PAPER

Management of 13 cases of canine respiratory disease using inhaled corticosteroids

OBJECTIVES: To determine the value of inhaled corticosteroids in the management of chronic inflammatory airway disease in dogs.

METHODS: Medical records of dogs that were presented for the investigation of respiratory disease were reviewed retrospectively. Criteria for inclusion were knowledge of previous medical treatment including side effects, diagnosis of the underlying disease, use of inhaled corticosteroids and at least two-months follow-up data.

RESULTS: Thirteen dogs that fulfilled the criteria were identified. Ten dogs were diagnosed with chronic bronchitis and three with eosinophilic bronchopneumopathy. Four dogs had not previously received corticosteroid treatment for their respiratory disease, and all these showed a reduction or a resolution of clinical signs without obvious side effects after inhaled corticosteroid therapy. Nine dogs had previously received oral or parenteral corticosteroids for treatment of their respiratory disease, and all had exhibited side effects. Five of these dogs were treated with inhaled corticosteroids alone, and all exhibited an improvement in clinical signs without observable side effects. The remaining four dogs were treated with a combination of inhaled and oral corticosteroids, and all showed improvement in clinical signs and reduction in side effects. Inhaled medication was well tolerated in all dogs.

CLINICAL SIGNIFICANCE: Inhaled corticosteroids were used for the management of chronic bronchitis and eosinophilic bronchopneumopathy in 13 dogs, and these may have the advantage of reducing side effects associated with oral corticosteroids.

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INTRODUCTION

Several respiratory diseases in dogs, such as chronic bronchitis and eosinophilic bronchopneumopathy (EBP), require the use of chronic anti-inflammatory or even immunosuppressive doses of corticosteroids (Corcoran and others 1991, Clercx and others 2000, McKiernan 2000). Long-term oral or parenteral corticosteroid therapy is associated with well-recognised side effects in many animals (Huang and others 1999). Iatrogenic hyperadrenocorticism results from excessive administration of corticosteroids, and the most common clinical signs are polyuria and polydipsia together with cutaneous and conformational abnormalities (Huang and others 1999). Biochemical alterations are also common in dogs with iatrogenic hyperadrenocorticism (Huang and others 1999). Furthermore, the hypothalamic-pituitary-adrenal (HPA) axis in dogs is readily suppressed by exogenous corticosteroids, and adrenal gland atrophy due to a severely depressed HPA axis can be caused by long-term corticosteroid use (Moore and Hoenig 1992).

Inhaled corticosteroid (ICS) therapy is the preferred treatment for a wide range of respiratory diseases in human beings; for example, it is currently considered to be the most effective anti-inflammatory therapy for patients with asthma (Fitzgerald and others 1998) and is also effective in people with other respiratory disorders such as chronic bronchitis and eosinophilic bronchitis (Joo and others 2002, Mapel 2004).

ICS therapy is preferred to systemic steroid therapy in human beings since it has the advantage of allowing direct absorption of the drug into the lung, hence diminishing systemic effects (Rohatagi and others 1999). Inhalation of corticosteroids results in a high local concentration of drug in both central and peripheral lung tissues, while the concentration in plasma remains low at corresponding time points (Van den Bosch and others 1993). Studies in human beings have also demonstrated that ICSs allow a marked reduction in oral steroid dosage in steroid-dependent patients (Hummel and Lehtonen 1992).

ICSs are seldom used in small animal medicine due to the perceived lack of patient compliance and scarcity of information regarding dosing regimens and success rates. ICSs for the management of feline asthma have been successful (Padrid 2000), although controlled clinical trials

have not yet been reported. The aim of the present retrospective study was to determine whether ICSs could be used in the management of respiratory diseases in dogs.

MATERIALS AND METHODS

The medical records of all dogs referred to the Queen's Veterinary School Hospital, University of Cambridge, from September 2001 to October 2004, were reviewed. Criteria for inclusion in the study were the following:

- complete medical records and investigations leading to a diagnosis of the underlying inflammatory airway disease;
- treatment with ICSs for a minimum of two months; and
- at least two-months follow-up data.

