Veterinary Pharmacology
Endocrine System
Corticosteroids

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Goudarz Sadeghi, DVM, PhD, DSc
Associate Professor of Pharmacology
Corticosteroids are synthesized in the adrenal gland under the control of ACTH.
The major circulating corticosteroid in most species is hydrocortisone (cortisol).

The pituitary release of ACTH is controlled by CRH from the hypothalamus.

stress $\Rightarrow$ ↑ Cortisol secretion

Negative feedback of cortisol on ACTH secretion occurs at:
- The pituitary level
- The hypothalamic level
Physiological Effects of Corticosteroids

- Hepatic gluconeogenesis, glycogenesis and protein synthesis
- Peripheral glucose utilization
- Proteolysis (mobilization of amino acids from skeletal muscle to liver)
- Lipolysis in adipose tissue
- Mineralocorticoid activity (mild) which promotes Na⁺/H₂O retention

Pharmacological Effects of Corticosteroids

- Anti-inflammatory/immune modulation
  - Activation phospholipase A2
  - Macrophage cytokine production/release
  - Endothelial leukocyte adhesion
Anti-inflammatory Actions - 1

- Exogenous administration or during chronic stress ⇒ ↑ concentrations ⇒ ↓ the inflammatory response
- Inhibition of PLA2 ⇒ ↓ the breakdown of arachidonic acid ⇒ ↓ PGs & LTs
Anti-inflammatory Actions - 2

- Inhibition of the production or release of inflammatory cytokines from leukocytes.
- They also:
  - ↓ leukocyte migration to inflammatory sites
  - ↓ the phagocytic activity of the reticulo-endothelial system
  - ↓ fibroblast proliferation and collagen deposition
Immune-Modulating Actions - 1

- At even higher doses, corticosteroids are **immunosuppressive**.
- The anti-inflammatory and immune actions are linked (inhibition of leukocyte and macrophage functions).
- No prevention of humoral or cell-mediated immune responses but rather inhibit the manifestations of these reactions.
Their inhibitory effects are mediated by the inhibition of cytokine release and response, and include:

1) ↓ IL-1 and TNF release by activated macrophages
2) ↓ IL-2 release by T lymphocytes
3) ↓ action of IL-2 on T lymphocytes
4) ↓ IFN's effects on macrophages
Corticosteroids share the same basic steroid structure.
Chemical Formulations - 2

- **Essential for CS activity**: the keto groups at C3 and C20, the double bonds at C4-5, and the hydroxyl group at C11.
- The **potency** of CSs: compared to hydrocortisone (value of 1).
- Double bond at C1-2 (e.g. prednisone) $\Rightarrow \uparrow$ potency by 4 times.
- Methylation of prednisone at 6$\alpha$ $\Rightarrow \uparrow$ CS activity slightly but $\downarrow$ MC activity.
- Fluorination at the 9$\alpha$ (e.g. dexamethasone, triamcinolone) $\Rightarrow \uparrow$ CS potency and $\downarrow$ MC activity.
Ester group at C21 ⇒ alters the water solubility and the duration of action.
Phosphate and hemi-succinate esters (readily water soluble) ⇒ a rapid onset and short duration of action when given parenterally
Acetate and diacetate esters (poorly water soluble): can be given as repository IM or SC injections
Acetonide esters: rapid onset and an intermediate duration of action
<table>
<thead>
<tr>
<th>Drug</th>
<th>Glucocorticoid Potency</th>
<th>Substitution</th>
<th>Mineralocorticoid Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4</td>
<td>Double Bond C1-2</td>
<td>0.8</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
<td>Double Bond C1-2</td>
<td></td>
</tr>
<tr>
<td>Methylprednisone</td>
<td>5</td>
<td>6α Methylolation</td>
<td>0.5</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5</td>
<td>Double Bond C1-2, 9 Fluorination, 16α Hydroxylation</td>
<td>0</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25</td>
<td>Double Bond C1-2, 9 Fluorination, 16α Methylolation</td>
<td>0</td>
</tr>
</tbody>
</table>
Uses of Corticosteroids

Replacement Therapy

- Physiological CS replacement therapy is required with hypo-adrenocorticism.
- Animals produce approximately 1 mg of cortisol/kg/day, an equipotent dose of prednisone (0.1-0.2 mg/kg) is used for physiological daily replacement.
- During stressful episodes: the replacement dose is increased 2-5 times.
Uses of Corticosteroids

Shock Therapy

- Controversial in some types!
  - Septic or endotoxic shock is the most responsive.
  - The best therapy for shock is aggressive fluid therapy.

- Inject 30-50 mg/ kg IV ⇒ some benefit
  - Methylprednisolone sodium succinate
  - Hydrocortisone sodium succinate
Uses of Corticosteroids

Anti-Inflammatory - 1

- The most common use in vet med!
- Anti-inflammatory doses of prednisone (0.5-1.0 mg/kg/day): used to treat inflammatory or allergic disorders, particularly those involving the skin and respiratory tract.
- Some rules should be considered.
  - Identify and remove the cause of inflammation before use.
  - CSs work non-specifically ⇒ they will decrease inflammation due to any stimuli.
Establish a goal for therapy and then attempt to use the smallest dose for the shortest period of time possible.

