Intranasal infusion of enilconazole for treatment of sinonasal aspergillosis in dogs

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Objective—To determine effectiveness of infusion of 1 and 2% enilconazole for treatment of nasal and sinusal aspergillosis, respectively, in dogs.

Design—Case series.

Animals—26 client-owned dogs with aspergillosis.

Procedure—All dogs had typical clinical signs of aspergillosis and rhinoscopically visible intrasinusal or intranasal fungal plaques associated with turbinate destruction. During rhinoscopy, affected nasal cavities and frontal sinuses were debrided meticulously. Nineteen dogs (group A) were treated with 1% enilconazole by use of a modified noninvasive infusion procedure. Seven dogs (group B) were treated with 2% enilconazole via catheters that were placed via endoscopic guidance into the frontal sinuses. All dogs underwent follow-up rhinoscopy for determination of further treatment until cure was established.

Results—Age, disease duration, clinical score, and rhinoscopic score were similar for both groups before treatment. In group A, 17 of 19 dogs were cured; 9, 6, and 2 dogs were cured after 1, 2, or 3 treatments, respectively. The remaining 2 dogs were euthanatized before the end of the treatment protocol. In group B, all dogs were cured; 6 dogs and 1 dog were cured after 1 or 2 treatments, respectively. Only minor adverse effects such as nasal discharge, epistaxis, and sneezing developed.

Conclusions and Clinical Relevance—After extensive rhinoscopic debridement, 1 and 2% enilconazole infused into the nasal cavities and the frontal sinuses, respectively, were effective for treatment of aspergillosis in dogs. Intrasinusal administration via endoscopically placed catheters appeared to require fewer infusions for success. Follow-up rhinoscopy is strongly advised. (*J Am Med Vet Assoc* 2002;221: 1421–1425)

Sinonasal aspergillosis is a common disease that affects between 12 and 34% of dogs evaluated for chronic sinonasal disease.[1] Aspergillosis in dogs typically causes destructive rhinitis and sinusitis.[2] In most instances, *Aspergillus fumigatus* is the etiologic agent, but *A niger*, *A nidulans*, and *A flavus* may also be involved.[1,3] Dogs most often evaluated for fungal rhinitis are young to middle-aged and of mesaticephalic and dolichocephalic breeds.[1-4] Clinical signs associated with the disease in decreasing frequency included profuse nasal discharge, signs of nasal pain, ulceration of external nares, sanguinopurulent discharge, osteomyelitis of the frontal sinuses, and epistaxis.[2,3] Aspergillosis may be suspected on the basis of results of physical examination and confirmed via rhinoscopy, radiography, **computed tomography (CT)**, mycologic culture, and serologic findings.[1-3,5]

Effective treatment of sinonasal aspergillosis in dogs is difficult. Treatments include surgery as well as systemic and topical administration of antimycotic medication. Systemic administration of antifungal agents requires prolonged administration because of poor efficacy. Clinical cures are obtained in only about 50% of patients treated with thiabendazole[1,6,7] and ketoconazole,[1,6,8] and as many as 70% of patients treated with itraconazole or fluconazole.[6,7,9] Topical treatment has been associated with greater success and has improved management of this previously intractable condition. Various procedures have been developed to administer medication topically, and these procedures vary in invasiveness and ease of performance. For several years, the standard treatment consisted of an enilconazole emulsion delivered via tubes surgically implanted into the nasal cavities and frontal sinus and twice daily irrigation for 7 to 14 days.[1,2,10] More recently, a noninvasive technique using nonsurgically placed catheters has been developed to infuse the drug topically into the nasal cavities and frontal sinus via general anesthesia.[3,4,11] Presently, several treatment protocols with variations of this technique are under investigation in order to improve treatment success, tolerance by the animal, and compliance by the owners.[5,12-15]

The purpose of the study reported here was to determine the effectiveness of 2 noninvasive infusion techniques in dogs with nasal aspergillosis and frontal sinus involvement by use of either a 1% emulsion of enilconazole infused through placed intranasal catheters or a 2% emulsion of enilconazole infused through endoscopically placed catheters in the frontal sinus.