Details of each dog's signalment, history, previous medical therapy including the response and the side effects, physical examination, diagnosis, treatment and outcome were obtained from the records completed at the time of initial patient evaluation. A telephone contact was also made with the owners to discuss each dog's response to treatment. The owners subjectively assessed the response to treatment and the side effects. The owners were asked to decide if there had been any change in clinical signs, such as coughing, exercise tolerance and lethargy after treatment with ICS, and to define the change as 'no change', 'worsening' or 'improving'.

Details of the side effects were recorded from both the clinical records and by telephone contact with the owners. The owners were questioned about their dog's intake of water, urination, appetite, weight, exercise tolerance and general demeanour. For instance, the owners were asked if they had noted any difference in the amount of time their dog spent in drinking water or if there had been any change in the frequency of water needed to be replaced. The owners were also asked if they had noted any additional changes in their dog's behaviour following therapy with ICSs and how the ICS administration had been tolerated.

As part of the diagnostic investigation, all cases had thoracic radiography, haematological and biochemical evaluation, faecal analysis for respiratory parasites, rigid or fibreoptic bronchoscopy and bronchoalveolar lavage. For all cases, the bronchoalveolar samples were submitted for cytology and culture. Additional tests performed in some cases included tracheal washing (n=2), bronchial biopsy (n=3), echocardiography (n=6) and blood gas analysis (n=6). Additional tests were decided at the time of initial investigation and varied depending on the clinician's preference and results of other investigations. For instance, animals with a heart murmur or cardiac abnormalities on thoracic radiography also had echocardiography. Blood gas analysis was generally performed as an investigation before general anaesthesia. Animals with an evidence of laryngeal paralysis (n=2) also had electromyelography and peripheral nerve conduction velocities as part of their investigation.

A diagnosis of chronic bronchitis was made according to previous criteria, which included a history of chronic cough and absence of other potential causes (such as heart failure, bronchopneumonia or pulmonary neoplasia), as determined by physical examination, thoracic radiography, bronchoscopy and laboratory tests, including tracheobronchial cytology, culture of bronchial secretion, haematology and faecal examination for respiratory parasites (Wheeldon and others 1977, Prueter and Sherding 1985). EBP was diagnosed using the criteria described by Clercx and others (2000). Briefly, this was based on the presence of compatible clinical signs including cough, cytological evidence of bronchial and bronchoalveolar eosinophilic infiltrate and exclusion of other specific causes of eosinophilic airway cytology.

A diagnosis of laryngeal paralysis was made if there was any evidence of poor arytenoid movement under a light plane of anaesthesia and associated clinical signs such as dysphonia and inspiratory stridor (White 1989).

Ten dogs were treated with inhaled beclomethasone dipropionate (Becloforte Inhaler; Allen & Hanburys) and three with fluticasone propionate (Flixotide Evohaler; Allen & Hanburys). The decision to use a particular product was related to the clinician's preference. ICSs were administered via a metered dose inhaler into a spacer device (Volumatic Paediatric Spacer Device; Allen & Hanburys) and a face mask (Animal Mask; GaleMed Corporation) in all cases (Fig 1). The stipulated dose of medication was discharged into the spacer device and the mask was held over the dog's nose for approximately five to 10 breaths (Fig 2). The dose of inhaled medication varied slightly between patients, but the majority of animals treated with beclomethasone dipropionate received a dose of 250 µg twice daily. The dose of fluticasone propionate used in all three dogs was 125 µg twice daily.

RESULTS

From the records, 13 dogs that fulfilled the criteria were identified (Table 1). Two underlying diseases were diagnosed that were subsequently treated with ICSs. The most common disease was chronic bronchitis (n=10), followed by EBP (n=3). Two dogs were diagnosed with laryngeal paralysis, and these dogs also had chronic bronchitis. Coughing was the most prevalent clinical sign and was present in all dogs. Lethargy (n=2) and exercise intolerance (n=6) were also documented. Two dogs diagnosed with chronic bronchitis exhibited expectoration. Both the dogs with laryngeal paralysis exhibited inspiratory stridor and dysphonia.

