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Intranasal Nystatin Therapy in Patients with Chronic Illness Associated with Mold and Mycotoxins

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Abstract

We have previously reported that patients with chronic illness frequently had a history of prior exposure to water damaged buildings (WDB) and mold. These patients were found to have elevated levels of mycotoxins in the urine. We postulated that the mycotoxin producing molds colonize the sinuses of these patients and lead to chronic symptoms. In a recent observational analysis of patients treated with intranasal antifungal agents, either amphotericin B (AMB) or itraconazole (ITR), we showed that 94

Index terms— toxic mold, mycotoxin, chronic fatigue syndrome, intranasal antifungal therapy, nystatin.

1 I. Introduction

xposure to WDB, mycotoxin producing molds and mycotoxins may result in numerous health problems [1,2]. We have studied the association of mycotoxins and chronic illness, the prototype being chronic fatigue syndrome (CFS) [2]. The vast majority of these patients recalled an exposure to WDB and mold. In the study noted, we found thataflatoxins (AT), ochratoxin A (OT) and/or macrocyclic trichothecenes (MT) were present in 93% of CFS cases utilizing a sensitive and specific assay for these mycotoxins as opposed to a healthy control group in which all urine assays were negative for the mycotoxins [2]. The persistence of illness years after leaving the point of exposure, as well as the presence of mycotoxins in the urine assay, suggested internal mold may be present and represents a reservoir for ongoing internalmycotoxin production, either continuous or intermittent.

Furthermore, we described the concept that the sinuses may be the major internal reservoirs where the mold is harbored [3]. This presence of mold can lead to the generation of mycotoxins internally. A recent observational analysis of intranasal therapy with either AMB or ITR has been published indicating excellent improvements in the patients that did not have AE and remained on therapy [4]. Treatment of nasal colonization with AMB, however, was associated with a significant number of local AE (34%), which resulted in discontinuation. For these patients, we had been looking for alternative intranasal antifungal therapy regimens that would be effective and better tolerated. As mentioned in the discussion section of the prior paper, intranasal NYS appeared to be an attractive alternative, however, it was not available at the time those patients were treated. Since that analysis was done, an intranasal preparation of NYS was developed that could be delivered into the nose and sinuses via an atomizer. The present analysis, expand our findings with intranasal therapy in a group of patients that were treated with intranasal NYS.

2 II. Materials and Methods

3 a) Patients

The patients reported herein were largely a subgroup of the prior patients, thus, the patient demographics and characteristics have been previously reported [4]. All patients discussed here fulfilled the same criteria as previously published [4]. The majority of the current cases came from the group that developed local AE with AMB and discontinued the therapy. There were a few patients that were ”new starts” on intranasal therapy. These patients were offered either AMB or NYS and opted for NYS.

The rationale for the treatment with intranasal antifungal therapy was outlined in our previous paper regarding the role of naso-sinus colonization with toxic mold [3]. The concepts relating to such therapy were discussed with thesepatients at the time of a clinic visit. In patients that wanted to proceed with NYS therapy, a prescription was then sent to ASL Pharmacy (see below).The patients were typically seen in follow up within three to six months after initiating therapy. All patients reported herein were seen at least once in follow up after they started therapy.

Institutional Review Board exemption was previously granted after review of these treatments by K Solutions IRB (Protocol #1FEB15-40). This was based on the fact that these patients were treated as part of their clinical management in the medical practice and not deemed to represent human subjects research.

4 b) Treatment

The therapy prescribed consisted of intranasal medication(s) administered via an atomizer device. About half of these patients administered an agent (CHE) used to break up biofilm (which was described in our previous paper) along with NYS. The remainder of the patients used intranasal NYS alone in the atomizer without the CHE. Prescriptions were sent to ASL Pharmacy, Camarillo, California and then dispensed to the patients by ASL. The intranasal antifungal agent in this report was NYS. Each capsule contained 50,000 units of NYS admixed with xylitol as an excipient. The capsule contents were mixed by the patient with 5 mL of either saline solution or distilled water and then added to the atomizer. All intranasal applications were delivered via the NasaTouch atomizer device provided to the patient by ASL Pharmacy. Patients administered the atomizer treatments once daily for each agent. If the patients were receiving CHE along with NYS, they were advised to administer the CHE first, followed by the NYS. Patients generally remained on therapy unless they discontinued it due to an AE. The period of treatment observation reported herein ran for 12 months, June 2014 to June 2015.

5 c) Clinical assessments

The clinical assessments followed the same criteria as previously reported, including assessments of clinical improvements and AE. [4].

