Combined clotrimazole irrigation and depot therapy for canine nasal aspergillosis

OBJECTIVES: To evaluate the effect of short duration 1 per cent clotrimazole flush when combined with 1 per cent clotrimazole cream instilled into the frontal sinuses for the treatment of nasal aspergillosis in 14 dogs.

METHODS: Fourteen dogs with clinical, radiological, serological and rhinoscopic findings consistent with nasal aspergillosis were treated by frontal sinus trephination and a short, five-minute flushing of 1 per cent topical clotrimazole solution followed by a 1 per cent clotrimazole cream instilled as a depot agent.

RESULTS: Twelve of the 14 dogs (86 per cent) responded well to treatment and either had no clinical signs after treatment or had signs consistent with mild rhinitis during a minimum follow-up period of six months. Only one dog required multiple treatments. Treatment was well tolerated by all patients, with minimal complications.

CLINICAL SIGNIFICANCE: This treatment compares favourably to previously published data using one-hour topical clotrimazole or enilconazole flushing treatment protocols. The treatment technique significantly reduced treatment time under anaesthesia.

INTRODUCTION

Infection of the nasal and paranasal sinus with *Aspergillus* species is a well-recognised entity in the dog (Lane and Warnock 1977, Harvey 1984, Sharp and others 1984, 1991, Davidson and Pappagianis 1995, Mathews and others 1996, Sharp 1998). Affected dogs are presented with chronic mucopurulent nasal discharge, depigmentation and ulceration of the nasal planum, and intermittent bouts of epistaxis. Fungal colonies become established primarily in the frontal sinuses, although the disease results in widespread damage to surrounding structures, including the turbinates within the nasal sinuses. There is no consistently reliable diagnostic test for *Aspergillus* infection, and therefore diagnosis usually rests on the recognition of clinical signs, evidence of radiological and rhinoscopic changes in the nasal and paranasal sinuses, and the detection of antibodies to *Aspergillus* species on serological tests (Sharp 1998).

Effective control of the disease has often been difficult to achieve, and a wide variety of treatment modalities have been investigated, including topical and systemic administration of antifungal agents or combinations of the two routes of administration (Sharp and others 1984, 1991, 1993, Sharp and Sullivan 1986, 1989, Bray and others 1998, Mathews and others 1998, Friend and others 2002). Systemic administration of antifungal agents has been shown to have poor efficacy, with cure rates only approaching 50 per cent (Sharp and others 1984, Sharp and Sullivan 1989). Cure rates of up to 60 to 70 per cent with itraconazole has been reported when used in multiple treatment protocols; however, hepatotoxicity, anorexia and cutaneous drug eruptions have shown to still present serious complications from systemic antifungal treatment (Legendere 1995).

