



# Administering Corticosteroids in Neurologic Diseases

Simon R. Platt, BVM&S, DACVIM (Neurology), DECVN, MRCVS<sup>a</sup>

Carley J. Abramson, DVM, DACVIM (Neurology), MRCVS<sup>b</sup>

Laurent S. Garosi, DVM, DECVN, MRCVS<sup>a</sup>

<sup>a</sup>The Animal Health Trust, Centre for Small Animal Studies  
Newmarket, Suffolk, England

<sup>b</sup>The Ohio State University

## ABSTRACT:

The main pharmacologic effects of glucocorticosteroids pertain to their antiinflammatory properties, immunosuppressive effects, and potential tumoricidal role. Central nervous system (CNS) trauma involves multiple and complex pathophysiologic processes that may benefit from corticosteroid administration. Unfortunately, clinical trials of these drugs have not proven that they have a definitive or superior role in treating CNS trauma. CNS inflammation may be infectious, but in many cases a specific pathogen is not confirmed as the cause; in either case, patients may benefit from the actions of steroids in the initial period. Other neurologic diseases, such as cerebrovascular disease, may not benefit from corticosteroid therapy, whereas for some types of neurologic neoplasia, it may be the only beneficial treatment available.

**G**lucocorticosteroids are commonly used in veterinary medicine. Their uses are broad ranging, but these drugs are mainly used for their antiinflammatory and immunosuppressive effects. There are considerable long- and short-term side effects associated with administering these drugs; therefore, their administration should be limited to specific conditions in which their benefits outweigh their risks. Neurologic diseases often require steroidal therapy. The beneficial effects of steroidal therapy, particularly regarding brain and spinal cord disease, include protection from free radicals, reduced intracranial pressure by decreasing production of cerebrospinal fluid (CSF), and maintenance of normal microvasculature integrity.<sup>1</sup> This article discusses the specific uses and contraindications

of glucocorticosteroids in veterinary neurology based on experimental and clinical research evidence.

## PHYSIOLOGY AND MECHANISM OF ACTION

Corticosteroids are primarily produced by the zona glomerulosa (which produces aldosterone) and zona fasciculata (which produces cortisol and corticosterone) of the adrenal gland and have a plethora of functions.<sup>2</sup> Corticosteroids are constantly synthesized under the control of the hypothalamus (via the effect of corticotropin-releasing hormone on the pituitary) and pituitary (via adrenocorticotropic hormone [ACTH]). Cortisol and corticosterone concentrations in plasma influence ACTH secretion in such a way that increased concentrations inhibit release of ACTH and reduced concentrations

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stimulate release of ACTH.<sup>3</sup> Exogenous corticosteroid administration can also suppress ACTH secretion, with the degree of suppression depending on the particular drug administered.<sup>4</sup>

At least three steroid receptors have been identified and associated with different physiologic effects.<sup>5</sup> Every cell type has glucocorticosteroid receptors, with the type and concentration of the particular receptor varying between species and tissue.<sup>3</sup> Glucocorticoid receptors are located in the cytoplasm of the target cell and are inactivated until bound to a steroid ligand.<sup>3</sup> Steroids are thought to enter the cell by passive diffusion; after they have bound to the receptor, the glucocorticosteroid-receptor complex translocates to the nucleus, where it binds to regulatory proteins of target genes.<sup>3</sup> Transcription of the gene and subsequent formation of the targeted protein is either induced or inhibited. The pro-

permeability of the distal renal tubules to water via a direct action.<sup>4</sup>

Glucocorticoids are most frequently used in clinical medicine for their antiinflammatory and immunosuppressive actions. Their action is on leukocyte numbers as well as function, ultimately impacting both humoral and cell-mediated arms of the immune response.<sup>2</sup> Specifically, glucocorticosteroids inhibit the enzyme phospholipase A<sub>2</sub> via lipocortin, which converts arachidonic acid to prostaglandin and leukotriene metabolites.<sup>2</sup> Glucocorticoids also inhibit release of tumor necrosis factor and interleukin-2 from activated macrophages. Tumor necrosis factor induces cytotoxicity and can enhance neutrophil and eosinophil function.<sup>3</sup>

The immunosuppressive effects of glucocorticosteroids are more pronounced on the cellular arm than on the humoral arm of the immune system.<sup>4</sup> Glucocorticoids

## ***A definitive diagnosis of neurologic disease is often required before glucocorticosteroid administration can be advised in an appropriate regimen.***

teins encoded by these genes are responsible for physiologic and hence pharmacologic effects of the glucocorticosteroids.<sup>3</sup>

