GLUCOCORTICOID AGENTS, GENERAL INFORMATION

Glucocorticoid Comparison Table

DRUG	EQUIV. ANTI-INFLAMMATORY DOSE (MG)	RELATIVE ANTI-INFLAMMATORY POTENCY	RELATIVE MINERAL-CORTICOID ACTIVITY	PLASMA HALF-LIFE DOGS (MIN) [HUMANS]	DURATION OF ACTION AFTER ORAL/IV [IM]
Hydrocortisone (Cortisol)	20	1	1–2	52–57 [90]	<12 hrs
Betamethasone Sod. Succ./ Sod. Phos.	0.6	25	0	[300+]	>48 hrs
Dexamethasone Sod. Succ./ Sod. Phos.	0.75	30	0	119–136 [200–300+]	>48 hrs
Flumethasone	1.5	15–30	?	?	
Isoflupredone		17			
Methylpred-nisolone	4	5	0	91 [200]	12–36 hrs
Prednisolone	5	4	1	69–197 [115–212]	12–36 hrs
Prednisone	5	4	1	[60]	12–36 hrs
Triamcinolone Acetonide	4	5	0	[200+]	12–36 hrs [weeks]

Uses/Indications

Glucocorticoids have been used in an attempt to treat practically every malady that afflicts man or animal, but there are three broad uses and dosage ranges for use of these agents. **1)** Replacement of glucocorticoid activity in patients with adrenal insufficiency, **2)** as an antiinflammatory agent, and **3)** as an immunosuppressive. Among some of the uses for glucocorticoids include treatment of: endocrine conditions (*e.g.*, adrenal insufficiency), rheumatic diseases (*e.g.*, rheumatoid arthritis), collagen diseases (*e.g.*, systemic lupus), allergic states, respiratory diseases (*e.g.*, asthma), dermatologic diseases (*e.g.*, pemphigus, allergic dermatoses), hematologic disorders (*e.g.*, thrombocytopenias, autoimmune hemolytic anemias), neoplasias, nervous system disorders (increased CSF pressure), GI diseases (*e.g.*, ulcerative colitis exacerbations), and renal diseases (*e.g.*, nephrotic syndrome). Some glucocorticoids are used topically in the eye and skin for various conditions or are injected intra-articularly or intra-lesionally. The above listing is certainly not complete. For specific dosages and indications refer to the Doses section for each glucocorticoid drug monograph.

Pharmacology/Actions

Glucocorticoids have effects on virtually every cell type and system in mammals. An overview of the effects of these agents follows:

Cardiovascular System: Glucocorticoids can reduce capillary permeability and enhance vasoconstriction. A relatively clinically insignificant positive inotropic effect can occur after glucocorticoid administration. Increased blood pressure can result from both the drugs' vasoconstrictive properties and increased blood volume that may be produced.

Cells: Glucocorticoids inhibit fibroblast proliferation, macrophage response to migration inhibiting factor, sensitization of lymphocytes and the cellular response to mediators of inflammation. Glucocorticoids stabilize lysosomal membranes.

CNS/Autonomic Nervous System: Glucocorticoids can lower seizure threshold, alter mood and behavior, diminish the response to pyrogens, stimulate appetite and maintain alpha rhythm. Glucocorticoids are necessary for normal adrenergic receptor sensitivity.

Endocrine System: When animals are not stressed, glucocorticoids will suppress the release of ACTH from the anterior pituitary, thereby reducing or preventing the release of endogenous corticosteroids. Stress factors (*e.g.*, renal disease, liver disease, diabetes) may sometimes nullify the suppressing aspects of exogenously administered steroids. Release of thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), prolactin, and luteinizing hormone (LH) may all be reduced when glucocorticoids are administered at pharmacological doses. Conversion of thyroxine (T_4) to triiodothyronine (T_3) may be reduced by glucocorticoids; and plasma levels of parathyroid hormone increased. Glucocorticoids may inhibit osteoblast function. Vasopressin (ADH) activity is reduced at the renal tubules and diuresis may occur. Glucocorticoids inhibit insulin binding to insulin-receptors and the post-receptor effects of insulin.

Hematopoietic System: Glucocorticoids can increase the numbers of circulating platelets, neutrophils and red blood cells, but platelet aggregation is inhibited. Decreased amounts of lymphocytes (peripheral), monocytes and eosinophils are seen as glucocorticoids can sequester these cells into the lungs and spleen and prompt decreased release from the bone marrow. Removal of old red blood cells becomes diminished. Glucocorticoids can cause involution of lymphoid tissue.

