Safety and efficacy of Sofenz ceruminolytic solution

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Abstract
We conducted an open-label study of 109 untreated patients who had excessive or impacted cerumen. Our goal was to evaluate the safety and efficacy of Sofenz Cerumenolytic Solution, a methyltrypsin-containing earwax removal solution. Each patient’s external auditory canal was filled with Sofenz for 15 minutes. The primary measure of efficacy—visibility of the tympanic membrane—was assessed after the solution had been drained from the canal and again after the canal had been irrigated with lukewarm water. If the tympanic membrane was not completely visible following either application, the procedure was repeated. A safety examination was conducted 1 to 3 days after treatment. Secondary outcomes measures included relief of otologic symptoms (e.g., hearing loss, tinnitus, etc.) and patients’ overall satisfaction with treatment. Immediately after treatment, we found that the external auditory canal was completely visible in 81 patients (74.3%) after 1 application of Sofenz and subsequent irrigation, and in 98 patients (89.9%) after 2 applications of each. At the safety follow-up visit, we determined that the number of otologic symptoms had declined by 93.2%. A self-reported assessment completed by each patient following the procedure revealed a high degree of satisfaction with treatment. A total of 58 adverse events were reported, but only 16 were directly related to treatment, and all were transient and either mild or moderate. We conclude that 1 or 2 applications of Sofenz followed by irrigation with lukewarm water is a safe, well-tolerated, and effective treatment for excessive or impacted cerumen in the external auditory canal.

Introduction
Excessive and impacted earwax in the external auditory canal affects up to 6% of the Western population; approximately 150,000 earwax removal procedures are performed each week in the United States.\(^1,2\)

The accumulated cerumen is made up of a mixture of keratin debris and the secretory products of the ceruminous and sebaceous glands in the external auditory canal.\(^2-4\) Occlusion of the external auditory canal by excessive amounts of cerumen can cause temporary hearing loss, discomfort, pruritus, tinnitus, pain, occasional cough, and dizziness, and it can promote infection.\(^5,6\) Earwax can be removed mechanically, but patients’ routine attempts to clean the external auditory canal with cotton-tipped swabs may actually exacerbate cerumen impaction.\(^7,8\) Other common methods of earwax removal, such as syringing and irrigation with dental jets, may cause serious ear injury, including tympanic membrane rupture and ossicular disruption.\(^1,9-11\)

In light of the hazards of mechanical removal, it is often preferable to use a ceruminolytic agent to soften or dissolve an impaction or to loosen it from the tympanic membrane. Such treatment facilitates the removal of earwax by gentle irrigation with water. However, the use of products that require sophisticated instruments to achieve cerumen removal (e.g., suction and flushing equipment) may limit the ability of many pediatricians and general practitioners to treat such patients, and they could lead to otic damage if used incorrectly.\(^1,12\) Agents in current use or under evaluation include various formulations of oleic acid polypeptide complex, triethanolamine polypeptide, carbamide peroxide, olive oil, mineral oil, sodium bicarbonate, acetic acid, and docusate sodium.\(^12-20\) The efficacy and tolerability of these agents vary; olive oil has repeatedly been found to be ineffective.

We conducted a study of a relatively new ceruminolytic: Sofenz Cerumenolytic Solution, which has been approved in Europe and is under evaluation in the United States. Sofenz is a methyltrypsin solution in an aqueous buffered vehicle. Although preclinical toxicology studies demonstrated that Sofenz carries only a minimal risk to the middle ear mucosa, its labeling includes a precaution that it should not be used by patients who have a perforated tympanic membrane.
In this article, we describe our evaluation of the safety and efficacy of Sofenz in the treatment of patients with excessive or impacted cerumen in the external auditory canal.

Patients and methods
Patients. Between Sept. 18 and Nov. 22, 2001, we conducted an open-label trial of Sofenz in 109 patients—60 females (55.0%) and 49 males (45.0%), aged 2 to 93 years (mean: 56 ± 22)—who had excessive or impacted cerumen that had caused a partial or complete occlusion of at least one ear canal. (We had originally planned to include approximately 100 evaluable patients in this study, a number that was based on feasibility rather than on any formal sample-size calculation.) One patient (0.9%) was younger than 12 years, 4 patients (3.7%) were aged 12 to 17 years, 57 patients (52.3%) were aged 18 to 64 years, and 47 patients (43.1%) were 65 years of age or older. When both ears met the study eligibility criteria, the right ear was designated the study ear; in all, the study ear was the right ear in 70 patients (64.2%).