By comparison, topical treatment for nasal aspergillosis has been shown to have considerably better efficacy (Sharp and others 1993, Bray and others 1998, Mathews and others 1998, Smith and others 1998). Instillation of the antifungal agent into the nasal and paranasal sinuses is performed following either surgical placement of catheters (invasive topical treatment) or by non-surgical placement of catheters into the nasal sinuses via the nostrils (non-invasive topical treatment). Enilconazole administered as an invasive topical treatment has shown to be successful in approximately 90 per cent of cases (Sharp and others 1993). However, this requires multiple treatments over a period of 10 days and is poorly tolerated. Clotrimazole has been used as a topical agent both invasively and non-invasively with similar success rates (Richardson and Mathews 1995, Mathews and others 1998, Smith and others 1998). Although a recent report using topical clotrimazole revealed that in most cases only one treatment is necessary to provide clinical
introduction of a 10 French gauge Jacques frontal bone was trephined to permit the preparation and draping of the skin, the sinuses to drain rostrally. Following asepsis of any fluid debris and the head tilted rolled cotton gauze to prevent aspiration recumbency with the pharynx packed with were administered iv at induction of 4 mg/kg carprofen (Rimadyl; Pfizer) cillin (Augmentin; GlaxoSmithKline) and 20 mg/kg clavulanate-potentiated amoxicillin (IsoFlo; Abbot) in oxygen. A dose of nously (iv) and maintained with isoflurane kg propofol (PropoFlo; Abbot) intrave- and anaesthesia was induced with 4 mg/ kg methadone (Physeptone; Martindale Laboratory) intramuscularly (im), and anaesthesia was induced with 4 mg/ kg propofol (PropoFlo; Abbot) intravenously (iv) and maintained with isoflurane (IsoFlo; Abbot) in oxygen. A dose of 20 mg/kg clavulenate-potentiated amoxi- cillin (Augmentin; GlaxoSmithKline) and 4 mg/kg carprofen (Rimadyl; Pfizer) were administered iv at induction of anaesthesia. Patients were positioned in sternal recumbency with the pharynx packed with rolled cotton gauze to prevent aspiration of any fluid debris and the head tilted downwards to allow fluid from the nasal sinuses to drain rostrally. Following aseptic preparation and draping of the skin, the frontal bone was trephined to permit the introduction of a 10 French gauge Jacques urethral catheter (Rüsch) into each sinus. The sinuses were irrigated with 500 ml of warm saline (at approximately 30°C) over five minutes to confirm appropriate catheter placement and ensure patency of the nasofrontal ostium. The sinuses were further irrigated with 1 per cent clotrimazole in propylene glycol solution for over five minutes. (Canesten 1 per cent solution; Bayer). For dogs weighing more than 10 kg, a total of 1 g of clotrimazole solution was used (50 ml per side). For dogs less than 10 kg, a total of 500 mg was used (25 ml per side). Clotrimazole cream (Canesten 1 per cent cream; Bayer) was then introduced into the frontal sinuses; for dogs weighing less than 10 kg, a total of 20 g was used (10 g each side) and for dogs weighing more than 10 kg, a total of 40 g (20 g each side) was used. The catheters were removed, and the skin incisions were repaired. Any excess fluid was allowed to drain from the nasal sinuses before the pharyngeal gauze packing was removed and the patient recovered. Patients received ongoing opioid (0-01 mg/kg buprenorphine [Vetergesic; Alstoe Animal Health] im) and non-steroidal anti-inflammatory analgesia postoperatively. Antibiotic and non-steroidal anti-inflammatory therapy was continued for a further seven days. Patient follow-up included re-examination at four weeks and thereafter by phone contact with owners after a minimum period of six months. The outcome of treatment was classified as: • without any clinical signs, • intermittent discharge, or • presenting symptoms continuing unchanged. Patients with ongoing signs at four weeks were eligible for re-treatment using the above technique.

RESULTS
A total of 14 dogs were included in this study (Table 1). Patients ranged from one to 13 years of age, with nine males and five females. All dogs included in this study had clinical, radiological, rhinoscopic and serological findings consistent with active nasal aspergillosis infection. Immediate postoperative complications were minimal, the most common complication being extravasation of the clotrimazole cream through the trephination holes (n=4). Mild subcutaneous emphysema in the region of the trephined holes was also noted in one animal. The mean (sd) duration for the procedure was 31.7 (±2) minutes. The treatment was well tolerated by the patients, with most allowing gentle cleaning of discharge or cream from the nasal planum and trephination area while hospitalised. All patients were discharged within 48 hours of treatment. All patients had evidence of the cream in the nasal discharge throughout the period of hospitalisation.

Telephone follow-up (ranging from 6 to 24 months) revealed that 10 patients remained symptom free. Two patients were considered by their owners to have intermittent, mild mucopurulent or serous nasal discharge. Two patients showed initial transitory improvement, but had a recurrence of mucopurulent discharge similar to that at the time of presentation. Of the 14 dogs in this study, two were considered treatment failures (14 per cent). One of these dogs was re-treated on three occasions. The overall treatment success rate for this study was 86 per cent.