Four dogs had not previously received corticosteroid treatment for their respiratory disease, and two of them were currently receiving non-steroidal anti-inflammatory drug (NSAID) therapy for osteoarthritis. All four dogs had previously

FIG 1. The spacer connected to a metered dose inhaler and face mask

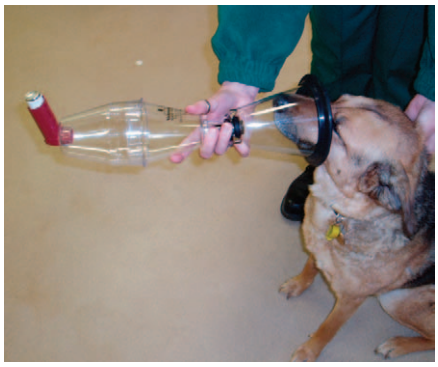

FIG 2. Beclomethasone dipropionate metered dose inhaler being administered via a spacer device and mask

received antibiotic therapy, but this had failed to provide improvement in clinical signs. These four dogs showed a resolution (n=2) or a reduction (n=2) in clinical signs (coughing) following treatment with ICSs. None of these dogs developed obvious side effects, as subjectively assessed by the owners, from inhaled medication.

The remaining nine dogs had previously received oral or parenteral corticosteroids, and all showed side effects. Side effects were attributed directly to corticosteroid treatment and occurred shortly after commencing therapy and consisted of polyuria in all cases, with animals exhibiting polydipsia (n=6), nocturia (n=1), polyphagia (n=2), weight gain (n=3) and muscle weakness (n=3). Response to previous oral or parenteral corticosteroid therapy had been variable in these dogs, and side effects necessitated a dose reduction or a withdrawal of therapy. No dog was on corticosteroid therapy at the time of referral, and all dogs had been off oral corticosteroid treatment for a minimum of three weeks.

In five of the nine dogs that had previously received corticosteroids, therapy with oral or parenteral corticosteroids was not re-commenced and treatment instigated with ICSs alone. This resulted in a resolution of clinical signs (n=1) or a marked reduction in clinical signs (n=4) without obvious side effects. In animals that experienced a marked reduction in clinical signs, the reduction was due to a decreased frequency of coughing (n=4), decreased gagging (n=1) and expectoration (n=1).

The remaining four dogs received ICSs in combination with oral prednisolone (Prednicare Tablets; Animalcare). The oral corticosteroid dose was dictated by the individual clinician and ranged from 0·6 mg/kg once a day to 0·1 mg/kg every other day, which was lower than that previously prescribed. In all these dogs, the use of ICSs resulted in reduced owner-observed side effects, including reduced polyuria (n=4), polydipsia (n=3) and weakness (n=1), compared with those seen with previous oral or parenteral therapy, and also resulted in reduced clinical signs including coughing (n=4), exercise intolerance (n=2) and lethargy (n=2), compared with those documented on oral therapy alone. One of these dogs was subsequently transferred to ICS treatment alone. In one dog with chronic bronchitis and subsequent smoke inhalation, after an initial two-month period of improvement, deterioration occurred due to the development of bronchopneumonia. Treatments with ICS and oral corticosteroid in this dog were stopped, and supportive therapy was instigated.

DISCUSSION

This study documents the use of ICSs in the management of respiratory diseases in 13 dogs. The animals in this study were treated with ICSs for several reasons: oral corticosteroids were avoided in two dogs because of concurrent NSAID therapy and in a further two dogs because of potential side effects associated with oral corticosteroid therapy. Therapy with ICSs was used in the remaining dogs since they had already suffered side effects at doses inadequate to control clinical signs. Additionally, inhaled therapy was chosen due to the expected therapeutic benefit over oral corticosteroids in the treatment of these respiratory diseases.

All dogs treated with ICSs were diagnosed with either chronic bronchitis or EBP. Similarly, these two diseases represent the most common cause of coughing in dogs that were presented to another referral institute (Brownlie 1990).

Chronic bronchitis in dogs is defined as a condition of chronic or recurrent excessive mucus production in the bronchial tree for at least two consecutive months in the previous year, manifested clinically by chronic coughing (Prueter and Sherding 1985). EBP is a disease characterised by eosinophilic infiltration of the lung and bronchial mucosa. It has been described in human beings and dogs (Clercx and others 2002).