Patients with any abnormality of the study ear other than impacted cerumen had been excluded from participation. These conditions included the presence of a tympanostomy tube at any time during the previous 12 months, an intact tympanic membrane, a known or suspected ear infection, mastoiditis or any other suppurative noninfectious ear disorder, a structural anomaly of the external auditory canal, otorrhea, and bleeding. Other exclusion criteria included the use of any ototopical drug or earwax-removal product (with the exception of water or physiologic saline) during the preceding 3 days, diabetes mellitus, pregnancy, breastfeeding, and inadequate contraception.

Intervention. The active ingredient in Sofenz is methyltrypsin (200 Alcon units per ml, corresponding to a concentration of ~0.025% w/v). The solution was packaged in a single-use container with two compartments, one containing the methyltrypsin and the other the vehicle (sodium bicarbonate, glycerin, and a citrate buffer).

Patients were required to visit the office twice. At the first visit, patients underwent a screening and baseline examination, which was followed by treatment and a posttreatment examination. Between 1 and 3 days later, patients returned or a follow-up assessment of the agent’s safety.

While undergoing treatment, patients reclined on their side or sat up with the head tilted at a 45° angle and the study ear up. The investigator instilled the reconstituted solution into the ear canal. The solution was applied until it completely filled the external auditory canal; this usually required 1 to 2 ml. The Sofenz was allowed to remain in place for 15 minutes. Afterward, each patient turned over and allowed the fluid to drain from the ear. Residual fluid and any debris were wiped from the outer edge of the ear canal but not from the inside. The investigator then inspected the ear, gently irrigated it with lukewarm water, and assessed it again. When the initial treatment was unsuccessful in removing the occlusion, the investigator repeated the procedure. When a repeat application was unsuccessful, a treatment failure was declared and the patient was treated outside the study protocol as appropriate.

Occlusion. The investigators rated the degree of occlusion of the external auditory canal, as determined by their ability to see the tympanic membrane, as either none, mild, moderate, or complete. These determinations were made at baseline and as many as four times subsequently: (1) after draining the first application of Sofenz, (2) after the subsequent irrigation, (3) after draining the second application of Sofenz if performed, and (4) after the second irrigation if performed. The primary measure of efficacy was visibility of the tympanic membrane following treatment. This surrogate outcome was graded on a scale of 1 to 5:

1: Cerumen occlusion did not impair visibility of the tympanic membrane after 1 application and draining of Sofenz.
2: Cerumen did not impair visibility after 1 application and draining of Sofenz and 1 irrigation with lukewarm water.
3: Cerumen did not impair visibility after 2 applications and drainings of Sofenz.
4: Cerumen did not impair visibility after 2 applications and drainings of Sofenz and 2 irrigations with lukewarm water.
5: Cerumen partially or completely impaired visibility of the tympanic membrane after 2 applications of Sofenz and 2 irrigations.

Clinical outcome scores of 1 to 4 were considered to represent a treatment success, and a score of 5 was classified as a treatment failure.

Symptoms. The investigators also evaluated six otologic symptoms—(1) hearing loss, (2) aural fullness, (3) ear discomfort, (4) ear pruritus, (5) tinnitus, and (6) ear pain—on a binary scale (yes/no) at baseline, after the completion of treatment, and at the follow-up visit.

Patient satisfaction. Patient satisfaction with treatment was assessed immediately after treatment on a scale of 1 (no satisfaction) to 7 (complete satisfaction). Twelve parameters were evaluated: (1) amelioration of hearing, (2) control of ear discomfort, (3) control of ear pruritus, (4) control of ear pain, (5) control of dizziness, (6) relief of irritability, (7) relief of anxiety, (8) relief of restlessness, (9) expected effect of treatment on improving leisure activities, (10) expected effect of treatment on improving each patient’s family activities, (11) overall comfort during treatment, and (12) overall satisfaction with treatment.