Materials and Methods

Dogs—Twenty-six dogs evaluated for chronic nasal discharge and with a diagnosis of aspergillosis in the nasal cavities and frontal sinus were included in this study. The diagnosis of aspergillosis was based on results of physical examination; rhinoscopy, radiography, or CT scan; and mycologic culture. All dogs had clinical signs of aspergillosis, and rhinoscopic evaluation revealed typical intrasinusal or intranasal fungal plaques associated with turbinate destruction. The first 19 dogs underwent treatment via intranasal infusion; the remaining 7 dogs underwent a modified treatment that involved intrasinusal infusion through nonsurgically placed catheters.

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Clinical scoring of lesions—After physical examination, a clinical score was calculated, and a maximum value of 14 was determined on the basis of the presence and characteristics of nasal discharge (degree of discharge for each nostril, absent = 0, mild = 1, severe = 2; nature of discharge, serous = 0, mucoid = 1, purulent = 2; number of episodes of acute epistaxis, 0 to 2); signs of nasal pain (0 or 2); ulceration of the nasal planum (0 or 1); systemic illness and signs of depression (0 or 1); sneezing or reverse sneezing (0 or 1); and increased nasal airflow (0 or 1), as measured by alternately placing a thin piece of cotton wool in front of each nostril.

Rhinoscopic scoring of lesions—For rhinoscopy, all dogs were sedated with medetomidine[a] (25 to 35 µg/kg [11.4 to 15.9 µg/lb], IM) or acepromazine[b] (0.025 to 0.05 mg/kg [0.011 to 0.023 mg/lb], IM) and methadone[c] (0.2 to 0.4 mg/kg [0.09 to 0.18 mg/lb], IM) and anesthetized with thiopentone[d] (5 to 10 mg/kg [2.27 to 4.54 mg/lb], IV) or propofol[e] (2 to 6 mg/kg [0.9 to 2.7 mg/lb], IV); anesthesia was maintained with isoflurane[f] in oxygen. Nasal cavities were explored with a rigid endoscope[g] that allowed exploration of the frontal sinus (**Fig 1**). A pediatric bronchoscope[h] designed for endoscopically guided debridement and fluid injection was also used. A rhinoscopic score (maximum score, 16) was arbitrarily calculated on the basis of turbinate destruction (absent = 0, moderate = 1, severe = 2) for each side, involvement of the frontal sinus (0 or 2), destruction of the nasal septum (0 or 2), severity of intranasal or sinusal fungal plaques (0 to 4), unilateral or bilateral presence of mucopurulent material (0 to 2), and damage to the nasal mucosa (0 to 2). Each affected mucosal area was brushed or biopsied for fungal and bacteriologic culture and cytologic or histologic examination to confirm mycologic infection.

Treatment—Before infusion of enilconazole, meticulous debridement was performed endoscopically by means of forceps, a suction catheter, and copious lavage with saline (0.9% NaCl) solution until most plaques and necrotic material were removed.