6 d) Mycotoxin testing

The urine mycotoxin testing of specimens were performed at RealTime Laboratories. The details of the assay have been previously described [2].

7 III. Results

During the 12-month period of observation, 80 patients initiated therapy with NYS (with or without CHE). It is worth stating at this point that no discernable differences were noted with or without the CHE. Thus, the data is not presented separately and aggregated together. The clinical results are summarized in Table 1. Six patients that received NYS had repeat mycotoxin urine testing done. Those results are found in Table 2. Additionally, two patients discontinued therapy after improvement and had repeat urine mycotoxin testing after discontinuation (one test was done 3 months after stopping therapy and the other at 4 months). The repeat testing on these two patients is summarized in Table 3. In summarizing the results from our patient observations, treatment with intranasal NYS resulted in clinical improvement (reduction in symptoms). In looking at the total group, 73% improved. Of the patients that remained on therapy without AE or tolerable AE (n = 70), 83% improved. Of the patients that improved and remained on therapy, 10 (14%) ranked their status as markedly improved (definition of markedly improved previously published) during this period of observation. At the time of evaluation (follow up clinic visit), the majority of patients reported ongoing, progressive improvement. Thus, the degree of improvement seemed to increase over time (data not shown).

Repeat urine testing for mycotoxins in six patients (Table 2) showed similar results to our prior study with AMB and ITR. OT and MT levels decreased in virtually all the cases (OT remained the same in one patient). As noted, in several patients the levels for both OT and MT decreased to zero.

Also, as we reported with AMB (and ITR) in our prior analysis, patients that went off therapy at 6 months or earlier, are prone to relapse. Although we only assessed post-discontinuation urine mycotoxin testing in two cases, one showed increased levels of OT and both showed increased MT (even higher than baseline).

Systemic AE were the most common AE, occurring in 25% of the patients, which led to discontinuation of therapy in 8(10%). Local AE were uncommon, only seen in 5% of the cases (4 patients). Looking at these local AE cases more closely, all were on CHE. No patients reported local AE on NYS alone.

8 IV. Discussion

Exposure to WDB, in particular, toxic mold, has been associated with numerous adverse health consequences [1,2]. We have studied patients with chronic illness, with the prototype being CFS. We found the chronic illness was highly associated with exposure to WDB/mold in the past and the ongoing presence of mycotoxins, detected with a sensitive and specific urine assay [2]. As we analyzed these patients, it became apparent that many of the patients with chronic illness and the presence of mycotoxins could trace their illness to past exposure but not

recent or present exposure. We postulated that these patients may have harbored internal mycotoxin producing mold species and that such mold was likely in the sinuses, embedded in biofilm. A review of the literature and patient data supporting this idea was previously published [3]. It seemed intuitive that therapies directed at reduction or elimination of this mold, could potentially lead to clinical improvements.

We previously reported the use of either intranasal AMB or ITR to see if we could reduce or eliminate the mold in the sinuses [4]. In that paper, we analyzed if such intranasal therapy would lead to symptomatic improvement.AMB was associated with clinical improvement in 94% of the cases that continued on therapy. Unfortunately, approximately one third of the patients that initiated therapy with AMB developed local AE severe enough that the therapy was discontinued. We also found good clinical responses with ITR but the numbers evaluated were much smaller (only 14 patients). We set out to determine if there were alternative therapies that would be effective but better tolerated. Intranasal NYS surfaced as an interesting option to explore [4,5]. Although used for decades as a topical agent for yeast infections, NYS actually has good in vitro activity for molds [5]. Since NYS is a polyene antifungal agent (similar to AMB), it would be predicated to have similar effects. We postulated that there might be less local AE since topical NYS has been well tolerated for yeast infections of the oral cavity (thrush) [6].

Most of the patients reported herein were patients that were in the previous analysis but became intolerant to AMB secondary to local AE. Additionally, there was a smaller subset of the patients reported here that were starting intranasal antifungal therapy for the first time and opted for the NYS.

In the analysis reported herein, NYS was very promising. We found that 83% of the patients that remained on therapy (generally for 6 months minimum) improved clinically. Intranasal therapies with AMP and NYS were comparable in the two studies. NYS was very effective as a therapy for treating mold in the sinuses.

Repeat urine mycotoxin testing done in a small subset of these patients (n = 6) showed very similar results to our prior findings with AMB. The mycotoxins consistently decrease with intranasal therapy (in some cases the levels drop to zero). This drop in mycotoxin levels correlates very well with clinical improvement.