Adverse events. The investigators documented adverse
events throughout the study period. An adverse event was considered to have occurred when there was (1) any increase from baseline in otologic symptom score and (2) a clinically significant otologic symptom score after treatment in patients whose tympanic membrane could not be visualized. The investigators classified the relationship of adverse events to the Sofenz application procedure according to five categories: definitely unrelated, unlikely to be related, and possibly, probably, or definitely related.

Statistical analysis. All 109 patients were included in the safety and intent-to-treat efficacy analyses; a per-protocol analysis was not performed. The primary statistical objective of this study was to describe the efficacy of Sofenz, and the primary efficacy variable was the degree of occlusion of the auditory canal after each application of Sofenz before and after irrigation. Secondary efficacy variables included relief of symptoms and patient satisfaction.

This study was performed in Belgium in compliance with Good Clinical Practice, Declaration of Helsinki, International Conference on Harmonization (ICH), and European Commission (EC) guidelines. All patients (or in the case of minors, a parent or legal guardian) provided written informed consent.

Results
Of the 109 patients enrolled in this study, all received at least 1 application of Sofenz. However, 1 patient decided to withdraw before the second application, and this patient was placed in the treatment failure category. A total of 16 patients were involved in 19 protocol violations.

Baseline findings. At the baseline examination, all patients presented with occlusion of the external auditory canal. The occlusion was complete in 68 patients (62.4%), moderate in 36 patients (33.0%), and mild in 5 patients (4.6%). Hearing loss was present in 69 patients (63.3%), aural fullness in 53 patients (48.6%), ear discomfort in 38 patients (34.9%), ear pruritus in 28 patients (25.7%), tinnitus in 23 patients (21.1%), and ear pain in 9 patients (8.3%). The consistency of cerumen was evaluated in all but 5 patients; based on the total population of 109 patients, 26 (23.9%) had soft cerumen, 46 patients (42.2%) had medium-soft to medium cerumen, and 32 patients (29.4%) had medium-hard to hard cerumen.

Treatment efficacy. Of the 109 patients, 81 (74.3%) were successfully treated with only 1 application of Sofenz and irrigation, and 17 others (15.6%) were successfully treated after 2 applications of each (table 1). Overall, treatment was successful in 98 patients (89.9%), while 11 (10.1%) were considered to be treatment failures, including the 1 patient who dropped out of the study after 1 unsuccessful application. Irrigation increased the success rate of Sofenz application considerably, after both the first application (from 0.9 to 74.3%) and the second application (from 77.1 to 89.9%).

Symptoms. Otologic symptoms generally abated after treatment, as determined by both posttreatment and follow-up examinations (table 2). The percentage of patients with hearing loss declined from 63.3% at baseline to 11.0% immediately after treatment; reductions were also seen with regard to aural fullness (from 48.6 to 7.3%), discomfort (from 34.9 to 5.5%), pruritus (from 25.7 to 8.3%), tinnitus (from 21.1 to 5.5%), and pain (from 8.3 to 3.7%). Further reductions were noted at the follow-up visit.

Patients required a mean of only 1.2 applications (95% confidence interval [CI]: 1.18 to 1.22).

Patient satisfaction. On average, patients were well satisfied with outcomes in terms of the 12 measured parameters. On the 7-point scale, the mean satisfaction ratings ranged from 4.9 to 6.3.

Adverse events. At the baseline examination, we were able to assess the external ear canal in 58 patients (53.2%); after treatment, assessment was possible in all 109 patients. Erythema was noted in 15 of the 58 patients (25.9%) at baseline, in 43 of the 109 patients (39.4%) posttreatment, and in only 9 patients (8.3%) at the safety follow-up. The corresponding figures with regard to edema of the external canal were 7 (12.1%), 15 (13.8%), and 1 (0.9%). Obviously, not all cases of erythema and edema necessarily represented adverse effects of treatment, since these findings were present at baseline in some patients.

Immediately after treatment, the tympanic membrane could be assessed in 106 patients, and inflammation of the tympanic membrane was seen in 14 of them (13.2%). However, at the safety follow-up visit, the number had fallen to 4 of 109 patients (3.7%). The position of the tympanic membrane was normal in 103 of 106 patients (97.2%) posttherapy and in 108 of 109 patients (99.1%) at the safety follow-up visit. No tympanic membrane perforation occurred.