Nineteen dogs (group A) underwent a standardized treatment with a 1% enilconazole[i] emulsion by use of a modification of the noninvasive infusion procedure described by Mathews et al.[4] After sedation with a mixture of acepromazine (0.025 to 0.05 mg/kg, IM) and methadone (0.2 to 0.4 mg/kg, IM) and induction with thiopentone (5 to 10 mg/kg, IV), each dog was intubated. Anesthesia was maintained with isoflurane in oxygen and administered via a circle system. Intermittent positive-pressure ventilation was initiated, and sufentanyl[j] was administered IV (0.2 µg/kg [0.09 µg/lb]) in bolus increments, as needed. The dog was positioned in dorsal recumbency with the hard palate parallel to the table, and a 20-F Foley catheter was inserted into the nasopharynx with a right-angle forceps. Gauze sponges were placed around the base of the catheter in the pharynx, and the 30-mL balloon was inflated with saline solution so that the Foley catheter was securely fixed in place at the junction between the hard and soft palate. A 12-F fenestrated catheter was inserted dorsomedially through each nostril as far as possible. The 12-F catheters were used as infusion catheters and were connected via a T-shaped connecting piece to a manometer tube and a 60-mL infusion syringe. The nostrils were occluded by use of a 16-F Foley catheter (with a 5-mL balloon) and towel clamps. Finally, all Foley catheters were occluded by clamps. Constant infusion was performed by use of a syringe driver. The infusion pump, tip of the syringe, and base of the manometer tube were positioned at the level of the nose. Infusion of 120 mL of 1% enilconazole (60 mL in each nasal cavity) was started at a rate of 100 mL/h. Intranasal pressure was recorded every 5 minutes. The head of the dog was turned to the left or the right side for 3 minutes every 15 minutes. At the end of the intranasal infusion, the head was tilted downward at an angle of 30°, the catheters and gauze sponges were removed, and the nasal cavities were allowed to drain for 20 minutes. The pharynx and larynx were examined before the dog was allowed to recover from anesthesia. Antimicrobial treatment was started at induction of anesthesia with cefazoline[k] (20 mg/kg [9.1 mg/lb], IV), followed by 1 injection after 6 hours at the same dose, and continued with cephalexine[l] (20 mg/kg, q 12 h) administered PO for 5 days. Dogs were hospitalized overnight. Three to 4 weeks after treatment, follow-up rhinoscopy was performed to assess effectiveness of the treatment. If rhinoscopy revealed persistence of fungal plaques, the infusion treatment was repeated as many as 2 times, and a further rhinoscopy was performed 3 to 4 weeks later. If fungus persisted, dogs received ketoconazole[m] (10 mg/kg, PO, q 12 h) for 4 to 6 weeks. In all dogs, treatment was continued until cure was confirmed by rhinoscopy.

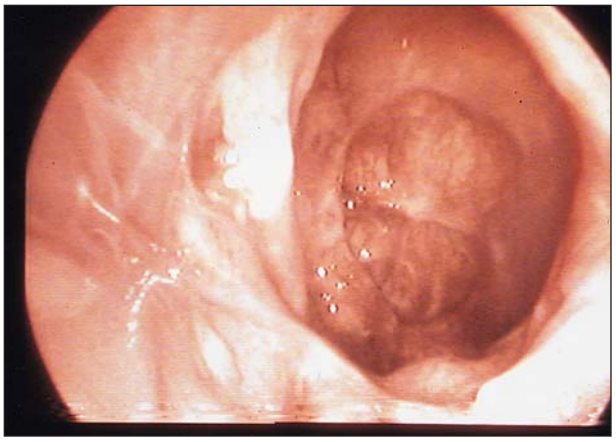

Figure 1—Rhinoscopic view (angled dorsally 30°) of the left frontal sinus in a dog after cure of fungal rhinitis. This view was only possible because of extensive turbinate destruction that permitted access to the nasosinusal opening.

After treatment of 19 dogs, the treatment protocol was modified on the basis of acquired clinical experience and applied to the last 7 dogs (group B) in an attempt to reduce the number of infusion procedures. During the diagnostic rhinoscopy procedure, infusion catheters were placed under endoscopic guidance with a flexible bronchoscope into the caudal part of the frontal sinus.[6] Apart from the use of 150 mL of a 2% emulsion of enilconazole, the rest of the procedure was kept identical. If fungal plaques and necrotic material were detected at follow-up rhinoscopy, a second infusion was performed after endoscopic debridement. If follow-up rhinoscopy revealed only sparse fungal plaques, the dog received treatment with ketoconazole (10 mg/kg, PO, q 12 h) for 4 to 6 weeks.

Statistical analyses—Statistical analysis to compare clinical and rhinoscopic scores before treatment, 1 month after the first treatment, and at time of cure was performed by use of ANOVA for repeated measures. Values of $P < 0.01$ were considered significant.