Anti-inflammatory therapy is the most important aspect in the treatment of chronic bronchitis, and oral corticosteroids form the basis of chronic therapy (McKiernan 2000). Oral corticosteroids are also the mainstay of treatment of EBP (Corcoran and others 1991, Clercx and others 2000). Since these conditions are often chronic and persistent, ongoing anti-inflammatory or even immunosuppressive doses of corticosteroids are required. For instance, relapses occur in up to 70 per cent of cases of EBP within months of drug discontinuation (Clercx and others 2000).

ICSs are preferred in human medicine for the treatment of a wide range of respiratory diseases since this method of drug delivery substantially improves the therapeutic ratio compared with the oral route. For example, inhaled beclomethasone dipropionate is approximately 30 to 50 times more potent in improving asthma control than oral prednisolone, whereas oral prednisolone is approximately seven times more potent in inducing steroid-related side effects (Toogood and others 1989). Thus, the use of ICSs allows most human patients to discontinue oral corticosteroid medication (Nelson and others 1999).

Although asthma is very common in human beings, a disease with similar pathophysiology is not recognised in canine patients. The majority of dogs in this study were suffering from chronic bronchitis. In human beings, the inflammatory factors associated with chronic bronchitis are generally less affected by ICSs than those seen in asthma (Hattotuwa and others 2002). Nevertheless, clinical trials in human patients with bronchitis have shown that ICSs are associated with improved baseline pulmonary function, reduced chronic respiratory symptoms, reduced disease exacerbation frequency and severity, and improved quality of life (Mapel 2004). For this reason, it is

Table 1. Summary of case details

Breed	Age	Sex	Clinical signs	Previous medical therapy	Side effects due to previous medical therapy	Diagnosis	Treatment	Outcome
Standard poodle	Eight years	MN	Chronic cough, exercise intolerance	Antibiotics	None	CB	BC	Resolution of coughing; improved exercise tolerance; maintained on alternate day therapy; no side effects
Dalmatian	Five years	MN	Chronic cough, expectoration, mild exercise intolerance	Antibiotics	None	EBP	FP	Resolution of clinical signs; maintained on daily therapy; no side effects
Labrador retriever	11 years	ME	Chronic cough, inspiratory stridor, dysphonia	NSAIDs, antibiotics	None	CB, laryngeal paralysis	BC	Reduction in cough; dysphonia persisted; maintained on daily therapy; no side effects
Sheltie	Nine years	ME	Chronic cough, exercise intolerance	NSAIDs, antibiotics	None	CB	FP	Reduction in severity and frequency of coughing; maintained on daily therapy; no side effects
Crossbreed	Six years	MN	Chronic cough, gagging	Prednisolone	PU, PD, polyphagia, weight gain	CB	FP, weight reduction	Resolution of coughing and gagging; no side effects
Labrador retriever	10 years	FN	Chronic cough	Prednisolone	PU, PD, hindlimb weakness	CB	BC	Reduction in coughing; no side effects
Great Dane	Three years six months	FN	Chronic cough, dysphonia, inspiratory stridor, exercise intolerance	Parenteral dexamethasone, antibiotics, frusemide, NSAIDs	PU, muscle weakness	CB, laryngeal paralysis	BC	Reduction in frequency of coughing; improved exercise tolerance; dysphonia persists; no side effects
Terrier cross	Six years	ME	Chronic cough, expectoration	Prednisolone, bronchodilators, antibiotics	PU, nocturia	CB	BC, BD	Reduction in coughing to early morning only; reduced expectoration; no side effects
Dalmatian	10 years	FN	Chronic cough	Prednisolone, frusemide, ACE inhibitor	PU, PD	CB	BC	Reduction in coughing; no side effects
Welsh springer spaniel	Two years three months	ME	Chronic cough	Prednisolone	PU, PD	EBP	Prednisolone and BC on alternate days	Reduced clinical signs and side effects; subsequently transferred to inhaled beclomethasone dipropionate only; clinical signs resolved; no side effects
Jack Russell terrier	One year six months	FN	Chronic cough, lethargy	Prednisolone, antibiotics	PU, PD, weight gain	EBP	Daily BC and a reduced dose of prednisolone	Coughing reduced, lethargy persisted; maintained on alternate day inhaled and oral corticosteroids; side effects present (PU, PD) but reduced from previously
Labrador retriever	Two years	FN	Chronic cough, lethargy, exercise intolerance	Prednisolone, antibiotics, bronchodilators	PU, weight gain, weakness	CB, smoke inhalation	Inhaled BC, prednisolone, antibiotics	Initial improvement in clinical signs and side effects; later deterioration and corticosteroid treatment ceased; transferred to antibiotic therapy only
Border collie	Two years six months	ME	Chronic cough, collapse on exercise, exercise intolerance	Prednisolone, antibiotics	PU, PD, polyphagia	CB	Prednisolone and BC on alternate days; BD	Improvement in clinical signs and reduction in side effects; still PU and PD; disease control worse on days when oral corticosteroids were used