Short-acting oral CSs (prednisone) should be used preferentially with a goal of eventually establishing alternate-day therapy (ADT).
  - The side effects can be dramatically decreased.
Uses of Corticosteroids

Immunosuppressive Therapy

- Prednisone (2 mg Al/day) is commonly employed as first-line therapy for immune disorders such as immune-mediated hemolytic anemia, thrombocytopenia, polyarthritis, and systemic lupus erythematosus.
- High doses $\Rightarrow$ disease is in remission $\Rightarrow$ slowly tapered to the lowest dose that keeps the disease in remission (preferably given as ADT).
- If high doses of CSs are necessary to maintain remission, alternate immunosuppressive drugs should be added to the therapy to permit lowering of the CS dose.
The most important side effects of short-term (<2 weeks) corticosteroid therapy are:

- 1) Increased susceptibility to infection
- 2) Polyuria with secondary polydipsia
- 3) Polyphagia
- 4) Behavioral and mood changes
  - Depression
  - Panting
  - Lethargy
- 5) Diarrhea
- 6) Development of pancreatitis
The use of CSs in dogs with spinal cord trauma to decrease cord swelling has been associated with an increased risk of *colonic perforation*.

In dogs, CSs:
- ↑ ALP
- ↑ ALT & AST
- Result in *glycogen deposition* in the liver, causing *steroid hepatopathy*
  - Although seldom associated with functional hepatic failure, they frequently complicate the *biochemical evaluation of liver function*. 
Side Effects - 3

- Parturition in late pregnancy
- Teratogenic in early pregnancy
- In horses: laminitis
- Alteration of circulating blood cell counts
- Animals develop a mature neutrophilic leukocytosis with a monocytosis, eosinopenia, and lymphopenia.
- The red cell volume is often high normal due to CS enhancement of erythropoietin production.
Side Effects - 4

- The **gluconeogenic** effects of CSs can lead to pancreatic β cell exhaustion and the development of **diabetes mellitus**.

- The most serious consequence of long-term CS use: suppression of the hypothalamic-pituitary adrenal axis ⇒
  - Adrenal atrophy (secondary adrenocortisol deficiency)
  - Iatrogenic Cushing's syndrome
Side Effects - 5

- Affected animals develop clinical signs similar to dogs with spontaneous hyper-adrenocorticism including:
  - loss of hair
  - thinning of skin
  - muscle wasting and weakness
  - abdominal redistribution of fat stores (potbellied appearance)
  - recurrent infections
  - reproductive disorders
Withdrawal from long-term CS use should be gradual to allow time to re-establish a normal hypothalamic-pituitary-adrenal axis.

Signs of too rapid corticosteroid withdrawal include:
- Mental dullness
- Weakness
- Anorexia
- Vomiting
- Behavioral changes
<table>
<thead>
<tr>
<th>Effect</th>
<th>Due to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyuria/polydipsia</td>
<td>Mineralocorticoid action</td>
</tr>
<tr>
<td>Increased susceptibility to infection</td>
<td>Anti-inflammatory/immune modulation</td>
</tr>
<tr>
<td>Gastrointestinal ulceration</td>
<td>Inhibition of GI prostaglandin production</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>? Change in viscosity pancreatic secretion</td>
</tr>
<tr>
<td>Laminitis (horses)</td>
<td>? Potentiation of catecholamine-mediated vasoconstriction</td>
</tr>
<tr>
<td>Steroid hepatopathy (dogs&gt;cats)</td>
<td>↑ Hepatic glycogen production</td>
</tr>
<tr>
<td>Increased serum Alkaline phosphatase (dog)</td>
<td>Induction of corticosteroid isoenzyme</td>
</tr>
<tr>
<td>Mild polycythemia</td>
<td>↑ Erythropoietin</td>
</tr>
<tr>
<td>Mature neutrophilia</td>
<td>↑ Release from bone marrow ↓ Marginization</td>
</tr>
<tr>
<td>Lymphopenia/eosinopenia</td>
<td>Redistribution away from periphery</td>
</tr>
<tr>
<td>Polyphagia, mood alteration</td>
<td>? CNS effects of corticosteroids</td>
</tr>
</tbody>
</table>
| Hyperglycemia/glucose intolerance/diabetes mellitus | Acute: ↑ hepatic gluconeogenesis with ↓ peripheral utilization of glucose  
           | Chronic: pancreatic β cell exhaustion                                  |
| Iatrogenic Hyperadrenocorticism            | Chronic suppression of hypothalamic-pituitary-adrenal axis with adrenal atrophy |
My Website
http://www.gsadeeghi.com

My E-Mail
gsadeeghi@ut.ac.ir