GLUCOCORTICOIDS FOR NEUROLOGIC DISEASE

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I. MECHANISMS OF ACTION:

A. Genomic ("Classical") Effects[1,2]:

1. Glucocorticoids bind to receptors in the cytoplasm which dimerize and translocate to the nucleus.
2. Within the nucleus, these receptor-glucocorticoid dimers bind to glucocorticoid response elements (GREs) in the promoter regions of certain genes (almost 100 now identified).
3. This leads to gene transcription, mRNA translation and increased populations of certain proteins within cells.
4. Glucocorticoids may also interact with transcription factors to alter the efficiency of mRNA production
5. Anti-inflammatory properties of glucocorticoids may be mediated directly by proteins like lipocortin-A, which blocks the arachadonic acid pathway via interactions with phospholipase A2
6. Glucocorticoids also alter the balance of cytokines, decreasing IL-1 and increasing IL-10, which leads to a blunted inflammatory response
7. Glucocorticoids also reduce vasogenic edema via inhibition of VEGF and other proteins that influence vascular permiability
8. Numerous other classical effects exist including alteration of thyroid axis, effects on B2 receptors and catabolic effects (prevention of glucose and amino acid entrance into cells)

B. Non-genomic ("Non-classical") Effects[3]:

1. Glucocorticoids are highly lipophilic molecules and easily integrate into cell membranes
2. Integration into membranes may "stabilize" them, making cells more resistant to oxidative stress and inflammation. This ultimately leads to the prevention of lipid peroxidation chain reactions in the cell membrane
3. By preventing lipid peroxidation, ionic homeostasis, spinal cord blood flow, and mitochondrial energy metabolism are preserved. Excessive release of glutamate is also prevented.
4. Glucocorticoids also may exert post-translational and post-transcriptional modifications on proteins and mRNA
5. Interaction with 2nd messenger systems is also another speculated non-genomic mechanism

6. The non-classical pathway is faster in its onset and is likely responsible for many of the "high dose" protective effects seen with methyprednisolone administration in experimental spinal cord injury

Acute Spinal Cord Trauma with Significant Myelopathy:

1. All patients with spinal cord trauma, even those that are seemingly euhydrated, should receive fluids.[4,5]
2. Appropriate analgesia is also important as it will reduce catecholamine and endogenous corticosteroid release
3. Most corticosteroids are strictly contra-indicated in acute spinal cord trauma. These drugs at traditional doses probably act only through the "classical" pathway on intra-nuclear steroid receptors.
4. While reduction of inflammation secondary to injury might be theoretically beneficial, catabolic effects are not. Glucocorticoids can prevent nutrient entry into neurons and drive cells down catabolic pathways.[4,6] They may also lead to excitotoxic neuronal dealth, PLA2 depletion-mediated membrane damage and oxidative stress.[6-8]
5. Methylprednisolone sodium succinate (MPSS, Solumedrol) has been used in humans and dogs with acute spinal cord trauma. The drug has "non-classical" steroid effects at high doses, acting as an anti-oxidant and membrane stabilizer. If used, MPSS needs to be administered within the first **8** hours of the event at a bolus of 30 mg/kg. Again, evidence points to the fact that neuro-protection occurs mainly due to membrane stabilization, not reduction of inflammation.[8]
6. Smaller bolus doses provide a smaller membrane "stabilizing" effect. Mega doses (60 mg/kg) lead to a loss of this neuro-protection
7. Methyprednisolone sodium succinate that is administered more than 8 hours after the traumatic event leads to a worse prognosis.[4,9-12] The reason for this may be that after the 8 hour window, lipid peroxidation of membranes has already occurred. Treatment of these patients exposes them to only steroid side effects such as immunosupression, thromboembolism and neuronal catabolism
8. Based on the NASCIS III trial, methyprednisolone treatment should be continued at 5.4 mg/Kg/hr as a CRI for 24 hours if the patient presents within the first 3 hours of the injury or continued for 48 hours if the patient is treated within 3-8 hours. Single bolus treatments without CRI are discouraged by the NASCIS as these single boluses will only lead to transient reduction of lipid peroxidation.
9. While there is some evidence to suggest that MPSS treatment is beneficial, even advocates will admit that benefits are small. In humans treated within the 8 hour window and continued on CRI, small improvements in both sensory and motor function are achieved.[13-15] These benefits did not result in a change in quality of living index and were not present by 1 year follow-up.[11,16,17] Many investigators

have pointed to statistical and study design issues associated with the NASCIS trials and feel that even these small benefits may not be real.[16,18]