GI Tract and Hepatic System: Glucocorticoids increase the secretion of gastric acid, pepsin, and trypsin. They alter the structure of mucin and decrease mucosal cell proliferation. Iron salts and calcium absorption are decreased while fat absorption is increased. Hepatic changes can include increased fat and glycogen deposits within hepatocytes, increased serum levels of alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT). Significant increases can be seen in serum alkaline phosphatase levels. Glucocorticoids can cause minor increases in BSP (bromosulfophthalein) retention time.

Immune System (also see Cells and Hematopoietic System): Glucocorticoids can decrease circulating levels of T-lymphocytes; inhibit lymphokines; inhibit neutrophil, macrophage, and monocyte migration; reduce production of interferon; inhibit phagocytosis and chemotaxis; antigen processing; and diminish intracellular killing. Specific acquired immunity is affected less than nonspecific immune responses. Glucocorticoids can also antagonize the complement cascade and mask the clinical signs of infection. Mast cells are decreased in number and histamine synthesis is suppressed. Many of these effects only occur at high or very high doses and there are species differences in response.

Metabolic effects: Glucocorticoids stimulate gluconeogenesis. Lipogenesis is enhanced in certain areas of the body (*e.g.*, abdomen) and adipose tissue can be redistributed away from the extremities to the trunk. Fatty acids are mobilized from tissues and their oxidation is increased. Plasma levels of triglycerides, cholesterol, and glycerol are increased. Protein is mobilized from most areas of the body (not the liver).

Musculoskeletal: Glucocorticoids may cause muscular weakness (also caused if there is a lack of glucocorticoids), atrophy, and os-

teoporosis. Bone growth can be inhibited via growth hormone and somatomedin inhibition, increased calcium excretion and inhibition of vitamin D activation. Resorption of bone can be enhanced. Fibrocartilage growth is also inhibited.

Ophthalmic: Prolonged corticosteroid use (both systemic or topically to the eye) can cause increased intraocular pressure and glaucoma, cataracts, and exophthalmos.

Renal, Fluid, & Electrolytes: Glucocorticoids can increase potassium and calcium excretion, sodium and chloride reabsorption, and extracellular fluid volume. Hypokalemia and/or hypocalcemia rarely occur. Diuresis may develop following glucocorticoid administration.

Skin: Thinning of dermal tissue and skin atrophy can be seen with glucocorticoid therapy. Hair follicles can become distended and alopecia may occur.

Contraindications/Precautions/Warnings

Systemic use of glucocorticoids is generally considered contraindicated in systemic fungal infections (unless used for replacement therapy in Addison's), when administered IM in patients with idiopathic thrombocytopenia, and in patients hypersensitive to a particular compound. Use of sustained-release injectable glucocorticoids is considered contraindicated for chronic corticosteroid therapy of systemic diseases.

Animals that have received glucocorticoids systemically, other than with "burst" therapy, should be tapered off the drugs. Patients who have received the drugs chronically should be tapered off slowly as endogenous ACTH and corticosteroid function may return slowly. Should the animal undergo a "stressor" (*e.g.*, surgery, trauma, illness, etc.) during the tapering process or until normal adrenal and pituitary function resume, additional glucocorticoids should be administered.

Adverse Effects

Adverse effects are generally associated with long-term administration of these drugs, especially if given at high dosages or not on an alternate day regimen. Effects generally manifest as clinical signs of hyperadrenocorticism. When administered to young, growing animals, glucocorticoids can retard growth. Many of the potential effects, adverse and otherwise, are outlined above in the Pharmacology section.

In dogs, polydipsia (PD), polyphagia (PP), and polyuria (PU) may all be seen with short-term "burst" therapy as well as with alternate-day maintenance therapy on days when the drug is given. Adverse effects in dogs can include: dull, dry haircoat, weight gain, panting, vomiting, diarrhea, elevated liver enzymes, pancreatitis, GI ulceration, lipidemias, activation or worsening of diabetes mellitus, muscle wasting and behavioral changes (depression, lethargy, viciousness). Discontinuation of the drug may be necessary; changing to an alternate steroid may also alleviate the problem. With the exception of PU/PD/PP, adverse effects associated with short-term antiinflammatory therapy occur relatively uncommonly. Adverse effects associated with immunosuppressive doses are more common and potentially more severe.

