Glucocorticoids: Pharmacology and practical implications

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Introduction

Endogenous adrenal corticosteroids are essential for homeostasis and play a supportive role during stress responses via the hypothalamic pituitary adrenal axis. There is pulsatile glucocorticoid release during the day with increased amplitude at the start of the active period. Stress responses are superimposed over this ultradian background. Protein bound glucocorticoid (corticosteroid binding globulin and albumen) is not biologically available. Glucocorticoid activity is also regulated by 11\(\beta\)-hydroxysteroid dehydrogenase enzymes that convert active 11-hydroxy-glucocorticoids to their inactive 11-keto forms at a cellular level. Cellular activity of these enzymes affects ligand bioavailability however in the liver, fat and brain active glucocorticoids can be re-formed from inactive metabolites. Tissue bioavailability of glucocorticoids is also regulated by organ specific aspects eg the p-glycoprotein pump in the brain.

The use of exogenous glucocorticoids in medicine dates back to 1948 with their introduction as a therapeutic agent for rheumatoid arthritis. Glucocorticoids are powerful drugs used to modulate inflammation but their therapeutic benefits need to be balanced against detrimental physiological effects, especially in long-term use. Understanding how glucocorticoids work helps us make better therapeutic decisions when utilising these medications and also paves the way for development of more selective glucocorticoids with greater safety.

How do glucocorticoids work?

1. Corticosteroids receptors:

Glucocorticoids (GC) exert their action via glucocorticoid receptors (GR). These are intracellular and are closely related to other Class 1 steroid receptors including the oestrogen, progesterone and androgen receptors. The receptor structure is highly conserved with an N-terminal end (containing the ligand-independent activation function 1), a centrally located DNA binding domain and the C terminal end containing the ligand-binding pocket of the hormone. The DNA binding domain confers specificity for binding to the cortisol response element of DNA while binding of the cognate ligand in the C terminal end triggers conformational changes in the GR resulting in nuclear translocation. GR variants (isoforms) exist with differing transcriptional activities expressed in a tissue dependent manner. GR isoform (a) is biological active while isoform GR (b) undergoes DNA binding after cortisol activation but fails to induce transcription. Steroid resistance can occur associated with decreased expression of GR(a) or increased expression of GR(b). Also worth noting is that certain cytokines, particularly IL-2, IL-4, and IL-13, which are over expressed in sensitised atopic individuals can reduce GR ligand binding affinity in T lymphocytes AND increase GR phosphorylation inactivating the GR resulting in local resistance to the anti-inflammatory actions of glucocorticoids.

Post cortisol binding to the GR there is a covalent addition of ubiquitin that marks the GR for degradation in the proteasome. This process is cell type specific and allows for further tissue specific regulation of glucocorticoid activity.

Receptor expression is in high levels in the immune system, bone, lungs, liver, adipose tissue and brain, which helps explain the diversity of actions and side effects of glucocorticoids.

2. Mechanism of action:

Non-genomic effects are acute or immediate effects of glucocorticoids (GCs) and are mediated via membrane receptors and second messengers. By definition they can be detected within 5 minutes. Recent findings suggest that the glucocorticoid transporter (“steroid hormone recognition and effector complex”, SHREC) may be involved with transportation of GC into the cell and be involved in initial triggering of non-genomic effects followed later by genomic events.

Non-genomic effects are exerted by direct actions on membrane lipids (affecting membrane fluidity), membrane proteins (e.g. ion channels and neurotransmitter receptors), and cytoplasmic proteins (e.g.
mitogen activated protein kinases (MAPKs), phospholipases etc). These actions may be direct receptor binding or be indirect due to proteins that dissociate after GC binding to the GR. Non-genomic effects are less well understood then the genomic effects but do appear to be clinically relevant. Specificity for non-genomic activity may occur amongst the different GCs. It is worth noting that the adverse events associated with long term GC therapy relate to genomic effects. The development of GC that specifically triggers non-genomic events would improve safety.

