

Nasal amphotericin irrigation in chronic rhinosinusitis

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Purpose of review

To review the literature on the use of amphotericin irrigation for the treatment of chronic rhinosinusitis.

Recent findings

Although the etiology of acute rhinosinusitis is usually bacterial in nature, the exact etiology of chronic rhinosinusitis is unclear. Recent literature reports pointed to fungal colonization as a likely pathogenesis. It was hypothesized that a nonallergic eosinophilic immunoglobulin response to these fungi by the host was the cause of the symptoms, not a fungal invasion into the mucosa. The paper reviews the most recent articles investigating the use of amphotericin irrigation, as well as sprays and oral medications, of the nasal and sinus mucosa in patients with chronic rhinosinusitis.

Summary

The use of amphotericin for patients with chronic rhinosinusitis is not substantiated by the majority of publications. Although some studies found improvement on radiographic images, the symptoms of the disorder were not improved even with fungal eradication. Further studies need to be carried out to determine if changes in dosage, treatment time or route of administration could improve results.

Keywords

allergic fungal rhinosinusitis, amphotericin, antifungal, chronic rhinosinusitis, fungi

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Introduction

The etiology of chronic rhinosinusitis (CRS) is unclear. Although acute rhinosinusitis is usually bacterial and cleared with antibiotics, CRS remains more difficult to treat [1]. CRS as defined by the Rhinosinusitis Task Force consists of major symptoms such as facial pain or pressure, nasal drainage and congestion, postnasal drip, and altered sense of smell. Minor symptoms include headache, fever, halitosis, fatigue, dental pain, cough and ear pain or pressure. Two or more major symptoms or one major and two minor symptoms for greater than 12 weeks qualify as CRS [2]. Many causes have been proposed such as anatomical variants, microbial infection and/or colonization, fungal stimulation, atopic response, acetylsalicylic acid intolerance, and a combination of the above [3]. Most recently, the fungal role has been investigated by the literature; however, what has been discussed is not a fungal invasion, but rather fungal colonization followed by an allergic or a T helper 2-type immunologic reaction by the host [4]. Here, we summarize the results of the most recent articles published on this subject and form a conclusion on the usefulness of amphotericin in this setting.

Amphotericin irrigation

A way to test the theory of allergic fungal sinusitis is the use of antifungals in various forms to eradicate fungal colonies in patients with CRS. Although oral treatment is the easiest method to administer, there are many side effects from systemic use. Consequently, the use of irrigation and sprays employed by researchers to bypass the systemic toxicity and apply the agents directly into the sinus mucosa.

In 2002, Ponikau *et al.* [1] published a prospective open-label trial using amphotericin B in 51 randomly selected patients with CRS. The authors reasoned that since antibiotics and antihistamines did not benefit these patients it was worthwhile to study the effects of an antifungal. Furthermore, although corticosteroids provide some benefit, their utility is somewhat limited long-term by side effects. In a previous study by Ponikau *et al.* [4], sinus tissue eosinophilia and fungal organisms were found in 96% of patients with CRS, suggesting these organisms may play a role in the pathogenesis. The majority of healthy control subjects, however, also demonstrated the presence of fungal organisms in

sinonasal washings. It was therefore hypothesized that an immune response to the fungi in predisposed individuals caused the symptoms of CRS. Consequently, reduction in the fungal load in these patients should have reduced symptoms. This intense eosinophilic inflammation is independent of both nasal polyposis and atopy, and absent in healthy controls [4,5]. The antifungal agent was applied intranasally as 20 ml of a 100 µg/ml solution twice daily. This study found symptomatic improvement in 75% of patients and objective improvement on endoscopic exam in 74%, but only after lengthy treatment (4–12 weeks). They concluded that mucoadministration of amphotericin was both safe and effective, and warranted further studies. In particular, a placebo-controlled trial needed to be performed to account for the therapeutic effect of irrigation itself, which is known to be beneficial in these patients [6].

Similar to the Ponikau study, an unblinded, uncontrolled study with 74 patients having medically resistant nasal polyposis found a 39% cure rate after a 4-week period of 20 ml amphotericin nasal washings [7]. This prompted a randomized, double-blind trial in 2004 by Weschta *et al.* [8] in Germany. In Weschta's study, 200 µl per nostril of amphotericin B (3 mg/ml) saline nasal spray four times daily was prescribed over an 8-week period. The spray was used to avoid interference caused by irrigation. They found that the described dosing and time schedule was ineffective, and actually worsened symptom scores in the amphotericin group. Consequently, they found no benefit for the use of amphotericin nasal therapy. These results were repeated in another prospective, 3-month trial by Helbling *et al.* [9], who looked at the effect of amphotericin on nasal polyps and also found deterioration in symptoms in the treatment group. In addition, no positive effect was seen on the nasal polyps.

Ponikau *et al.* [10] responded with a randomized, placebo-controlled, double-blind trial in 2005 in order to test intranasal amphotericin for a longer period of time. In this case, 20 ml (250 µg/ml) of placebo was applied to each nostril twice daily for 6 months. Twenty-four patients completed the trial and were monitored objectively with computed tomography scan and endoscopy. They found reduced inflammatory mucosal thickening on both computed tomography and endoscopy as well as decreased intranasal markers of eosinophilic inflammation. The application of such objective markers to symptomatic improvement was, however, not found. No significant differences in symptoms could be detected. Furthermore, the study did not reach desired enrollment for various reasons.