Results

Among the 26 dogs, 14 breeds were represented. The most commonly represented breeds were Rottweiler (n = 4), Golden Retriever (4), Labrador Retriever (3), and German Shepherd Dog (3). Nineteen dogs were male, 7 were female, and ages ranged from 5 months to 10 years (mean ± SD age, 4.7 ± 2.6 years; median, 5 years). Duration of clinical signs ranged

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from 3 to 52 weeks (mean ± SD duration, 13.4 ± 11.0 weeks; median, 9.0 weeks). Age and duration of clinical signs were similar for the 2 groups.

For all 26 dogs, clinical features included nasal discharge (25), sneezing or reverse sneezing (23), epistaxis (20), signs of nasal pain (18), illness or signs of depression (18), ulceration of the nares (18), and increased nasal airflow (14). Rhinoscopic findings included destruction of turbinates (26; bilateral in 7), intranasal mucopurulent secretions (26), fungal plaques (26; **Fig 2**), roughening of the mucosa (23), involvement of the frontal sinus (22), and destruction of the nasal septum (9).

The clinical scores and rhinoscopic scores were not statistically different for group A and B before and after the first treatment and at the time of cure in patients that required more than 1 treatment (**Fig 3**). After the first treatment, clinical scores and rhinoscopic scores decreased significantly, and there was a significant difference between scores obtained after the first procedure and those obtained at cure in patients that required more than 1 treatment. The same pattern of scores was noted in both groups. After the first treatment, general condition always improved, and nasal discharge and signs of nasal pain disappeared. There was a decrease in the amount of intranasal and intrasinusal fungal material, although destruction of the nasal septum and turbinates obviously remained.

In group A, 17 of the 19 dogs were cured; 9 dogs were cured after 1 treatment, 6 dogs after 2 treatments, 1 dog after 3 treatments, and 1 dog after 3 infusion treatments and oral administration of ketoconazole. After a third treatment, and despite satisfactory improvement after the first 2 treatments, findings in the latter dog were worse at the last rhinoscopic follow-up examination. The dog was then treated with ketoconazole (10 mg/kg, PO, q 12 h, for 6 weeks), and follow-up rhinoscopy performed 6 weeks later revealed complete cure. Two dogs were dropped from the study because they were euthanatized at the owners' request before the end of treatment, despite obvious clinical improvement.

In group B, all dogs were cured; 6 were cured after 1 treatment and 1 was cured after 2 treatments. Additional ketoconazole was administered orally in 3 dogs, because some suspect material was seen at follow-up rhinoscopy 1 month after the first infusion. In both groups, all cured dogs remained clinically disease-free throughout a follow-up period of at least 8 months, according to the owners.

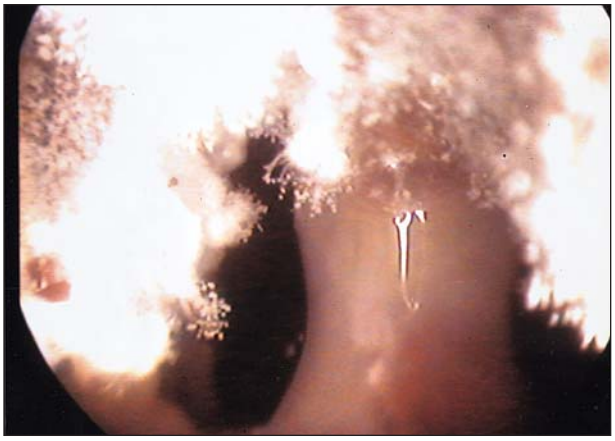

Figure 2—Rhinoscopic view of intranasal fungal plaques in a dog.