Genomic actions occur more slowly after hormone binding to the receptor. Ligand binding results in conformational change with detachment of the chaperone proteins (hsp70, hsp 90, immunophilin). This uncovers nuclear localisation signal motifs in the hinge area of the receptor and translocation of the receptor to the nucleus is facilitated by proteins of the importin family. Critical to the outcome of the genomic effect of the GR is the recognition or highly specific DNA sites, the response elements (GRE). These areas promote stable binding to facilitate recruitment of co-regulating proteins. Binding to the GRE causes allosteric changes promoting a protein surface that attracts co-regulatory proteins. The nucleotide sequence of the GRE determines the magnitude of the outcome. Variations if GRE binding affinities for the GR and for affinities for binding adjacent co-regulator sites results in variability in outcome. Both positive GREs and negative GREs have been identified with nGRE causing repression rather than activation. Co-regulator proteins are enzymically active proteins that once recruited alter the chromatin environment thereby facilitating or inhibiting assembly of the basal transcription machinery and the initiation of transcription by RNA polymerase II.

The transcriptional outcome is also dependent on the structure of the promoter region of the target gene and can result in activation (transactivation) or repression (transrepression) of the gene. Transactivation is triggered by recruitment of other transcription proteins such as activator protein 1 and nuclear factor-κB while transrepression occurs due to GR inhibition of transcriptional factors.

In summary:
Glucocorticoid binding to the GR results in conformational change to the receptor and nuclear translocation, DNA binding, co-regulator recruitment and chromatic re-organisation. There is considerable variation in outcome possible with glucocorticoid therapy based on

1. Non-genomic effects
2. Bioavailability of the drug (ligand) to bind the GR
3. The affinity for GR binding
4. The agonist potential of the drug (ability to induce receptor activation on binding)
5. Transcriptional potential of the GR (isoform expression)
6. Cell and tissue variability in receptor expression and target genes and cytokine influences on expression.
7. Affinity of GR for the GRE
8. Nucleotide sequence of the GRE
9. Binding affinity of GRE to co-regulatory sites
10. Transactivation versus transrepression

What do glucocorticoids do?
1. Physiological effects.
Restoring homeostasis involves intimate neuro-endocrine interactions. Cytokines and inflammatory mediators activate peripheral pain receptors whose axons project to the dorsal horn and synapse with the lemniscal tract, which in turn carries pain signals to the thalamus and the somatosensory cortex. Activation of this nociceptive pathway ultimately stimulates hypothalamic–pituitary–adrenal activity. Glucocorticoids inhibit the synthesis of cytokines and inflammatory mediators, thus forming a negative feedback loop. Cytokines can also act directly on the brain to activate the hypothalamic–pituitary–adrenal axis. Dysregulation of this neuroendocrine loop by hyperactivity (Cushing’s disease, chronic pain, stress) results in immunosuppression and hypoactivity (Addison’s disease) is mandatory to prevent excessive cytokine triggered tissue injury.
Table 1. **Tissue specific GC effects**