10. Few clinical studies have been done examining the efficacy of MPSS in dogs with acute spinal cord trauma. The limited investigations that are available have been restricted to dogs with IVDD.[19,20] MPSS or administration of similar steroids has not been associated with improved outcome in these patients.[19,20] Side-effects such as gastrointestinal ulcers and increased hospitalization time have been seen.[4,12,19-22]
11. Given the current literature available, MPSS treatment for spinal cord trauma in dogs and cats seems to be of dubious merit.
12. Other steroids, such as dexamethasone, have not been carefully evaluated in the clinical setting for beneficial effects at high doses. Some experimental rodent spinal trauma models do show neuroprotection after spinal cord injury with rapid administration of large amounts of dexamethasone; activity is probably by "non classical" pathways.[23,24] Other models reveal detrimental effects on recovery, and several investigation in companion animal species show no alteration in prognosis.[25-27] Dexamethasone, at high doses, can cause significant gastrointestinal ulceration and this, coupled with mixed evidence of benefit in experimental modeling and a lack of prospective clinical data, makes recommending high dose or low dose therapy difficult. Recent retrospective evidence shows that pre-surgical dexamethasone in dogs with disk herniation increases the odds of adverse events and does not improve recovery (Levine et al 2008, J Am Vet Med Assoc).

Suspected Disk Herniation with Mild Myelopathy that will be Managed Conservatively:

1. The cornerstones of therapy are analgesia, cage rest (4-6 weeks), and physiotherapy
2. Prednisone (or other glucocorticoids) may be used to reduce inflammation associated with disk herniation in patients with mild neurological deficits. Typically 0.5 mg/kg PO BID of prednisone for 7 days will be used.
3. Patients that are being managed conservatively for disk herniation usually have minimal myelopathy and so should not be susceptible to neuronal catabolic effects seen in patients with acute, severe spinal cord injury.
4. In humans, intra-discal and epidural corticosteroids and oral corticosteroids are frequently used in non-surgical cases of disk herniation.[28-30] Results are mixed and investigations have not been performed in veterinary medicine.
5. Recent evidence[31,32] suggests that in dogs with presumptive disk herniation that is medically managed, glucocorticoid therapy may be contra-indicated. In a report of 223 cases of medically managed thoracolumbar disk herniation, steroids were associated with a 0.48 odds of successful outcome and also were associated with lower quality of life scores, when adjustments were made for confounding factors such as neuroscore, age, breed, and weight.

Head Trauma:

1. Since the 1960s and 1970s steroids have been advocated for the treatment of head trauma in humans and veterinary species
2. The hypothesized benefits include reduction of vasogenic edema, inflammation and oxidative stress
3. A recent prospective, placebo controlled study evaluating the efficacy of high dose methyprednisolone for head trauma in 10,008 humans found that treatment with MPSS increased the risk of death at 2 week follow-up (21% vs. 18%).[33,34]
4. The study showed no benefit in Glasgow coma scale score at 2 week and 6 month follow-up[33,34]
5. At this time, high dose steroid therapy for head trauma in human medicine is not in concert with the standard of care and many veterinary neurologists view this treatment as contraindicated in dogs and cats with head trauma[35-37]
6. It is unclear why glucocorticoids are not generally effective for head trauma, but numerous hypotheses exist
7. Steroids lead to hyperglycemia and local lactate accumulation in the injured brain, failure of amino acids and glucose to enter the cell, and do not address cytotoxic edema present due to energy deprivation

For Encephalopathy:

1. Corticosteroids are frequently used in the management of CNS neoplasia to reduce peri-tumoral edema or tumor associated inflammation.[38,39] Prednisone can be given at 0.5 mg/kg PO BID for the duration of the disease.
2. In some cases animals present with dramatically worsening neurological signs (e.g. brain herniation) where brain tumor or encephalitis is suspected but not documented. In these patients corticosteroids can be life saving, but must be given with the knowledge, on the owner's part, that treatment is empirical. Advanced imaging and CSF analysis should be obtained ASAP. Usually we suggest trying mannitol/furosemide first due to the negative consequences of providing steroids without definitive diagnosis
3. Often Mannitol (1g/kg slow bolus over 20 minutes) is administered in cases where edema or brain herniation is suspected of leading to a per-acute worsening of signs. Mannitol reduces ICP by its direct osmotic effects and also improves RBC membrane dynamics, leads to cerebral vasoconstriction, and has anti-oxidant properties.[40] Remember, that mannitol may be contra-indicated in animals with known dehydration, kidney disease, or hypotension. Furosemide is usually given at 0.7mg/kg IV shortly after the mannitol bolus is administered.
4. Corticosteroids can also be utilized in cases of infectious or non-infectious inflammatory disease and have been shown to improve outcome in both humans and veterinary species.[41-44] Prednisone can be administered at 0.5 mg/kg PO BID for 7 days without taper in cases of known **infectious** encephalitis.

5. Prednisone can be given at 0.5-1.0 mg/kg PO BID for 2-3 months with 1 month taper for animals with **suspected non-infectious inflammatory** disease.[45,46] During the wean-down period if signs recur, steroid administration is resumed and an additional immunosuppressive is added (drugs to choose from include CCNU, azathioprine, cytosine arabinoside, cyclosporine, etc).[47]

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