Glucocorticoid Therapy in Small Animal Practice: What Do We Really Know?
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Glucocorticoids are among the most widely used (and misused) class of drugs in veterinary medicine. Despite this, scientific information on glucocorticoid therapy in most domestic species is difficult to identify, particularly with respect to optimal dosages and dosage intervals, physical and endocrine side effects, and efficacy in clinical applications. Therefore, therapeutic protocols are often the product of clinical experience, common sense, and information from human medicine.

Principles of rational glucocorticoid therapy
Because of their wide-ranging and nonspecific effects, reports of the clinical usage of glucocorticoids is replete with pragmatic recommendations regarding dosage, duration of therapy and severity of side effects. Much has been adopted from clinical use in man, and much more is known about the fine points of glucocorticoid therapy in dogs and cats than in other species. In the following discussion, most of the specific comments will apply to the use of glucocorticoids in the dog; however, when available, appropriate information for other species will be mentioned. It is important to recognize that glucocorticoids rarely cure disease, with the possible exception of spontaneous glucocorticoid deficiency; they suppress clinical signs hopefully long enough for a condition to run its natural course.

The following general principles should be considered when glucocorticoid therapy is employed:

1. Diagnose the disease first, if possible. Glucocorticoids are generally only palliative and do not provide a true cure for any disease. In addition, if used before all reasonable diagnostic tests have been completed, they may mask signs of underlying disease and complicate specific diagnosis and therapy. Though a definitive diagnosis is not always possible, a presumptive diagnosis should be proposed.

2. Classify the disorder into one of the following categories of glucocorticoid therapy, according to a definitive or presumptive diagnosis: physiologic replacement; intensive short-term; anti-inflammatory and antiallergic; immunosuppressive; and chronic palliative. Each of these usage classifications will be discussed in more detail. By using these classifications, the clinician clearly defines the goal of therapy and can choose a starting dose and formulation appropriate for the disorder.

3. Use glucocorticoids to accomplish specific objectives. It is important to decide on the therapeutic endpoint before therapy is started in order to objectively assess efficacy and determine the smallest effective dose. For example, in treatment of a dog with autoimmune hemolytic anemia, the goal for initial glucocorticoid therapy might be to raise the hematocrit from 10% to 25%. By defining a therapeutic objective, the clinician can then judge the efficacy of a treatment protocol and decide when the glucocorticoid dose should be altered or alternative therapy chosen.

4. The length of therapy should also be anticipated. For example, immunosuppressive therapy generally requires several months of glucocorticoid use. Accordingly, a plan for instituting and later decreasing the dose should be considered from the outset. In such a case, intermittent or alternate-day therapy would not be appropriate, and an intermediate- or long-acting glucocorticoid could be used.

5. Is the patient predisposed to any complications of glucocorticoid therapy? As many of the therapeutic effects of glucocorticoids are nonspecific, clinicians should anticipate the impact on the patient of the previously outlined complications of glucocorticoid use. In doing so, the risk/benefit ratio of using these potent agents is considered.

6. Dosages of glucocorticoids are derived by trial and error, and should be constantly reevaluated. It is important to understand the relative potency and, perhaps more important, the relative duration of action of a glucocorticoid preparation, as the duration of anti-inflammatory effects usually parallels the duration of effects on the hypothalamic-pituitary-adrenal axis. Success with alternate-day therapy, more commonly applied in small animal practice, depends on selecting a glucocorticoid preparation with slightly longer anti-inflammatory or immunosuppressive (beneficial) actions than HPAA-suppressive effects.