<table>
<thead>
<tr>
<th>Tissue System</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central Nervous System</strong></td>
<td>Euphoria and behavioural changes</td>
</tr>
<tr>
<td></td>
<td>Maintenance of alpha rhythm</td>
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<tr>
<td></td>
<td>Lower Seizure Threshold</td>
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<tr>
<td><strong>Autonomic Nervous System</strong></td>
<td>Required for normal sensitivity of adrenergic receptors</td>
</tr>
<tr>
<td><strong>Gastrointestinal Tract</strong></td>
<td>Decreased calcium and iron absorption</td>
</tr>
<tr>
<td></td>
<td>Facilitation of fat absorption</td>
</tr>
<tr>
<td></td>
<td>Increased acid, pepsin, and trypsin</td>
</tr>
<tr>
<td></td>
<td>Structural alteration of mucin</td>
</tr>
<tr>
<td></td>
<td>Increase insulin tolerance</td>
</tr>
<tr>
<td><strong>Skeletal Muscle</strong></td>
<td>Weakness (excess and deficiency)</td>
</tr>
<tr>
<td></td>
<td>Muscle atrophy (chronic excess)</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Atrophy and thinning (chronic excess)</td>
</tr>
<tr>
<td></td>
<td>Calcinosis Cutis</td>
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<tr>
<td><strong>Hematopoietic system</strong></td>
<td>Involvement of lymphoid tissue (species dependent)</td>
</tr>
<tr>
<td></td>
<td>Decrease in peripheral lymphocytes, monocytes, eosinophils</td>
</tr>
<tr>
<td></td>
<td>Increase in peripheral neutrophils, platelets, RBCs</td>
</tr>
<tr>
<td></td>
<td>Decreased Clotting Time</td>
</tr>
<tr>
<td></td>
<td>Decreased phagocyte competence</td>
</tr>
<tr>
<td><strong>Cardiovascular system</strong></td>
<td>Positive inotropic effect</td>
</tr>
<tr>
<td></td>
<td>Increased blood pressure (increased blood volume)</td>
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<tr>
<td><strong>Kidneys</strong></td>
<td>Increased reabsorption of water, sodium, chloride</td>
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<tr>
<td></td>
<td>Increased excretion of potassium, calcium</td>
</tr>
<tr>
<td></td>
<td>Increased extracellular fluid</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>Increased gluconeogenesis</td>
</tr>
<tr>
<td></td>
<td>Increase lipid storage</td>
</tr>
<tr>
<td><strong>Bone</strong></td>
<td>Inhibition of collagen synthesis by fibroblasts</td>
</tr>
<tr>
<td></td>
<td>Acceleration of Bone resorption</td>
</tr>
<tr>
<td></td>
<td>Antagonism of Vitamin D</td>
</tr>
<tr>
<td><strong>Cells</strong></td>
<td>&quot;Stabilization&quot; of liposomal membranes</td>
</tr>
<tr>
<td></td>
<td>Inhibition of macrophage response to migration inhibition factor</td>
</tr>
<tr>
<td></td>
<td>Lymphocyte sensitisation blocked</td>
</tr>
<tr>
<td></td>
<td>Cellular response to inflammatory mediators blocked</td>
</tr>
<tr>
<td></td>
<td>Inhibition of fibroblast proliferation</td>
</tr>
<tr>
<td><strong>Reproductive Tract</strong></td>
<td>Parturition induced during the latter part of pregnancy in ruminants and</td>
</tr>
<tr>
<td></td>
<td>horses</td>
</tr>
<tr>
<td></td>
<td>Less reliable in dogs and cats</td>
</tr>
<tr>
<td></td>
<td>Teratogenesis during early pregnancy.</td>
</tr>
</tbody>
</table>


### 2. Anti-inflammatory effects.

Inflammation occurs following any irritant, traumatic or infectious insult. Microbes that breach the epithelial barrier activate innate immunological sentinels (complement, toll-like receptors) triggering the synthesis and release of inflammatory mediators with acute effects on the vasculature. Vasodilation, increased vascular permeability, extravasation of plasma (and humoral) proteins, and chemotaxis of leukocytes results in the grossly visible features of inflammation. As the innate and adaptative immune responses clear the infectious agent inflammation resolves. Endogenous glucocorticoids with HPA axis activation are essential to this resolution.

Exogeneous glucocorticoids are indicated in sterile inflammation where homeostatic mechanisms fail and the inflammation (cytokine milieu) itself is responsible for the ongoing tissue injury.
GC inhibit prostaglandin synthesis by a number of independent pathways namely induction and activation of annexin 1 (lipocortin 1), induction of MAPK phosphatase 1 and repression of transcription of cyclooxygenase 2.

Annexin 1 interacts to inhibit cytosolic phospholipase 2 (cPLA2). cPLA2 when activated by inflammation moves from the cytosol to the perinuclear membrane and hydrolyses phospholipids releasing arachidonic acid that is then utilised to form inflammatory eicosanoids (prostaglandins, thromboxanes, prostacyclins, and leukotrienes).

MAPK cascades can be activated by viruses, UV light, inflammatory cytokines and bacteria. MAPK phosphorylation of intracellular kinases leads to binding to DNA sequences called activator protein 1 response elements and induce the transcription of numerous inflammatory and immune genes. Glucocorticoid-induced MAPK phosphatase 1 dephosphorylates and inactivates these kinases thus inhibiting transcription.