DISCUSSION
The technique described here for clotrimazole therapy offers a number of advantages over previously described invasive and non-invasive procedures. First, the duration of anaesthesia is substantially reduced by comparison with that required for other techniques necessitating anaesthesia during the drug contact period. The average duration of anaesthesia here was approximately 30 minutes, whereas an anaesthesia period of not less than 60 minutes can be anticipated for other invasive or non-invasive techniques (Friend and others 2002). Secondly, aspiration or pharyngeal oedema secondary to propylene glycol exposure reported for non-invasive techniques (Smith and others 1998) were not encountered, and complications associated with indwelling catheters (Sharp and others 1993) were avoided. A potential contraindication for topical application techniques is extension of the drug to the brain across a damaged cribriform plate (Sharp 1998). This risk appears to be low, but magnetic resonance imaging or computed tomography is recommended in patients where this is a potential concern (Sharp 1998). None of the patients included in the current study had evidence suggesting cribriform plate erosion. Finally, patients required only

MATERIALS AND METHODS
Fourteen dogs were presented between January 2001 and 2003 and underwent clinical, radiological and rhinoscopic confirmation of nasal aspergillosis. Serological sampling was performed (The Mycology Reference Centre, Leeds Public Health Laboratory). Patients were premedicated with 0-01 mg/kg acepromazine (ACP; C-Vet Veterinary Products) and 0.3 mg/ kg methadone (Physeptone; Martindale Pharmaceuticals) intramuscularly (im), and anaesthesia was induced with 4 mg/ kg propofol (PropoFlo; Abbot) intravenously (iv) and maintained with isoflurane (IsoFlo; Abbot) in oxygen. A dose of 10 mg/kg clavulenate-potentiated amoxicillin (Augmentin; GlaxoSmithKline) and 4 mg/kg carprofen (Rimadyl; Pfizer) were administered iv at induction of anaesthesia. Patients were premedicated with 0.1 mg/kg acepromazine (ACP; Bayer). For dogs weighing more than 10 kg, a total of 20 g was used (10 g each side) and for dogs weighing more than 10 kg, a total of 40 g (20 g each side) was used. The catheters were removed, and the skin incisions were repaired. Any excess fluid was allowed to drain from the nasal sinuses before the pharyngeal gauze packing was removed and the patient recovered. Patients received ongoing opioid (0-01 mg/kg buprenorphine [Vetergesic; Alstoe Animal Health] im) and non-steroidal anti-inflammatory analgesia postoperatively. Antibiotic and non-steroidal anti-inflammatory therapy was continued for a further seven days. Patient follow-up included re-examination at four weeks and thereafter by phone contact with owners after a minimum period of six months. The outcome of treatment was classified as:

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brief hospitalisation with most patients discharged within 24 hours of treatment and all discharged within 48 hours. All dogs tolerated the treatment well, and complications were relatively minor.

The viscosity of the cream preparation may provide greater persistence in the frontal sinus than the propylene glycol solution, thereby increasing drug contact time with the fungal colonies. Dissipation of the cream may also prolong the contact period with any fungal colonies in the nasal cavity and allow distribution of the drug throughout the nasal sinuses as the dog sneezes or moves its head throughout the day. Although it was not possible to quantify the duration of the preparation in the sinuses, the persistence of cream in the nasal discharge throughout the period of hospitalisation may suggest that drug-fungal contact time is greatly extended over that for other methods of administration.

The treatment outcome in this study compares favourably with those previously reported for topical clotrimazole (87 per cent) (Mathews and others 1998) and enilconazole (90 per cent) (Sharp and others 1993). Cessation of nasal discharge occurs in most dogs two weeks after topical treatment (Mathews and others 1998, Friend and others 2002). Follow-up reports in the present study were obtained at a minimum of six months after treatment. Ten of the patients in this study remained symptom free at six months. Recurrence of rhinitis due to recurrent fungal infection is uncommon once nasal discharge ceases after clotrimazole treatment (Sharp and others 1998).