MN Male neutered, ME Male entire, FN Female neutered, NSAIDs Non-steroidal anti-inflammatory drugs, ACE Angiotensin converting enzyme, PU Polyuria, PD Polydipsia, CB Chronic bronchitis, EBP Eosinophilic bronchopneumopathy, BC Beclomethasone dipropionate (inhaled), FP Fluticasone propionate (inhaled), BD Oral bronchodilator

hypothesised that ICSs might have similar benefits in canine chronic bronchitis.

Fluticasone propionate was used to treat two dogs with chronic bronchitis and one with EBP. It is an ICS with negligible oral systemic bioavailability (<1 per cent) in human beings because of poor absorption from the gastrointestinal tract and extensive first-pass hepatic metabolism (Harding 1990). Its high lipophilicity, combined with an increased affinity for the glucocorticoid receptor, results in an increased retention of the drug in the lung tissue relative to other ICSs (Hogger and Rohdewald 1994). Previous studies have shown a 2:1 efficacy advantage of fluticasone propionate over beclomethasone dipropionate in adults and children on ICSs (Barnes and others 1993, Fitzgerald and others 1998). It was not possible to compare the clinical response to treatment with fluticasone propionate over beclomethasone dipropionate in the present study due to the small treatment groups, differences in previous medications and lack of a standardised treatment regimen. Future prospective studies will attempt to compare the two drugs in an objective manner.

Inhaled medication was well tolerated in all cases, although one to two weeks were required to allow adaptation to this method of drug administration. This was achieved by initially placing just the mask over the dog's muzzle several times per day. The metered dose inhaler was also discharged into the spacer device at a distance away from the dog. Due to the retrospective nature of this study, it was not possible to standardise the formulation or dose of ICS. Treatment was initiated with twice daily dosing in all animals, as this has been shown to be more effective than once daily dosing in human patients (Boulet and others 2000). A low-resistance spacer device was used with all cases, which allowed inhaled medication to be administered without the need to coordinate breathing, and also decreased oropharyngeal deposition (Dolovich and others 1983).

All drugs deposited in the airways are eliminated via the systemic circulation and have, therefore, the potential to cause some side effects (Lotvall 1997). Depending on the formulation, only a small proportion of the emitted dose reaches the lung and the rest is deposited in the mouth and pharynx. ICSs have demonstrated a good safety profile at the doses used by most human patients. There is a low incidence of both systemic and local side effects seen at higher doses, although these side effects are less than those seen with oral corticosteroids (Roland and others 2004). Systemic side effects are dose dependent and include osteoporosis, adrenocortical suppression, bruising and skin thinning, cataracts and glaucoma. Local side effects include perioral dermatitis, tongue hypertrophy, oral and oropharyngeal candidiasis, pharyngeal inflammation, laryngeal disorders, cough during inhalation and sensation of thirst (Roland and others 2004).

Development of oral candidiasis is a relatively frequently reported side effect of ICS use in human patients, and its prevalence has been reported to be as high as 60 per cent in one study (Spector and others 1982). Between four and 16 per cent of human patients develop oral candidiasis within six months of commencing ICS therapy (Ellepola and Samaranayake 2001). There was no evidence of oropharyngeal infections at re-examination in these cases in the relatively short follow-up period, although it would be prudent to monitor for their occurrence with longer term ICS therapy.