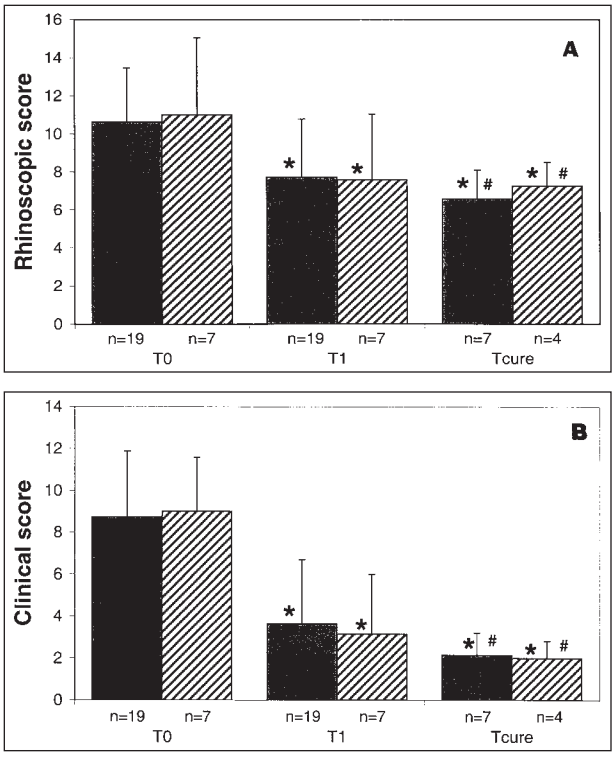

Figure 3—Histograms of rhinoscopic (A) and clinical (B) scores (mean ± SD) in dogs with fungal rhinitis or sinusitis that were treated by infusion of 1% (solid bars) or 2% (striped bars) enilconazole. T0 = Time zero (baseline). T1 = Scores after 1 treatment. Tcure = Scores at time of cure. *Significant ($P < 0.001$) difference from value at T0 in the same group. #Significant ($P < 0.01$) difference from value at T1 in the same group.

At the time of diagnosis, fungal plaques were seen in all dogs. Although results of culture on Sabouraud-chloramphenicol agar were negative in 9 dogs, *A fumigatus* was cultured from 17 dogs. Bacterial growth was obtained in 20 of 22 bacteriologic cultures. Bacterial growth involved a single species (5/22 cultures) or 2 or more species of bacteria (15/22 cultures). The most commonly encountered bacteria were *Staphylococcus* spp (15/22 cultures), *Escherichia coli* (10/22), and *Pseudomonas* spp (8/22). On the basis of results of bacterial culture and susceptibility testing, patients received a 10-day course of an appropriate antimicrobial, mostly amoxicillin-clavulanic acid,[n] enrofloxacin,[o] or cephalexin.

The most commonly encountered CT findings in our case series were moderate to severe cavitary destruction of turbinates with a variable amount of abnormal soft tissue in the nasal passages; nonspecific thickening of the mucosa adjacent to the inner surface of bones of the frontal sinus, maxillary recess, and nasal cavity; and thickened reactive bone. These were reported in detail in a previous article.[5] In 2 dogs, involvement of the cribriform plate was also detected, but despite that finding, these patients underwent the same treatment without complications.

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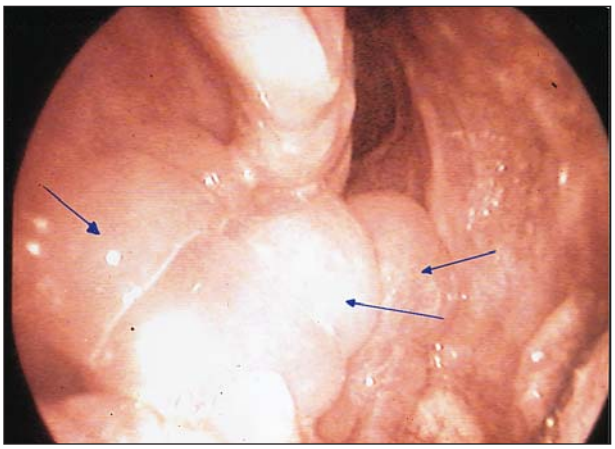

Figure 4—Rhinoscopic view of mucosal blebs (arrows) on the nasal mucosa of a dog after successful treatment for fungal rhinitis.

