Corticosteroids have been used for a wide variety of disorders in human and veterinary medicine for years. Few drugs have been used as extensively, as evidenced by the familiar adage “never let a patient die without the benefit of steroids.” This lecture will focus on the use of steroids for 2 common conditions in veterinary emergency medicine, neurotrauma and hypovolemic shock.

There are many glucocorticoid medications, which vary greatly in their potency, durations of biologic action, mineralocorticoid effects and other systemic effects. There are glucocorticoid receptors in the cytosol of almost every cell in the body, affording these drugs a wide range of cellular effects. Therefore, before using a glucocorticoid, the risk/benefit ratio and the potential for unrelated physiologic effects must be considered. The table below summarizes the relative potencies and durations of action of some of the more commonly prescribed glucocorticoids in veterinary medicine.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Glucocorticoid Potency</th>
<th>Relative Mineralocorticoid Potency</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>1</td>
<td>&lt; 12 hours</td>
</tr>
<tr>
<td>Prednisone/Prednisolone</td>
<td>4</td>
<td>0.8</td>
<td>12 – 24 hours</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>30</td>
<td>0</td>
<td>24 – 48 hours</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>0.5</td>
<td>12 – 24 hours</td>
</tr>
<tr>
<td>Trimacinolone</td>
<td>5</td>
<td>0</td>
<td>12 – 24 hours</td>
</tr>
</tbody>
</table>

Corticosteroid dosing is typically done in prednisone equivalents and three dosing ranges are commonly employed. Immunosuppressive dosing of 2-4 mg/kg/day of prednisone is typically use for immune mediated disease. Anti-inflammatory effects are typically achieved with dosing of 1-2 mg/kg/day. For Addisonian patients, 0.25-0.5 mg/kg/day is generally sufficient to replace baseline glucocorticoid requirements.

Glucocorticoids have permissive effects on many vital physiological processes, and in the absence of normal physiologic levels of these hormones, serious systemic sequelae occur. For example, in the gastrointestinal tract, mucus production and enterocyte turnover are dependent upon basal cortisol concentrations. Vascular tone, glucose homeostasis, calcium homeostasis, and immune function are also dependent upon normal glucocorticoid metabolism. However, high concentrations of glucocorticoids can also be detrimental. For example, high doses of glucocorticoids reduce mucus production in the GI tract leading to ulceration, and prostaglandin production in the kidney, essential for maintaining renal perfusion in the face of hypotension, is inhibited by high concentrations of these compounds. Therefore, clinical use of these drugs can have significant consequences on homeostasis, especially at higher doses.

**Traumatic brain injury**
Despite their traditional role in the treatment of CNS trauma, there is little evidence to support the use of glucocorticoids in victims of severe head trauma. Early experimental studies showed a neuroprotective effect of high dose methylprednisolone in head injured animals, but only when the drugs were administered before the traumatic injury. This protocol involves the intravenous administration of a 30-mg/kg bolus of methylprednisolone sodium succinate (Solu-Medrol) at time 0, and 15 mg/kg boluses at 2 hr and 6 hr. The “high-dose” protocol was suspected to provide therapeutic benefit via free-radical scavenging action, rather than by activation of steroid receptors. No studies have shown any efficacy of prednisone/prednisolone or dexamethasone for treatment of head injury.

Despite this, “standard” dosing protocols of prednisone and dexamethasone can be found in many veterinary formularies, and are commonly at doses far exceeding immunosuppression. Recent evidence from a large, prospective, randomized, placebo-controlled clinical trial (the CRASH-2 Trial) showed significantly increased mortality in people with traumatic brain injury treated with this high-dose protocol compared to a placebo group. Given this evidence of a detrimental effect in head injured people and the potential side effects of these drugs, including gastrointestinal ulceration, immunosuppression, and hyperglycemia, corticosteroids are no longer recommended in human patients with head trauma, and in fact are considered a contraindicated therapy. It is likely that the same approach should be followed in veterinary medicine.

**Spinal cord injury**
Corticosteroids have been proposed to ameliorate secondary injury after spinal cord trauma in both human and veterinary medicine. However, this is a highly controversial topic and has been the subject of intense debate in the human literature for over a decade. Experimental and clinical studies have documented both benefit and harm from the use of these drugs in patients with spinal cord injury. A thorough understanding of the evidence for both benefit and harm is essential for the clinician considering administration of these drugs. Methylprednisolone sodium succinate (MPSS) has been extensively studied in both experimental studies and clinical
trials as a therapy for secondary spinal cord injury. Proposed neuroprotective mechanisms include improvement of spinal cord blood flow, free-radical scavenging effects, and anti-inflammatory activity. Free radical scavenging has been shown experimentally to be the most important protective effect in patients with spinal cord injury. Other common corticosteroids (e.g., dexamethasone, prednisone) have minimal anti-oxidant effects, and are unlikely to have any significant neuroprotective effect, although they may reduce the discomfort associated with the injury.