Cats generally require higher dosages than dogs for clinical effect, but tend to develop fewer adverse effects. Occasionally, polydipsia, polyuria, polyphagia with weight gain, diarrhea, or depression can be seen. Long-term, high dose therapy can lead to "Cushingoid" effects, however.

Administration of dexamethasone or triamcinolone may play a role in the development of laminitis in horses.

Reproductive/Nursing Safety

Glucocorticoids are probably necessary for normal fetal development. They may be required for adequate surfactant production, myelin, retinal, pancreatic, and mammary development. Excessive dosages early in pregnancy may lead to teratogenic effects. In horses and ruminants, exogenous steroid administration may induce parturition when administered in the latter stages of pregnancy.

Glucocorticoids unbound to plasma proteins will enter milk. High dosages or prolonged administration to mothers may potentially inhibit the growth of nursing newborns. In humans, several studies suggest that amounts excreted in human breast milk are negligible with prednisone or prednisolone doses of 20 mg/day or less, or methylprednisolone doses less than or equal to 8 mg/day. Large doses for short periods may not harm the infant. Waiting 3–4 hours after the dose before nursing and using prednisolone rather than prednisone may result in a lower corticosteroid dose to offspring.

Overdosage/Acute Toxicity

Glucocorticoids when given short-term are unlikely to cause harmful effects, even in massive dosages. One incidence of a dog developing acute CNS effects after accidental ingestion of glucocorticoids has been reported. Should clinical signs occur, use supportive treatment if required.

Chronic usage of glucocorticoids can lead to serious adverse effects. Refer to Adverse Effects above for more information.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving glucocorticoids and may be of significance in veterinary patients:

- **AMPHOTERICIN B:** When administered concomitantly with glucocorticoids may cause hypokalemia
- **ANTICHOLINESTERASE AGENTS** (*e.g.*, **pyridostigmine**, **neostigmine**, etc.): In patients with myasthenia gravis, concomitant glucocorticoid with these agents may lead to profound muscle weakness. If possible, discontinue anticholinesterase medication at least 24 hours prior to corticosteroid administration.
- **ASPIRIN** (**salicylates**): Glucocorticoids may reduce salicylate blood levels
- **CYCLOPHOSPHAMIDE:** Glucocorticoids may also inhibit the hepatic metabolism of cyclophosphamide; dosage adjustments may be required.
- **CYCLOSPORINE:** Concomitant administration of may increase the blood levels of each, by mutually inhibiting the hepatic metabolism of each other; clinical significance of this interaction is not clear
- **DIGOXIN**: Secondary to hypokalemia, increased risk for arrhythmias
- **DIURETICS, POTASSIUM-DEPLETING** (**furosemide, thiazides**): When administered concomitantly with glucocorticoids may cause hypokalemia
- **EPHEDRINE**: May increase metabolism
- **ESTROGENS:** The effects of hydrocortisone, and possibly other glucocorticoids, may be potentiated by concomitant administration with estrogens
- **INSULIN**: Requirements may increase in patients receiving glucocorticoids
- **KETOCONAZOLE**: May decrease metabolism
- **MITOTANE:** May alter the metabolism of steroids; higher than usual doses of steroids may be necessary to treat mitotane-induced adrenal insufficiency
- **NSAIDS**: Administration of other ulcerogenic drugs with glucocorticoids may increase risk

- **PHENOBARBITAL**: May increase the metabolism of glucocorticoids
- **PHENYTOIN**: May increase the metabolism of glucocorticoids
- **RIFAMPIN**: May increase the metabolism of glucocorticoids
- **VACCINES**: Patients receiving corticosteroids at immunosuppressive dosages should generally not receive live attenuated-virus vaccines as virus replication may be augmented; a diminished immune response may occur after vaccine, toxoid, or bacterin administration in patients receiving glucocorticoids

Laboratory Considerations

- Glucocorticoids may increase serum **cholesterol** and **urine glucose** levels.
- Glucocorticoids may decrease serum **potassium**.
- Glucocorticoids can suppress the release of thyroid stimulating hormone (TSH) and reduce **T_3 & T_4** values. Thyroid gland atrophy has been reported after chronic glucocorticoid administration. Uptake of I^{131} by the thyroid may be decreased by glucocorticoids.
- Reactions to **skin tests** may be suppressed by glucocorticoids.
- False-negative results of the **nitroblue tetrazolium test for systemic bacterial infection**s may be induced by glucocorticoids.