In all, 32 patients (29.4%) were affected by a total of 58 adverse events. We determined that only 16 of these adverse events were related to treatment: canal erythema (n = 4), eardrum edema (n = 3), ear pruritus (n = 3), canal

<table>
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<tr>
<th>Treatment success/failure after application of Sofenz with or without irrigation</th>
<th>Individual n (%)</th>
<th>Cumulative n (%)</th>
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</thead>
<tbody>
<tr>
<td>Treatment success</td>
<td></td>
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<tr>
<td>After 1st application</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
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<tr>
<td>After 1st irrigation</td>
<td>80 (73.4)</td>
<td>81 (74.3)</td>
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<tr>
<td>After 2nd application</td>
<td>3 (2.8)</td>
<td>84 (77.1)</td>
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<tr>
<td>After 2nd irrigation</td>
<td>14 (12.8)</td>
<td>98 (89.9)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>11 (10.1)</td>
<td>11 (10.1)</td>
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edema (n = 1), and other ear disorders (n = 5); most of the other adverse events were attributed to the degree of cerumen impaction. None of these adverse events was serious. Most of these mild or moderate events resolved without treatment, and their presence did not interrupt the progress of the study.

Discussion
The findings of our study lead us to conclude that Sofenz is safe and well tolerated. The infrequent, transient, and minor local skin irritation that we observed might have been caused by the Sofenz and/or the procedure or by the cerumen plug itself. We did not observe any relevant or serious side effects of Sofenz therapy. This was not unexpected, however, because the incidence of serious complications requiring specialist therapy following other techniques of earwax removal is estimated to be only 0.1%. Of course, our sample size was too small to detect any such risk in this range.

In addition to being safe and well tolerated, 1 or 2 applications of Sofenz and subsequent irrigation with lukewarm water were found to be effective in the treatment of excessive or impacted cerumen in the external auditory canal. Cerumen was successfully removed in 98 of 109 patients (89.9%). It is also important to note that otologic symptoms such as hearing loss, aural fullness, discomfort, etc. resolved in most patients following treatment. This indicates that Sofenz treatment confers a beneficial effect with regard to not only a surrogate endpoint (i.e., visibility of the tympanic membrane), but on clinically relevant endpoints, as well.

Our study shows that it is advantageous to irrigate the external auditory canal with lukewarm water following Sofenz application rather than just allowing the solution to drain from the ear. Our success rate increased considerably after irrigation—from 0.9 to 74.3% after the first irrigation and from 77.1 to 89.9% after the second. This finding suggests that Sofenz does not fully dissolve the cerumen plug; rather, it softens and loosens the plug, thereby making it vulnerable to gentle irrigation. Also, irrigation appears to be necessary to remove residual methyltrypsin from the external auditory canal, thereby reducing the risk of skin irritation.

Our study shows that Sofenz compares favorably with other substances used to remove cerumen as tested in two other studies:

- Singer et al evaluated the ceruminolytic effect of docusate sodium and triethanolamine polypeptide. The endpoint was tympanic membrane visualization following drug application, irrigation, and additional means if drugs and irrigation were not effective. These researchers found that docusate sodium was successful in 81% of cases and triethanolamine polypeptide oleate condensate was effective in 35%; neither was as effective as Sofenz and irrigation (89.9%) in our study.
- Eekhof et al compared syringing after nightly applications of oil over 3 days and syringing after application of water drops for 15 minutes. Their endpoint was the mean number of syringing attempts required to remove a cerumen plug (6 attempts represented a treatment failure). They reported that the mean number of attempts was 2.4 in the oil group (95% CI: 1.7 to 3.1) and 3.0 in the water group (95% CI: 2.4 to 3.6). Our patients fared better than both groups in that they required a mean of only 1.2 applications (95% CI: 1.18 to 1.22).

In conclusion, we found that 1 or 2 applications of Sofenz to the external auditory canal over 15 minutes, followed by gentle irrigation with lukewarm water, is a safe, well-tolerated, and effective method of treating excessive and impacted cerumen in the external auditory canal.

Acknowledgment
The authors thank the staff of Harrison Clinical Research for providing assistance with study planning, regulatory requirements, and statistical analysis, for providing clerical support, and for proofreading the manuscript.

References