Classes of glucocorticoid usage
Physiologic replacement therapy
Replacement therapy involves use of glucocorticoids in amounts similar to those of the naturally occurring glucocorticoids (cortisol in virtually all domestic species) from the adrenal gland. Ideal replacement therapy should mimic the adrenal gland's hormonal output under basal conditions, with doses increasing if the animal is stressed by illness or surgery. Practically, this ideal is never achieved; however, the following regimens have been used successfully in adrenalectomized and Addisonian dogs or cats. As a general rule, animals produce approximately 1 mg/kg of cortisol (hydrocortisone) every day. It is not rational to employ alternate-day or...
intermittent glucocorticoid replacement therapy in a glucocorticoid-deficient animal as the animal’s metabolic wellbeing depends upon
the presence of glucocorticoids every day. Therefore, physiological replacement therapy is aimed at providing a small daily amount
of glucocorticoid. Physiological replacement therapy is rarely indicated or applied in large animals. In small animals, hydrocortisone
or cortisone at 0.2-1 mg/kg/day, or more commonly, equipotent amounts of prednisolone or prednisone orally at 0.1-0.2 mg/kg/day
once daily orally are indicated. There have been reports that the diurnal variation of cortisol results in a peak in the morning in dogs
and evening in cats; however, more recent studies have not confirmed this pattern. Therefore, the timing of the single daily dosage
would not appear to be critical, other than that it be provided approximately the same time each day. Because stress results in higher
adrenal output of glucocorticoids, this pattern should be mimicked; in general, in moderate stress, give 2 to 5 times the physiological
dosage, and in severe stress (e.g. surgery), administer 5 to 20 times this dosage until the stressful experience has ended.

**Intensive short term and shock therapy**
The effects of glucocorticoids in all forms of shock are still controversial; however, some evidence suggests that early treatment
(probably about 4 hours post-induction in dogs) may lead to increased survival, particularly in hemorrhagic and septic shock. The
nature of the formulation (particularly the ester) may affect the speed of cellular entry of glucocorticoids during shock; however, other
conclusions have also been reached. Glucocorticoids improve hemodynamics and enhance survival in canine models of endotoxic and
hemorrhagic shock. However, therapy for shock should also include aggressive fluid therapy. Septic (endotoxic) shock is the most
responsive form to glucocorticoid therapy; however, human trials have shown improved short-term survival, but may succumb to
clonic septicemia later. Suspected endotoxic shock should be treated with fluid therapy and a broad-spectrum antimicrobial, with or
without glucocorticoids. Glucocorticoids and antibiotics were synergistic when given within 2 hours of induction of septic shock in
baboons.

The potential detrimental effects of massive doses of glucocorticoids should always be considered. However, proponents of
glucocorticoid therapy for shock point out that short-term (~48 hours) glucocorticoid therapy has few negative effects and the positive
effects far outweigh the risks. Most human patients with sepsis survive beyond the acute stages of endotoxemia but succumb later to
chronic septicemia. Certainly, the immunosuppressive effects of glucocorticoids make their use contraindicated during chronic sepsis,
and those supporting glucocorticoid use in septic shock do not generally advocate use other than during the early acute hypotensive
state.

**Antinflammatory and antiallergy therapy**
A large proportion of glucocorticoid use in veterinary practice is designed to combat inflammation or allergy. Unfortunately, many
such diseases are difficult to definitively diagnose. Therefore, misuse of glucocorticoids is not uncommon in this category. Examples
of anti-inflammatory and antiallergic use of glucocorticoids include symptomatic treatment of pruritic dermatoses, allergic pulmonary
disease and allergic gastroenteritis. Guidelines for anti-inflammatory and antiallergic dosages vary from species to species. Prednisolone
or prednisone is most commonly used in small animals at 0.55 mg/kg q12h given orally for induction, then at 0.55-2.2
mg/kg every other day for maintenance. Although all dosages should be adjusted according to effect; a general, but undocumented
observation has been that cats require approximately twice the glucocorticoid dosage that dogs require to manage a similar condition.
Methylprednisolone acetate may also be administered subcutaneously or intramuscularly at 1.1 mg/kg every 1-3 weeks; however, use
of depot products brings the distinct disadvantage that the drug dosage cannot be stopped or reduced. Other long-acting injectable
products and their duration include: prednisolone acetate, 1-2 days; dexamethasone in polyethylene glycol, 1-7 days; triamcinolone
acetonide, 3-7 days; and betamethasone valerate, 7-60 days. For practical reasons of cost and potency, dexamethasone is the most
commonly used glucocorticoid in large animals.

**Immunosuppressive therapy**
Protracted glucocorticoid use generally is required for immunosuppression. Therefore, use of a corticosteroid with well-documented
side effects and efficacy is recommended. It is important to use the highest recommended dosage until clinical signs abate. After that
point, the dosage may be decreased in increments. In general, in small animals, the dosage may be decreased until the equivalent
prednisolone dosage of 1.1 mg/kg is being given on alternate days.