Nuclear factor-κB (NF-κB) plays a major role in upregulating inflammation. It is a cytosolic protein sequestered by an inhibitory protein IκB. TNF-α, interleukin-1, microbial pathogens, viral infections, and other inflammatory signals trigger signaling cascades that activate IκB kinases. Phosphorylation of IκB (by IκB kinases) leads to its ubiquitination and degradation by the proteasome, unmasking a nuclear localisation signal on NF-κB and leading to nuclear translocation. In the nucleus, NF-κB binds DNA sequences called NF-κB elements and stimulates he transcription of cytokines, chemokines, cell adhesion molecules, complement factors, and receptors for these molecules. NF-κB also induces the transcription of cyclooxygenase 2, an enzyme essential for prostaglandin production. Glucocorticoid- induced antagonism of NF-κB and repression of cyclooxygenase 2 are major mechanisms of GC anti-inflammatory actions. The many inflammatory cytokines inhibited by GCs are listed later under topical glucocorticoids (TG).

3. Anti-immunological effects
GC are potent immunomodulators/immunosuppressant agents depending on the dose and drug. They are reported to
- Induce redistribution of lymphocytes (species variable)
- Suppress cytokine and gene suppression
- Marked suppression of IL-1 and IL-6
- Retard neutrophil and macrophage chemotaxis
- Inhibit T-cell antigen recognition
- Inhibit T-cell proliferation
- Reduce Fc receptor mediated antibody dependent cytotoxicity and phagocytosis

Pharmacology
GC potency and duration of action is largely determined by the glucocorticoid base (unless the base is attached to an ester that prolongs its activity). In the case of orally administered drugs the ester is irrelevant as the esters are removed prior to absorption.

With injectable GCs the ester may control the amount of drug released into the circulatory system, which would also influence the magnitude of effect.
Table 2. Comparison of Glucocorticoid Bases.

<table>
<thead>
<tr>
<th>Base</th>
<th>Relative Potency</th>
<th>K/Na Effect</th>
<th>Equivalent Dose(^2) mg (Total dose)</th>
<th>Duration (HPA)(^3)</th>
<th>Structural Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>++</td>
<td>20</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4.0</td>
<td>+</td>
<td>5</td>
<td>12 - 36</td>
<td>1 = 2</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5.0</td>
<td>0</td>
<td>4</td>
<td>12 - 36</td>
<td>6-me; 1 = 2</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5.0</td>
<td>0</td>
<td>4</td>
<td>12 - 36</td>
<td>9-F; 16-OH; 1 = 2</td>
</tr>
<tr>
<td><strong>Long Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25</td>
<td>0</td>
<td>0.8</td>
<td>&gt;48</td>
<td>9-F; 16-bme; 1 = 2</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>30</td>
<td>0</td>
<td>0.7</td>
<td>&gt;48</td>
<td>9-F; 16-me; 1 = 2</td>
</tr>
</tbody>
</table>

1. Glucocorticoid potency  
2. Dose suggested is replacement therapy for a 20 kg. dog  
3. Durations for other effects are likely to be different (see mechanism of action notes).


Glucocorticoid Products

Drug selection of a GC will vary depending on the intended duration of action and the potency. It is advisable to use the MINIMUM EFFECTIVE dose and for the shortest duration of activity. This implies then that GC are being used AFTER a diagnosis has been reached and then only where additional intervention is necessary to control the inflammation. This means in cases where the clinician determines removal of the inciting cause of the inflammation does not achieve resolution of the inflammation by normal homeostatic mechanisms. In those cases the clinician will have an established therapeutic goal e.g. immunosuppression, anti-inflammatory and intended duration of action. This will allow for sensible therapeutic choices.

Oral

- The ester is irrelevant. All are separated from the base in the GI tract. The base drugs are well absorbed. Duration of action then is determined by the base. Dexamethasone is 7.5 X more potent than prednisolone and longer suppression of the HPA axis.