Monitoring

Monitoring of glucocorticoid therapy is dependent on its reason for use, dosage, agent used (amount of mineralocorticoid activity), dosage schedule (daily versus alternate day therapy), duration of therapy, and the animal's age and condition. The following list may not be appropriate or complete for all animals; use clinical assessment and judgment should adverse effects be noted:

- Weight, appetite, signs of edema
- Serum and/or urine electrolytes
- Total plasma proteins, albumin
- Blood glucose
- Growth and development in young animals
- ACTH stimulation test if necessary

Client Information

- Clients should carefully follow the dosage instructions and should not discontinue the drug abruptly without consulting with veterinarian beforehand.
- Clients should be briefed on the potential adverse effects that can be seen with these drugs and instructed to contact the veterinarian should these effects progress or become severe.

GLUCOSAMINE/CHONDROITIN SULFATE

(gloo-*kose*-a-meen/kon-droy-tin sul-fayt) Cosequin®

NUTRITIONAL SUPPLEMENT

Prescriber Highlights

- So-called nutraceutical that can be used as an adjunctive treatment for osteoarthritis or other painful conditions in horses, cats, dogs, etc; FLUTD in cats
- Well tolerated, but efficacy is uncertain
- Not a regulated drug; choose products carefully; large variation in commercially available products

Uses/Indications

These compounds may be useful in treating osteoarthritis or other painful conditions in domestic animals, but large, well-designed controlled clinical studies proving efficacy were not located. One study in dogs (McCarthy, O'Donovan et al. 2007) showed some positive effect, but this study was not placebo controlled and compared responses versus carprofen. Another placebo-controlled, blinded study in dogs (Moreau, Dupuis et al. 2003), did not demonstrate statistically significant improvement after 60 days of treatment.

These compounds potentially could be of benefit in cats with FLUTD (feline lower urinary tract disease) because of the presence of glycosaminoglycans as part of the protective layer of the urinary tract. Controlled studies have shown some positive effects in some cats, but overall did not appear to make a significant difference.

Pharmacology/Actions

Cartilage cells use glucosamine to produce glycosaminoglycans and hyaluronan. Glucosamine also regulates synthesis of collagen and proteoglycans in cartilage and has mild antiinflammatory effects due to its ability to scavenge free radicals. Chondrocytes normally produce ample quantities of glucosamine from glucose and amino acids, but this ability may diminish with age, disease, or trauma. Exogenously administered glucosamine appears to be able to be utilized by chondrocytes.

Chondroitin sulfate possesses several pharmacologic effects. It appears to inhibit destructive enzymes in joint fluid and cartilage. Thrombi formation in microvasculature may be reduced. In joint cartilage, it stimulates the production of glycosaminoglycans and proteoglycans.

While *in vitro* evidence exists, there is not solid evidence that using these compounds together improves clinical effect over either alone, but *in vivo* studies are ongoing.

Pharmacokinetics

The pharmacokinetics of these compounds are hard to evaluate due to the different salts, lack of standards, etc. Both glucosamine HCl and glucosamine sulfate are absorbed in the gut after the salt is cleaved in the stomach. There exists controversy as to whether either salt of glucosamine is superior to the other. Theoretically, if the amount of glucosamine base contained in the product is equivalent, the amount absorbed should be as well. Most clinical studies in veterinary species have been done with the HCl salt. Purified, low molecular weight chondroitin appears to be absorbed from the gut. Reported bioavailability in horses for chondroitin sulfate is about 25%; glucosamine, about 2%; bioavailability in dogs is reportedly about 5% for chondroitin sulfate and 12% for glucosamine.

Onset of any clinical efficacy may require 2–6 weeks of treatment.

Contraindications/Precautions/Warnings

No absolute contraindications were located for these compounds. As hypersensitivity reactions are a theoretical possibility, animals demonstrating prior hypersensitivity reactions to these compounds should not receive them.

In humans, glucosamine may exacerbate symptoms associated with asthma. Although this has not yet been reported in veterinary patients, caution is advised in patients with bronchoconstrictive conditions.

Adverse Effects

These products appear to be very well tolerated in dogs, cats, and horses. Adverse effects could potentially include some minor gastrointestinal effects (flatulence, stool softening). Since these products are often derived from natural sources, hypersensitivity reactions could occur.