In the current study, no side effects, including signs indicative of hypercortisolaemia, were directly attributed to ICSs, although both the response to therapy and assessment of side effects were subjective and assessed by the owners. Cases treated with ICSs alone did not show obvious side effects. In cases treated with a combination of oral corticosteroids and ICSs, side effects were reduced as compared with those seen with previous corticosteroid treatment. It is possible, however, that in the dogs receiving combination therapy, some of the documented side effects may have been associated with ICSs.

Corticosteroid medication was withdrawn in one dog after two months of therapy due to the development of bronchopneumonia. This dog had been diagnosed with chronic bronchitis based on previous criteria and at a later stage, it suffered smoke inhalation. The development of bronchopneumonia is not an unexpected finding in patients with inhalation injury such as in this one, since lung defence mechanisms are destroyed (Herndon and others 1987). This dog initially showed improvement in clinical signs and side effects on a reduced dose of oral corticosteroids in combination with ICSs. It is possible, however, that ICS treatment may have contributed to reduced immune function locally and the subsequent development of bronchopneumonia.

In two cases of chronic bronchitis, the administration of ICSs alone did not sufficiently alleviate clinical signs, so combination therapy with an orally administered bronchodilator was used. These cases did not show a noticeable improvement in clinical signs after bronchodilator therapy.

Although weight was not measured before, or during, ICS therapy, it is possible that the improvement in clinical signs seen in some animals may have been attributed to a reduction in weight. Environmental management changes had previously been used in the majority of animals, and no further change to the environment was recommended upon commencing therapy with ICSs. All animals had previously received anthelmintic treatment with fenbendazole before referral at a dose sufficient to eliminate *Angiostrongylus vasorum*. Anthelmintic therapy was not part of the subsequent treatment protocol.

Two dogs with concurrent laryngeal paralysis were treated with ICS. Corticosteroids are generally contraindicated in cases of laryngeal paralysis, as these animals are at an increased risk of aspiration pneumonia. The decision to use ICS was made in these cases due to the severity of clinical signs (coughing and inspiratory stridor) associated with concurrent chronic bronchitis. These two animals responded well to the treatment, with a reduction in coughing and improved exercise tolerance. Signs indicative of aspiration pneumonia were not observed during the follow-up period.

Due to the retrospective nature of this study, information regarding the systemic effects of ICSs on the biochemical parameters or the HPA axis was not documented, but it would be useful to determine this in subsequent studies. Although low doses of

ICSs are likely to cause minimal or no HPA axis suppression, long-term high-dose therapy may result in significant suppression by effectively replacing endogenous corticosteroid production (Dluhy 1998). The systemic effects of ICSs in these patients could be assessed by means of serial haematological evaluation or measurement of steroid-specific alkaline phosphatase in future studies. It may also be possible to obtain more objective information regarding systemic side effects by quantifying water intake.

The response to therapy was dependent on subjective assessment by the owners, and it is possible that it could cause a considerable placebo affect. Prospective, double-blinded, placebo-controlled studies, with more accurate methods of assessing response to therapy, such as testing of pulmonary function, are therefore warranted in the future. Ideally, controlled clinical trials to assess the effects of ICSs on the inflammatory cell population, as assessed by repeat bronchoalveolar sampling, would be useful. Due to the fact that the clinical signs were resolved or much reduced, it was difficult to justify this in the present study.

Conclusions

This study illustrates that ICSs can be used for the management of chronic bronchitis and EBP in dogs. The use of ICSs resulted in improvement in clinical signs in all cases. ICSs can allow a reduction of oral steroid dosage in steroid-dependent animals, thereby reducing the owner-observed side effects. ICSs should also be considered an alternative therapy when the use of oral corticosteroids is contraindicated. However, in some dogs, treatment with ICSs alone does not provide adequate control of clinical signs and adjunctive therapy may be required.

Further prospective studies are warranted to investigate the use of ICSs in a larger numbers of animals. Further studies are also required to define optimum treatment protocols and to investigate the potential side effects of ICSs in dogs.

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