IM, SQ, Intraliesional

- Rapidly absorbed products can be used as substitutes for oral preparations. Their absorption and duration are roughly equivalent to the oral base products (and salts). Dexamethasone sodium phosphate would be an example of a rapidly absorbed injectable. These products are not suitable for intraliesional use.
- Slowly absorbed (Depot) products are designed to provide either low concentrations of glucocorticoids for extended periods of time or high concentrations in a local area. The poorly soluble phenylpropionate ester of dexamethasone in Dexaforte would be an example. There is increased potential for local atrophogenic effects with depot injections and there are better administered IM than SQ.
- Intravenous use requires water soluble salts (prednisolone sodium succinate (Solu Delta Cortef®)). These reach sites of action 1/2 - 1 hour faster than oral but are otherwise similar in potency and are reserved for emergency therapy eg CNS trauma and shock.
Table 3. Available glucocorticoids

<table>
<thead>
<tr>
<th>Base</th>
<th>Oral</th>
<th>Intravenous Rapid IM, SC Absorption</th>
<th>Intravenous Slow IM, SC Absorption</th>
<th>Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone</td>
<td>Base</td>
<td>Na phosphate</td>
<td>Na phosphate + Acetate</td>
<td>Base Benzoate Dipropionate Valerate</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Base</td>
<td>Na phosphate</td>
<td>Acetate</td>
<td>Base</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Base</td>
<td>Na phosphate</td>
<td>Acetate</td>
<td>Base</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Base</td>
<td>Na succinate</td>
<td>Acetate</td>
<td>Acetate</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Base</td>
<td>Na phosphate</td>
<td>Acetate Tebutate Na phosphate + Acetate</td>
<td>Base Acetate Na succinate</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Base</td>
<td>Acetonide Diacetate</td>
<td>Acetonide Diacetate Hexacetonide</td>
<td>Base Acetonide</td>
</tr>
</tbody>
</table>


Anti-inflammatory Dosing

- Approximately 2-4 x replacement dose
- Usually 0.5 to 1 mg/kg prednisolone
- Alternate day therapy (or less) is recommended when treatment duration exceeds 4 weeks
- The HPA suppression potential of daily therapy is similar to the HPA suppression of eod therapy at 4 X the sid dose.
- 1/3 of dogs on long-term glucocorticoid therapy (> 6 months will have lower UTI)
- Targets for “safe” long term GC therapy (based on physiological cortisol levels in dogs) are 0.25 to 0.3mg/kg prednisolone twice weekly.
- Adjunctive, steroid sparing therapies are indicated in all dogs where long-term systemic GC therapy is needed at levels > 0.3mg/kg biw

Discontinuing therapy

- Cold turkey if glucocorticoid therapy of less than 2 to 4 weeks duration
- Taper off if Glucocorticoid therapy of greater than 2 weeks duration. Rate of taper should be proportional to duration of prior therapy. The longer the original therapy, the slower the rate of dose reduction.
- If on daily therapy reduce the alternate day dose by 25% per week to get to an eod dosage regime. Once on alternative day therapy treatment can be tapered rapidly.

Inhibit immunologic responses

Dosing

- Approximately 8- 16x replacement dose (daily)
- Usually initiate with 2-4 mg/kg prednisolone per day in two doses (2 mg/kg q12H)
- Avoids relatively remote potential for acute adverse effects
- Possibly reduces initial efficacy (versus one single daily dose)
- Aggression, lethargy and behavioural changes possible on high doses.

Reducing dose rates

- Goal is to MINIMUM EFFECTIVE dose. Tapering should begin as soon as the disease is in clinical remission.
- With autoimmune diseases steroid sparing adjunctive therapy is mandatory where the duration of treatment is expected to be longer than 4 weeks.
- When tapering this should be done slowly eg 2-week minimum between dose changes, as disease flare may require returning to original remission doses.
- NOTE. Alternative day therapy does NOT avoid GC side effects when the doses used are supra-physiological. Alternative day therapy though will reduce the severity of the side effects compared with daily therapy.
- Daily therapy is however more POTENT for early suppression on the disease. In human medicine 90mg SID has the anti-immunological effect of 200mg eod.
- Take home message for immune suppression is daily to remission then taper and use adjunctive immunosuppressant therapies in all cases where the diagnosis dictates therapy for greater than 4 weeks.

Topical glucocorticoids (TG)

To reach the target cells the drug needs to pass through the barrier defense of the stratum corneum (SC). For a topically applied formulation containing a glucocorticoid the percutaneous absorption involves the following steps:

- (a) Release from the formulation,
- (b) Penetration into the skin’s outermost layer, the SC and permeation/diffusion through the SC,
- (c) Partitioning from the SC into the viable epidermis and or dermis,
- (d) Within the viable epidermis/dermis, diffusion to reach the glucocorticoid receptor and binding.