A series of three human clinical trials (the National Acute Spinal Cord Injury Study or NASCIS) provide the primary evidence of a beneficial effect of MPSS in human patients with spinal cord injury. The only placebo-controlled trial (NASCIS 2) showed a mild improvement in motor scores at 6 weeks for patients treated with MPSS (30 mg/kg bolus, followed by a constant rate infusion of 5.4 mg/kg/hr for 48 hours) compared to the placebo group, but this effect was not present at 6 months or 1 year post-injury. Only in a post-hoc, sub-group analysis were the authors able to show an improvement in motor scores at 6 weeks, 6 months and 1 year in the group of patients treated with MPSS for 48 hours beginning 3-8 hours post injury. No difference in outcome between the treatment groups was noted at any of the time points for patients treated less than 3 hours or greater than 8 hours after injury. There were no differences in mortality between the groups, but there was an increased incidence of severe pneumonia and a trend for an increased risk of sepsis in the groups treated with MPSS for 48 hours at the 6 week time point.

There has been much debate in the human literature over the results of the NASCIS 2 trial. Although the use of high dose MPSS for patients with spinal cord injury continues to be considered standard of care, several surveys have shown a lack of confidence in this therapy among human neurosurgeons. No placebo-controlled trials evaluating the efficacy of MPSS in veterinary patients with spinal cord injury have been done. Studies have shown significant side effects of corticosteroid treatment in spinal cord injured dogs, including gastrointestinal ulceration as well as prolonged hospital stays. Given the prevalence of complications, the lack of clinical trials demonstrating efficacy in veterinary species, and the likelihood that the mild functional improvements noted in the NASCIS 2 trial would not correlate to significant improvements in quality of life in veterinary species, it is the author’s opinion that the risks of high dose steroid therapy outweigh the potential benefits.

### Hypovolemic shock

Hypovolemic shock results from loss of intravascular volume, leading to decreased tissue perfusion. The ensuing tissue hypoxia promotes the arachidonic acid cascade and leads to production of inflammatory cytokines. Systemic inflammation, vasodilation, and increased vascular permeability results. Ultimately platelet activation and neutrophil chemotaxis and adhesion occurs. Upon reperfusion, reactive oxygen species exacerbate tissue damage. Physical obstruction of capillaries by thrombi, activated platelets, and edematous endothelial cells exacerbate maldistribution of flow even after volume resuscitation.

Because of their anti-inflammatory effects, corticosteroids have potential benefits in limiting the inflammatory cascade triggered by hypovolemic shock. In addition, they antagonize vasoactive substances such as histamine and kinins that may cause vasodilation, and stabilize lysosomal and endothelial cell membranes. Some corticosteroids, most notably methylprednisolone, also limit the generation of free-radicals.

In experimental studies, short-term survival is improved when high dose glucocorticoids are administered with fluids within an hour of initiation of shock. Lysosomal enzyme release is decreased in canine hemorrhagic shock models, but only when animals are treated before the initiation of shock. No clinical study has ever shown a survival benefit of using corticosteroids in patients with hypovolemic shock.

The massive doses of corticosteroids recommended for shock have substantial negative effects, including gastric ulceration and bleeding via inhibition of cyclooxygenase-1 formation. Immunosuppression is also likely with these treatment protocols, increasing the risk of infection. Finally, by decreasing prostaglandin production in the kidney, acute kidney injury may be induced by blunting the normally protective auto-regulatory functions.

The use of corticosteroids in hemorrhagic shock has been discouraged in human medicine for decades. Two extensive meta-analyses published in 1967 and 1973 concluded that there was no indication for the use of glucocorticoids in hypovolemic shock, and these drugs are no longer considered standard of care in these cases. Finally, a veterinary review of the available literature published in 1998 concluded, “Although it has long been stated that no animal should die without the benefit of corticosteroids, it may be time that we allow some of our patients to live without them.” When considering the potential risks and benefits of steroids for hypovolemic shock, it is difficult to continue to recommend their use.

### References