With confounding data regarding the use of topical amphotericin, a larger, multicenter trial was devised. In 2006, Ebbens *et al.* [11•] in a large, double-blind,

placebo-controlled, multicenter study randomly selected 116 patients to use 25 ml amphotericin B (100 µg/ml) or placebo in each nostril twice daily for 3 months. This study found that no significant differences could be observed after 13 weeks using both objective and subjective measures. They concluded that amphotericin, in the above regimen, showed no additional benefit to intranasal steroids and irrigations, and that fungi are innocent bystanders in the upper respiratory tract of immunocompetent CRS patients.

One other prospective, double-blind, placebo-controlled clinical trial studied amphotericin B in an objective fashion. Weschta *et al.* [12•] examined the effect of nasal antifungal treatment on the levels of eosinophil cationic protein and tryptase in CRS patients. The purpose was to take another objective look at whether or not amphotericin could reduce the inflammation in the nasal mucosa of CRS patients. Sixty patients were evaluated using either 200 µl of amphotericin B (3 mg/ml) or placebo four times daily for 8 weeks. They found no effect on levels of eosinophil cationic protein ($P=0.17$) or tryptase ($P=0.09$). Furthermore, successful fungus eradication had no effect on the inflammatory markers. Their conclusion was that neither amphotericin nor fungal state before and after treatment had any influence on activation markers of inflammatory cells in CRS patients.

Due to the controversy in the literature regarding the use of amphotericin irrigation in CRS patients, in 2007 Shirazi *et al.* [13•] published an *in vitro* study on the use of amphotericin B against 10 fungal species commonly found in the nasal cavities. Each fungus was exposed to 20 ml of amphotericin at concentrations of 100, 200 or 300 µg/ml or sterile water for 6 weeks. They reported that the currently recommended and commercially available 100 µg/ml solution was ineffective in killing fungi *in vitro* during the 6-week period. The 300 and 200 µg/ml solutions, however, had a fungicidal effect after 5 and 6 weeks, respectively. Consequently, they recommended that higher concentrations of topical amphotericin B needed to be tested *in vivo* for a shorter time interval of 6 weeks in a randomized, placebo-controlled trial. The shortened treatment time could decrease treatment costs for the patient and increase compliance. The authors did recognize, however, the difficulty in administering amphotericin *in vivo*. Obstructive disease such as polyposis, in particular, poses huge difficulty in drug delivery. Since most authors believe that polypoid CRS has a greater association with fungus than nonpolypoid CRS [4], Shirazi *et al.* recommended primary endoscopic sinus surgery in patients with obstructive disease, followed by nasal irrigation therapy. Additionally, it was suggested that nasal saline rinse before topical antifungal therapy could improve results by removing gross mucopurulence and fungal debris.

High-dose oral agents

Much of this review has focused on topical administration of antifungal agents. There have, however, been trials studying the use of oral agents for chronic rhinosinusitis. In 2005, Kennedy *et al.* [14] published a randomized, double-blind, placebo-controlled, multicenter trial studying the use of high-dose oral terbinafine. Fifty-three adults with CRS received either 625 mg/day ($n=25$) terbinafine or placebo ($n=28$) once daily for 6 weeks. Computed tomography was graded for opacification at baseline and at week 6. They concluded that treatment with terbinafine failed to improve the radiographic appearance or symptoms even when nasal irrigation samples were positive for fungus on culture. Their cited reasons were that fungus might not be an exacerbating factor in CRS, that terbinafine is inadequately secreted into the mucosa or that the duration of therapy was inadequate.

Another study looking at the effects of oral antifungals was a 12-year chart review performed by Rains and Mineck [15]. They extracted data on 139 patients with allergic fungal sinusitis treated with high-dose itraconazole, short-burst corticosteroids, topical corticosteroids and endoscopic surgery. Although 50.3% experienced recurrence, only 20.5% required re-operation. No adverse effects were seen from the itraconazole over the 36 000 doses prescribed. Consequently, they concluded that the combined regimen above, including oral antifungals, was a safe and effective management strategy. Furthermore, they felt that the use of itraconazole may assist in avoiding revision surgery.

Conclusion

The use of amphotericin irrigation in patients with CRS is not justified by the majority of recent data. It has been shown that eradication of fungi in these patients does not alleviate symptoms. Although some studies reported improved scores radiographically, these results did not correlate with symptomatic improvement. In fact, some studies reported a worsening in symptoms. Further research needs to be performed to test whether variations in amphotericin B dosage, duration of treatment and oral antifungals could improve symptoms in CRS patients.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 98–99).

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- 11 Ebbens FA, Scadding GK, Badia L, *et al.* Amphotericin B nasal lavages: not a solution for patients with chronic rhinosinusitis. *J Allergy Clin Immunol* 2006; 118:1149–1156.
- This trial is one of the largest and most recent studies showing no benefit to amphotericin irrigation in chronic rhinosinusitis patients.
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- This study examined the effect of nasal antifungal treatment on inflammatory markers in the sinus mucosa and found no benefit with the antifungal compared to placebo.
- 13 Shirazi MA, Stankiewicz JA, Kammeyer P. Activity of nasal amphotericin B irrigation against fungal organisms *in vitro*. *Am J Rhinol* 2007; 21:145–148.
- This study examined the efficacy of amphotericin against fungal organisms *in vitro* and found the current concentration of commercially available topical amphotericin B to be ineffective in eradicating the fungi.
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