Two dogs continued to have intermittent nasal discharge but were considered free of fungal infection. This observation is consistent with previous reports that some patients may have discharge due to turbinate damage rather than ongoing mycosis (Mathews and others 1998). Some of these patients may have recurrent rhinitis that can be expected to respond to antibiotic therapy. Two dogs failed this treatment and did not respond to repeated therapy.

Owner evaluation of the treatment protocol was very positive, with the most common comment from owners reflecting the need for continued wiping of the nostrils for as much as a week after treatment. Owners also reported that the demeanour of their dog significantly improved compared to pretreatment starting approximately three to four days postoperatively. Ten of 14 owners experienced no further clinical signs in their dogs, and an additional two felt that there was a significant improvement in all respects except for an occasional antibiotic responsive rhinitis. The treatment failed to resolve clinical signs in the two remaining cases.

Re-evaluation by rhinoscopy was carried out on the two patients with continued clinical signs, but not for all the patients. Given the lack of clinical signs in the remaining patients, most owners felt reluctant to allow a second general anaesthetic and rhinoscopy, although this may have allowed a more complete assessment of treatment efficacy.

Infusion of clotrimazole cream into the frontal sinus by trephination provides a fast and effective treatment technique for canine aspergillosis. The treatment success rate from this preliminary study compares favourably with previously described techniques, but is easier to perform, requires shorter duration of anaesthesia and has a low morbidity rate. Further clinical evaluation of this technique using clotrimazole cream is underway to allow a larger group statistical comparison to other current topical treatment techniques.

References


Table 1. Signalment and outcome in 14 dogs treated with 1 per cent clotrimazole cream

<table>
<thead>
<tr>
<th>Case (n)</th>
<th>Breed</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Complications</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Labrador retriever</td>
<td>4</td>
<td>F</td>
<td>Mild cream discharge at trephination site</td>
<td>No clinical signs</td>
</tr>
<tr>
<td>2</td>
<td>German shepherd</td>
<td>7</td>
<td>M</td>
<td>None</td>
<td>No clinical signs</td>
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<tr>
<td>3</td>
<td>Staffordshire bull terrier</td>
<td>10</td>
<td>M</td>
<td>None</td>
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</tr>
<tr>
<td>4</td>
<td>Lurcher</td>
<td>13</td>
<td>FN</td>
<td>None</td>
<td>No clinical signs</td>
</tr>
<tr>
<td>5</td>
<td>Labrador retriever</td>
<td>2</td>
<td>FN</td>
<td>Mild cream discharge at trephination site</td>
<td>Occasional antibiotic responsive mucopurulent nasal discharge</td>
</tr>
<tr>
<td>6</td>
<td>Border collie</td>
<td>12</td>
<td>MN</td>
<td>Mild cream discharge at trephination site</td>
<td>Occasional antibiotic responsive mucopurulent nasal discharge</td>
</tr>
<tr>
<td>7</td>
<td>Golden retriever</td>
<td>1</td>
<td>M</td>
<td>None</td>
<td>No clinical signs</td>
</tr>
<tr>
<td>8</td>
<td>Labrador retriever</td>
<td>9</td>
<td>MN</td>
<td>None</td>
<td>No clinical signs</td>
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<tr>
<td>9*</td>
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<td>M</td>
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<td>MN</td>
<td>None</td>
<td>No clinical signs</td>
</tr>
<tr>
<td>12</td>
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<td>9</td>
<td>FN</td>
<td>None</td>
<td>Mild intermittent serous discharge</td>
</tr>
<tr>
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<td>4</td>
<td>M</td>
<td>None</td>
<td>No clinical signs</td>
</tr>
<tr>
<td>14</td>
<td>Staffordshire bull terrier</td>
<td>3</td>
<td>M</td>
<td>None</td>
<td>No clinical signs</td>
</tr>
</tbody>
</table>

F Female, M Male, N Neutered

*Treated for a total four treatments. All other cases treated only once
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