Long-term side effects of alternate-day therapy are few, and the dosage rarely must be decreased further. Therapy should not be
discontinued until the autoimmune disease is in remission for 2-3 months; otherwise, signs are likely to recur. Unlike other
immunosuppressants, glucocorticoids do not inhibit significantly antibody production by B-lymphocytes. If glucocorticoids provide
incomplete remission of an immune-mediated disorder, other immunosuppressant agents such as the alkylating agent
cyclophosphamide may be added to complement the effects of glucocorticoids. Furthermore, if side effects of the glucocorticoids are
too great, other immunosuppressants may be added to the regimen. If no clinical response is obtained with glucocorticoid therapy
alone, addition of other immunosuppressants is less likely to succeed. Immune-mediated thrombocytopenia and autoimmune
hemolytic anemia are examples of diseases treated with immunosuppressive doses of glucocorticoids.

In small animals, immunosuppression is generally accomplished with prednisolone at 2.2-6.6 mg/kg or equipotent dosage
dexamethasone at 0.33-1.1 mg/kg q12h for induction, and prednisolone at 1.0-2.2 mg/kg every other day for maintenance. Because its
duration of action exceeds 24 hours, dexamethasone is acceptable for induction but not for alternate-day maintenance therapy.
The adverse effects of chronic immunosuppressive doses of glucocorticoid use can be serious. Therefore, clinicians should eventually attempt to maintain a satisfactory therapeutic result with the smallest possible dose of glucocorticoids on alternate days, if possible. Nonsteroidal drugs (e.g. aspirin for inflammation or cyclophosphamide for immunosuppression) may be used as adjunctive therapy, if necessary.

**Chronic palliative therapy**

Glucocorticoids are commonly used in conjunction with nonsteroidal anti-inflammatory therapy, as in treating such conditions as chronic arthritis in most species or hip dysplasia in dogs. If nonsteroidal analgesics are not satisfactory, glucocorticoids may be used on an intermittent or alternate-day basis. Conversely, when intermittent glucocorticoid therapy alone leads to signs of disease on “off” day(s), nonsteroidal analgesics can be supplemented. It is important not to administer glucocorticoids erratically, as rapid withdrawal may itself precipitate signs of lameness or stiffness.

**Alternate-day therapy**

Side effects of long-term glucocorticoid use can be dramatically reduced by alternate-day therapy. Allowing the hypothalamic-pituitary-adrenal axis to recover on "off" days provides greater safety if therapy should suddenly be discontinued. Successful use of alternate-day therapy depends upon the therapeutic effects lasting longer than suppressive effects. As a result, this approach is not successful for all diseases. Several common pitfalls of alternate-day therapy should be avoided. Alternate-day therapy is rarely, if ever, effective as primary therapy. It is usually first necessary to use daily therapy to achieve the desired clinical effect. Alternate-day therapy with long-acting glucocorticoids is not rational. Particularly after prolonged high-dosage therapy, rapid change to alternate-day use may result in signs of glucocorticoid withdrawal (see below). It has been shown that administration of greater than 0.5 mg/kg/day of prednisolone or an equipotent dosage of a more potent drug for longer than 2 weeks should be considered chronic therapy. However, in one study, when 0.5 mg/kg q 12h (an anti-inflammatory dosage) was administered to dogs for 35 days and stopped abruptly, it took less than 2 weeks for the HPAA axis to totally recover.

**Withdrawal from glucocorticoids**

The identification of clinical signs of glucocorticoid deficiency may be very difficult. Signs of glucocorticoid withdrawal may include dullness, depression, decreased exercise tolerance, incoordination, unthriftiness and weight loss, loose stools, and behavioral changes. Significant adrenocortical suppression occurs in dogs within 2 weeks of initiating daily glucocorticoid therapy. Therefore, it is reasonable to assume that dogs and cats may require supplementation of glucocorticoids during episodes of stress, such as illness or surgery, particularly with signs of glucocorticoid withdrawal. It should be emphasized that short-term use of glucocorticoids in physiologic amounts has few risks despite the evidence that these "physiological" quantities significantly suppress the HPA axis resulting in adrenal atrophy.

**References/suggested reading**