The rate-limiting step is the penetration through the SC. This is affected by both the drug and the vehicle. Once through the SC the mechanism of action is the same as for systemic GCs. Modifying the chemistry of the drug alters the activity. Decreased mineralocorticoid and increased glucocorticoid activity (increased affinity for the GR) can be achieved by introduction of an additional double bond at C-1 and substitution at the C-16 position. The lipophilicity of the steroid and the duration of action are greatly increased by fluorination of the B ring at the C-9 and/or C-6 position. The lipophilicity and metabolic resistance of TG may also be increased by adding ester or acetal groups to the D-ring (e.g., betamethasone 17-valerate).

Methylprednisolone aceponate (Advantan ®) and hydrocortisone aceponate (Cortavance ®) and mometasone furoate (Elocon ®) were developed as “soft” TG with good anti-inflammatory effects but less atrophogenic effects. The improved safety profile is associated with minimal suppression of IL-1 and IL-6 on dermal fibroblasts but marked suppression of epidermal IL-1. Di-esters are also very lipophilic so penetrate SC well and have high affinity to GR. They are de-esterified to form the active monoester in the epidermis and dermal penetration is low. These products are epidermally active with low dermal activity.

Topical glucocorticoids are often more potent than systemic steroids and have much greater systemic safety profile than oral or injectable GCs. TGs are indicated whenever there is regional disease and where owner’s compliance and patient’s temperament and coat type allow. They are particular useful for epidermal driven diseases eg canine atopic dermatitis.

In humans the atopic keratinocytes release pro-inflammatory cytokines IL-1, TNF α (tumour necrosis factor) and GM-CSF (granulocyte macrophage colony stimulating factor) at increased rates. IL-1 and TNFα induce a cellular signal cascade that results in release of the nuclear activation factor from its inhibitory complex and results in up regulation of numerous gene transcription factors. These are genes coding for pro-
Inflammatory cytokines (IL-1, IL-2, IL-4, IL-6, IL-13, TNFα), chemotaxis proteins (e.g., GM-CSF), cellular adhesion molecules, i.e. intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1), AND also enzymes, i.e. phospholipase A2 (an enzyme responsible for the formation of prostaglandin and leukotrienes), inducible forms of cyclooxygenase (COX-2) and NO synthase (iNOS). All major players in inflammation. By inducing cellular adhesion molecules, pro-inflammatory cytokines and increase epidermal chemokine formation (CCL17, CCL22 RANTES, MCP-1 and CCL27) keratinocytes recruit and localize T-cells to the site of atopic inflammation AND ensure maximal activation of the cells.

By inhibiting these inflammatory cytokines, TGs interfere with the activation of a variety of immunologic cells. TGs inhibit the activation of epidermal dendritic cells that normally stimulate Th2 cells. Moreover, eosinophil and T cell apoptosis increases. TGs, as well as local anti-inflammatory and immunosuppressive effects have antiproliferative, and vasoconstrictive effects. The mechanism of action has been discussed previously. It is worth repeating though that TOPICAL steroids reach high enough concentrations to exert both genomic and non-genomic effects while systemic steroids may struggle to achieve high enough concentrations in vivo to exert non-genomic effects.

Topical glucocorticoids are very effective at shutting down the epidermal events of inflammation. Not all steroids are created equal! The choice of steroid will depend on the severity of the inflammation and the type of lesion. The vehicle affects efficacy. For the same active ingredient ointments > creams > lotions > sprays as far as potency goes, due to occlusion and greater penetration. As always we need to consider the risk/benefit ratio.