No complications were observed during intranasal infusion of enilconazole except leakage around the catheters, through the incisive ducts, or from the nasolacrimal system. Leakage around the catheter was immediately corrected by replacing the catheter. Leakage through the incisive ducts was treated by use of digital compression, and leakage through the nasolacrimal duct was treated by decreasing intranasal pressure and flushing the eye with sterile saline solution. Leakage around the nasal catheters was easily recognized, but leakage around the nasopharyngeal catheter was not always detected grossly. Gentle flushing of the catheters with air while all but 1 of the catheters were occluded before infusion and measurement of intranasal pressure during infusion allowed identification of leakage or dislodgment of the catheter. Two dogs had severe bleeding during withdrawal of catheters; however, bleeding stopped within a few minutes. In all dogs there were 2 major adverse effects during the immediate posttreatment period—profuse nasal discharge and sneezing. The adverse effects improved markedly within 24 hours. None of the dogs had anesthetic or neurologic complications. Final follow-up rhinoscopy in all dogs revealed the absence of fungus and the presence of mucosal blebs on the nasal and sinusal mucosa that resulted from the treatment procedure (**Fig 4**).

Discussion

The choice of the drug and treatment procedure in this study was based on the reported effectiveness of a technique that uses a single application of clotrimazole and on the fact that enilconazole is one of the most effective agents for the topical treatment of aspergillosis.[1,2,4,6,10,12] Compared with topically administered treatment through surgically placed catheters, the use of an intranasal topically administered infusion technique is easier, less invasive, better at distributing the drug into the sinuses, and associated with fewer complications.[3,4,12] Enilconazole, like the other azole derivatives, inhibits sterol synthesis and also inhibits synthesis of nucleic acids, triglycerides, fatty acids, and oxidative enzymes.[3,16] Fungistatic at low concentrations, imidazole derivatives are fungicidal at higher concentrations.[3,16] Enilconazole and clotrimazole have poor solubility and limited intestinal absorption and are therefore used topically.[3,10] Clotrimazole is irritating to the digestive system and is systemically toxic.[3] European preparations of clotrimazole contain isopropanol and propylene glycol and are consequently quite irritating to mucous membranes.[3,13] Enilconazole is less toxic and irritating, especially at low concentrations.[3,10] The only acute adverse effect observed for enilconazole at a dose of 640 mg/kg (290 mg/lb, PO) is emesis.[10] Oral administration of 20 mg/kg for 2 years in dogs induced sporadic emesis, ptyalism during administration, and inappetence.[10] Furthermore, enilconazole is also active in the vapor phase over a distance of as much as 1 cm.[6,10]

In a first protocol, we basically followed the noninvasive infusion procedure described by Mathews et al,[4] with the difference that we used 1% enilconazole instead of clotrimazole. Then, in an attempt to reduce the number of treatment procedures, this protocol was modified. Review of recent literature suggested that placement of the infusion catheters in the dorsal aspect of the frontal sinus could be beneficial.[6] Because of this, we began using endoscopically guided placement of the infusion catheters. Additionally, a higher concentration of enilconazole was used. We further hypothesized that if small amounts of fungal material persisted, a repeat infusion procedure was not necessary; in those dogs, we decided to administer antimycotic medication only orally, after removal of the remaining material.

Clinical scores and rhinoscopic scores were used to compare the clinical and rhinoscopic findings before and after treatment. The clinical score was adapted from the grading system described by Sharp et al,[8,9] whereas the rhinoscopic score was developed for this study. Both evaluation procedures were sufficiently detailed to grade the severity of the disease. Moreover, the scoring systems were good indicators of improvement after treatment, as assessed by follow-up rhinoscopy. However, some factors such as destruction of turbinates and lysis of the nasal septum, which were included in the rhinoscopic score system, are not influenced by clinical improvement, and therefore not all components of the score reflected the healing process.