We also reported on two patients that discontinued therapy after approximately 6 months of therapy. One relapsed clinically and both showed rises in their urine mycotoxin levels after discontinuation of therapy (MT levels even higher than baseline).

Local AE were basically non-existent with NYS. The four patients that reported local AE in the group were all on the CHE. None of the cases that received NYS without CHE had local AE. Furthermore, when the CHE was stopped in the patients on both agents (NYS continued), the local AE resolved (data not shown).

Systemic AE are thought to represent "die off" reactions. This concept was addressed in the previous paper in which AMB and ITR was used as the intranasal therapy [4]. As discussed previously, we postulated that the systemic "die off" reactions were due to enhanced mycotoxin release when the therapy was initiated, as a direct result of the antifungal agent interacting with the mold/fungi in the sinuses. In an in vitro model, Reeves et al demonstrated increased synthesis and release of gliotoxin from Aspergillus fumigatus upon exposure to amphotericin B [7]. Since NYS is not absorbed systemically, we feel it is highly unlikely these AE were due to the medication but rather represented "die off" [6]. Thus, the NYS appears to be extraordinarily safe, in terms of any AE due to the drug itself. These "die off" reactions can be problematic, however. As noted above, these reactions led to discontinuation in 10% of the patients. It is of interest that we seemed to see more systemic AE with NYS than we noted previously with AMB. This may a bit misleading. We have noted that these systemic AE tend to occur early on in the course of therapy (data not shown). Since a high percentage of the AMB cases had local AE early on and stopped their therapy, we may have under estimated the number of systemic AE (discussed in the previous paper) [4]. Also, it should be noted that the majority of the systemic AE cases continued on therapy and it did not result in discontinuation (15 out of 25). We have subsequently taken the approach of reducing the dose or frequency of dosing with the NYS if the systemic AE occur and persist longer than a few days.

9 V. Conclusions

The data presented herein, extends and compliments our prior experience with intranasal antifungal therapy. Intranasal NYS appears to be a very effective and well-tolerated alternative. A very high percentage of patients improved clinically and urine mycotoxin levels decreased on therapy. In terms of AE, the local AE were essentially absent when NYS was used. We did see systemic AE ("die off" reactions) in about one fourth of the NYS cases, however only 10% discontinued therapy. The goal of intranasal antifungal therapy in these types of patients is reduction or elimination of the mycotoxin producing molds in the sinuses. We now have several alternative agents to offer for such therapy with promising results.

10 VI. Future Directions

There continues to be a number of unanswered questions with regard to intranasal antifungal therapy in these types of patients. As noted in our prior paper, the agent of choice, proper dose, frequency of dosing, most effective way to administer the therapy and duration of therapy have not been fully elucidated. Additionally, the current analysis raises the question as to whether a "biofilm buster" is necessary. AMB (and presumably NYS, since it is a similar compound) can penetrate biofilm [8]. Thus, the question of using the antifungal alone (particularly

159 to reduce AE) as compared to using the antifungal along with an agent to break up the biofilm in the sinuses, remains unanswered. [1]

Figure 1: E

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Group	Number	%
NYS Total Patients	80	100
NYS Clinical Response: Improved *	58	73
NYS Local AE Total **	4	5
NYS Local AE Resulting in Discontinuation	2	2.5
NYS Systemic AE Total ***	20	25
NYS Systemic AE Resulting in Discontinuation	8	10
NYS Continued Therapy & Improved	58	83

* Improvement defined in Methods section previously published [4], ** Local AE defined in Methods section previously published [4], *** Systemic AE defined in Methods section, previously published [4]

Figure 2: Table 1 :

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			Mycotoxin Assays				
Rx	Imp	%	OT dec	%	MT dec	%	Total
NYS	6/6	100	5/6 *	83	6/6 *	100	6

*[Note: Rx: Treatment, Imp: improved, OT dec: ochratoxin A level decreased from baseline, MT dec: macrocyclic trichothecene level decreased from baseline, NYS: nystatin, * decreased down to a level of zero (OT 4/6, MT 2/6)]*

Figure 3: Table 2 :

3

Rx	Imp	%	Relap	%	OT inc		%	MT inc	%
NYS	2/2	100	1/2	50	1/2	50	2/2	100	

[Note: Rx: Treatment, Imp: improved, Relap: clinical relapse after discontinuation, OT inc: ochratoxin A level increased compared to baseline, MT inc: macrocyclic trichothecene level increased compared to baseline, NYS: nystatin]

Figure 4: Table 3 :

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