**Side effects of topical glucocorticoids.**

**Epidermal thinning**

- Number of keratinocyte mitoses is diminished
- Stratum corneum thickness reduced
- Granular layer reduced or absent
- Melanocyte pigment production inhibited
- Reduced Keratin 5 and keratin 14 synthesis
- Inhibited K6/16 synthesis (poor wound healing)

**Dermal thinning**

**Early Atrophy**

- Dermal volume reduced – decreased water content, loss of glycosaminoglycans
- Collagen and elastic fibres unchanged

**Late Atrophy** (Continuation of the Atrophogenic Process)

- Dermal volume reduced
- Collagen and elastic fibres diminished and abnormally aggregated
- Hypoactive fibroblasts
- Dermal vessels fragile, due to loss of fibrous and ground substance support (capillary fragility)
- Follicular atrophy
- Follicular comedones

Topical steroids may be used once or twice daily in the acute situation. These may include Elocon® (mometasone), Diprosone OV ® (betamethasone isopropionate), Cortavance ® (hydrocortisone aceponate) and Advantan ® (methyl prednisolone aceponate). The potency of steroids varies and compared to hydrocortisone the following potency is:

- 600 times more potent than hydrocortisone: Diprosone OV
- 100 times more potent: Elocon, Advantan, Diprosone cream or ointment (betamethasone valerate)
- 2-25 times more potent: Aristocort (triamcinolone acetonide)
• Hydrocortisone is considered mild

NOTE: Potency and atrophogenic effects are NOT correlated due to variable affinities for glucocorticoid receptor binding and the complex mechanism of action. Mometasone is very potent but is less atrophogenic than hydrocortisone, which has low potency. Remember also that penetration may be affected by anatomical location. In people there is variability in systemic absorption with topically applied steroids with the genitals and eyelids (30%) and face (7%) and armpits (4%) having the greatest potential for local and systemic side effects. Areas of thin skin like the axillae, groin, umbilical fold and scrotum I would monitor closely for atrophic changes even with the di-ester steroids.

General rules and tips

Ointments are generally water in oil and are occlusive. Creams are usually oil in water. Lotions have more water than creams and often have alcohols to allow for quick drying. Gels are variable and may be occlusive or rapidly disappear depending on their chemical nature.

1. The vehicle is as important as the drug you are applying to the skin. Most of the non-shampoo topical treatments come as one or more of a lotion, spray, cream, gel or ointment. Moist, exudative skin is best treated with a cream or carbomer gel. Dry, scaling or lichenified skin is best treated with an ointment (hygroscopic properties and increased contact time). Lotions are good for hairy areas (far less messy) and are appropriate for areas where the skin is essentially normal—that is not lichenified or too dry. Sprays are good for relatively normal skin where treating larger areas but hair may significantly impede penetration and so are often best used on lightly haired skin OR used more generously on haired skin to increase penetration through to the epidermis.

2. Severe, focally inflamed and thickened skin can benefit from occlusion. Where a more rapid response is required occlusion will significantly increase absorption of the medication. E.g. Elocon ointment followed by gladwrap coverage, then Coflex bandaging - repeat twice daily for 20 to 30 minutes if needed

3. Occlusion can also be useful in some cases where there is a severe ‘contact’ distribution of inflammation (i.e. areas normally contacting the ground). Perform hydrotherapy (put in the bath for 5 to 10 minutes with just water), dry gently; apply Elocon cream or ointment depending on how dry the skin was. Alternatively wet an old T-shirt, wring so not dripping but still damp and place wet T-shirt on the dog and leave for 20 to 30 minutes after application of the steroid treatment. Occlusion and hydrotherapy hydrate the skin and increases penetration of the steroid and gives rapid relief.

Concluding thoughts.

Glucocorticoids are potent drugs and the therapeutic benefit needs to be balanced against physiological side effects. They are indicated after a diagnosis has been made and where glucocorticoids are indicated for the management of that diagnosis. Topical glucocorticoids should be used where disease, patient and owner factors allow. The minimum effective dose should be chosen for systemic GCs and potency and vehicle should be matched to the lesion type with TGs. Potentially treatment failure with GCs may occur in severe Th2 disease due to loss in genomic function. Better understanding of the non-genomic events may help with future treatment choices in these GC resistant cases. The current challenge in human medicine is to develop safer glucocorticoids. The greater understanding in intracellular events may lead to further development of selective agonists the selectively repress cytokine transcription without up regulating metabolic pathways (the selective glucocorticoid receptor agonists SEGRAs). It is likely that we will have safer tools in the future but for now it is worth remembering that all GCs are not created equal and choose appropriate dose, potency and type of GC based on the clinical diagnosis.
Further Reading