The overall success rate of 17 of 19 dogs in group A and 7 of 7 dogs in group B compares favorably with the 80 to 90% cure after topical treatment through surgically or noninvasively implanted catheters and the 50 to 70% recovery after systemic treatment.[1-3,12] Nevertheless, cure after a single infusion was achieved in 6 of 7 dogs in group B, and in only 9 of 17 dogs in group A. The discrepancy between group A and B was probably the result of better positioning of the infusion catheters and higher concentration of enilconazole in group B. In only 1 previous study was endoscopic placement of the catheters into the frontal sinus reported with a success rate of 100% in 6 dogs after 2 or 3 treatments.[6] The combination of topically and systemically administered treatments in group B may also have influenced the overall success rate.

At the time of diagnosis, fungal rhinitis was associated with concomitant bacterial rhinitis in 90% of the

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dogs. In certain dogs that were cured of fungal rhinitis, persistence or recurrence of bacterial infection of the frontal sinus or the nasal cavities was responsible for the persistence of nasal discharge.

Because clinical improvement was obvious after 1 treatment, persistence of fungal plaques can be easily missed without follow-up rhinoscopy. Additionally, bacterial rhinitis and sinusitis, frequent sequelae of extensive turbinate destruction, cannot be distinguished from persistent fungal infection. Rhinoscopy was the chosen method to detect fungi and establish cure. Although strongly material- and operator-dependent,[6] rhinoscopy is, in our hands, the most reliable diagnostic tool and provides information that is useful for management of treatment. For dogs confirmed to be free of fungus at the end of antifungal drug treatment, long-term prognosis appears to be good.

No major complications were observed with use of a 1 or 2% emulsion of enilconazole. At these concentrations, enilconazole is fluid, and good diffusion without any irritating effect can be obtained. Leakage around the catheters or through the incisive ducts or the nasolacrymal system did not seem to have any negative consequences. Pressure < 15 cm of water after 20 minutes of infusion seems to be a good indicator of leakage around the nasopharyngal catheter.[4] We did not observe prolonged recovery from anesthesia or upper airway obstruction as reported for clotrimazole; neurologic signs were also not detected.[13,14] Nasal discharge and epistaxis immediately after treatment can be copious, but even severe bleeding always stopped within a few minutes. Mucosal blebs in association with this treatment have never been reported before but do not appear to have clinical relevance.

In our study, both protocols had good efficacy for treatment of nasal aspergillosis with involvement of the frontal sinuses. Infusion of 2% enilconazole into the frontal sinuses and nasal cavities through endoscopically placed catheters and extensive rhinoscopic debridement prior to infusion appears particularly useful, because the number of infusion procedures can be reduced. Follow-up rhinoscopy is strongly advised.

[a]Domitor, Pfizer Animal Health SA, Louvain-La-Neuve, Belgium.
[b]Combistress, Phenix SA, Brussels, Belgium.
[c]Mephenon, Federa SC, Brussels, Belgium.
[d]Nesdonal, Rhône-Poulenc SA, Lyon, France.
[e]Diprivan, AstraZeneca SA, Brussels, Belgium.
[f]Forene, Abbott SA, Ottignies-LLN, Belgium.
[g]Cystoscope K Storz SL 30°, Ref BA 3059308, Karl-Storz-Endoscopy Belgium SA, Strombeek-Bever, Belgium.
[h]Fujinon EB-4105, Onys SA, Brussels, Belgium.
[i]Imaverol, Janssen-Cilag SA, Beerse, Belgium.
[j]Sufenta, Janssen-Cilag SA, Beerse, Belgium.
[k]Cefacidal, Bristol-Myres Squibb Belgium SA, Brussels, Belgium.
[l]Keforal, Eli Lilly Benelux SA, Brussels, Belgium.
[m]Nizoral, Janssen-Cilag SA, Beerse, Belgium.
[n]Synulox, Pfizer Animal Health SA, Louvain-La-Neuve, Belgium.
[o]Baytril, Bayer SA, Brussels, Belgium.

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