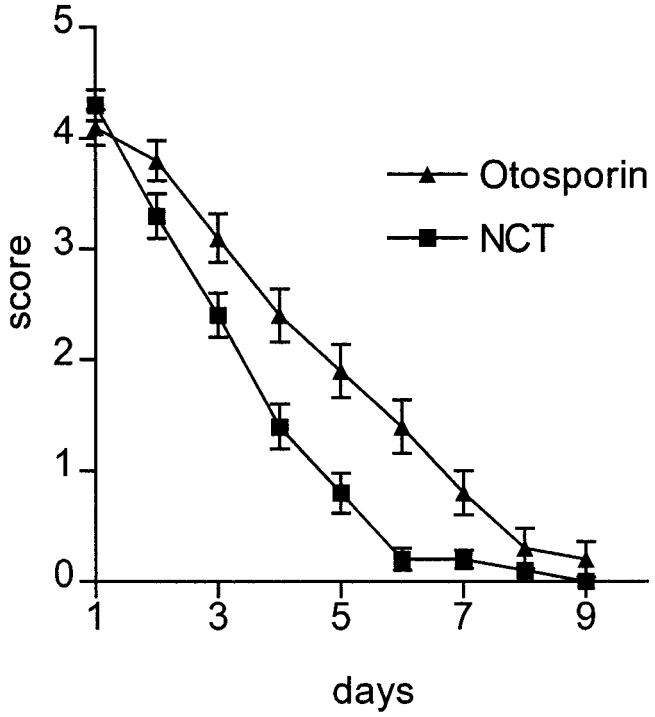

Fig. 1. Scores of inflammation during the period of treatment. Mean values ± standard errors of the mean of 25 subjects per group. NCT = N-chlorotaurine.

from 6.3 ± 2.3 on day 1 to 3.6 ± 2.2 on day 2. On day 3, a decrease to 2.0 ± 1.9 was observed, followed by a further decrease to 0.8 ± 1.1 on day 4. Finally, a score of 0.2 ± 0.6 on day 5 (mean values ± SD) was reached. The respective values for Otosporin were 6.5 ± 2.6 (day 1), 5.4 ± 2.7 (day 2), 3.8 ± 2.8 (day 3), 1.8 ± 1.8 (day 4), and 0.8 ± 0.9 (day 5). The difference between these values for the two groups was significant for day 2 ($P = .014$) and for day 3 ($P = .048$). Although not specifically evaluated, clinicians had the impression that the ear canal became dry more rapidly in the NCT group.

DISCUSSION

Application and Tolerability of the Substances

Topical treatment is the method of choice in otitis externa because agents come in direct contact with the pathogens at a microbicidal concentration. Out of the relatively large number of substances available (e.g., antibiotics, acetic acid, and corticoids), Otosporin was chosen as standard therapy because it includes a variety of components active against relevant pathogens and is approved for the particular application. The combination of neomycin and polymyxin B usually covers the spectrum of causative pathogens, and hydrocortisone probably reduces the swelling of the auditory canal.[1] Because patients with severe infections and swollen tissues in the external auditory canal were included, a rolled cotton pad with a wick-like function was used for the delivery of the agents. This kind of application can be easily used with NCT as well as Otosporin solution. The pain in otitis externa caused by therapy was similar in both study groups and originated at least in part from the placement of the ear wicks. Additional burning caused by the test substance NCT was only observed previously on ulcerated, but not on intact, skin.[8]

Allergy

As expected, the local tolerability of both solutions applied in our study was very good. No allergic or irritative side effects were observed. Because of the endogenous nature of NCT, an allergic reaction against this substance is generally improbable and has never been recorded in other clinical trials.[5–8] As an antiseptic, it has the advantage of use without preservatives or additives, which could cause allergy.

Tolerability in Other Studies

The good tolerability was also reported in studies on the eye, the bladder, and in crural ulcer.[5–8] First signs of efficacy of NCT have been found in bacterial conjunctivitis,[7] which encouraged the investigators to apply the substance to other diseases where antimicrobial action and local application of the agent is desired. The only side effect on application to the human eye was a temporary, moderate burning caused by the mild oxidizing activity of the substance.[7]

In a recent double-blind study, NCT was as effective as chloramine T in removal of purulent coating of crural ulcers.[8] However, NCT was significantly better tolerated in crural ulcer than chloramine T, an agent that is commonly used for its treatment.[8]

In otitis externa, NCT seems to be superior to the standard medication. Although double blinding of application was not possible when comparing the two substances, the advantage of NCT was clearly demonstrated by the progress of treatment. Healing could be achieved 1.8 days earlier in the test group ($P < .001$), which is a considerable advantage probably realized because of the excellent antimicrobial activity of the drug.

Cytotoxicity

Cytotoxicity of NCT against keratinocytes and other human cells is markedly lower than that of more reactive oxidants such as chloramine T, which could be the reason for its excellent tolerability.[19–22] NCT decomposes to the endogenous components taurine and chloride within approximately 2 hours in human inflamed tissue.[5,6,14] Therefore, no toxic derivatives may occur. This feature of NCT is particularly important in severe otitis externa, in which swelling is pronounced and a perforation of the tympanic membrane cannot be excluded. In such cases, ototoxic agents such as aminoglycosides should generally be avoided because of the risk of cochlear damage. Because of its hydrophilic properties, rapid diffusion of NCT through the intact tympanic membrane and the round and oval window is generally improbable. The low risk of this occurring with NCT was confirmed by the absence of cochlear damage subsequent to instillation of NCT to the middle ear of mice and guinea pigs.[9] Accordingly, no affect on hearing was observed in our patients at the end of the therapy.

Efficacy when Applied to Specific Pathogens

Application of NCT provides a cidal effect on the main pathogens of otitis externa but also against fungi, which can be found as causative in about 10% of cases.[2] Although fungi were not identified as pathogens in the group of patients under study, the fungicidal activity of NCT could be an additional advantage. In contrast with other disinfectants, its activity is enhanced in human exudates and mucus, allowing for a rapid inactivation of pathogens.[14,17] In addition, short contact with NCT has been demonstrated to attenuate the virulence of staphylococci, streptococci, and yeasts.[15,16,23] The unspecific mechanism of action (i.e., oxidation of mainly thio and amino groups)[18] does not enable resistance development during therapy.[14] Because of these features, NCT may be generally useful as an alternative in treatment of infections not responding to antibiotics.

In addition to the antimicrobial properties, NCT is considered to be involved in immune regulation. In vitro it has been reported to down-regulate pro-inflammatory cytokines of macrophages, dendritic cells, and T cells, namely tumor necrosis factor α, nitric oxide, prostaglandin E_2, and interleukins 1β, 2, 6,8, 10, and 12.[21,24–26] Possibly, such mechanisms play a role in clinical application by contributing to decrease of edema and swelling or to a drying effect, which would be very beneficial in otitis externa.

CONCLUSION

In summary, NCT proved to be superior to a standard medication with Otosporin in otitis externa. The main advantages are its endogenous nature, its excellent tolerability, and its broad spectrum activity as an antiseptic.

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