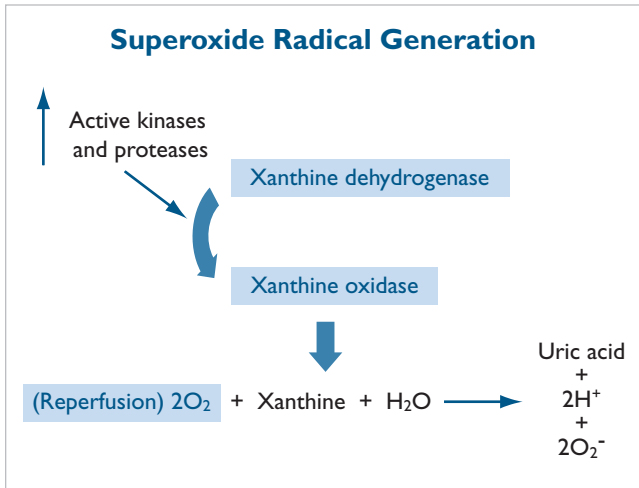
The natural function of glucocorticosteroids is to protect glucose-dependent cerebral functions by stimulating formation of glucose by the liver, decreasing its peripheral use, and promoting its storage as glycogen.<sup>2</sup> Gluconeogenesis is the result of increased precursors and induction of hepatic enzymes that catalyze reactions, which are both necessary for glucose synthesis. Increased breakdown of proteins, particularly skeletal muscle and collagen, provides gluconeogenic precursors. This effect can be exhibited clinically as muscle wasting and delayed wound healing. The metabolism of lipids is also affected by glucocorticosteroids, which promote lipolysis and inhibit long-chain fatty acid synthesis.<sup>4</sup> Glucocorticoids influence water and electrolyte balance through mineralocorticoid actions. Synthetic glucocorticoids possess varying degrees of mineralocorticoid activity, but all have less than 1% of the mineralocorticoid activity of aldosterone. Glucocorticoids also impart a permissive effect on tubular mechanisms that maintain the glomerular filtration rate; they have an inhibitory effect on antidiuretic hormone and may decrease the

have minimal effects on plasma immunoglobulin concentrations but can modulate immunoglobulin function, inhibiting such processes as bacterial opsonization. The immunosuppressive actions of glucocorticosteroids, like their antiinflammatory actions, involve disruption of the intercellular communication of leukocytes via interference with lymphokine production, biologic action, or both.<sup>3</sup>

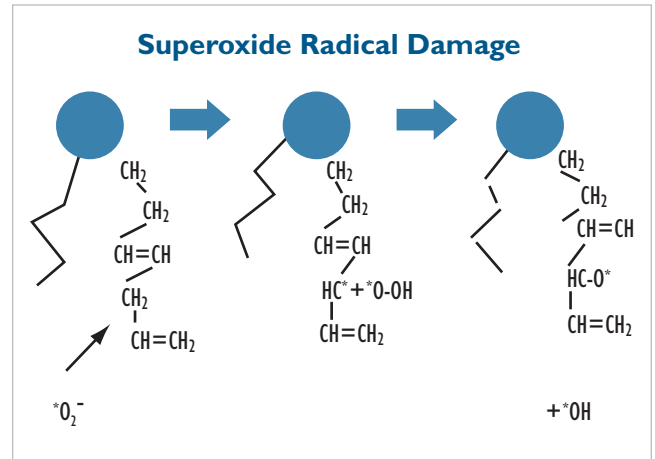
The effects of glucocorticosteroids on the central nervous system (CNS) are well documented. Indirectly, glucocorticosteroids maintain adequate plasma concentrations of glucose for cerebral functions, maintain cerebral blood flow, and influence electrolyte balance in the CNS.<sup>3</sup> In humans, glucocorticosteroids are believed to influence mood (including euphoria), behavior, and brain excitability.<sup>3</sup> The euphoric effect commonly recognized in dogs is likely to reflect differences in glucocorticosteroid receptors.<sup>3</sup>

### **TRAUMA** **Head Trauma**

Severe head trauma is associated with a high level of mortality in human and veterinary patients.<sup>6</sup> The appropriate therapy for head trauma patients remains contro-



**Figure 1.** Reactive oxygen species such as the superoxide radical ( $O_2^-$ ) are produced from xanthine after a period of reperfusion. This reaction also requires the enzyme xanthine oxidase, which is produced in the presence of increased posttraumatic kinases and proteases.



**Figure 2.** Representation of a phospholipid component of a neuronal cell wall. Superoxide radicals ( $O_2^-$ ) attack susceptible carbon atoms in the phospholipid, damaging the structural integrity of the membrane and producing reactive lipoxyl radicals and hydroxyl radicals ( $-OH$ ), further propagating the damage. (\* = free radicals, C = carbon; H = hydrogen)

versial because there have not been retrospective studies focused on treating dogs and cats. However, it is agreed that treatment should be immediate to allow patients to recover to a level that is both functional and acceptable to owners. Glucocorticoids have long been used in treating head trauma, and their administration is theoretically beneficial for many reasons. The most well-documented benefit of glucocorticoids for nervous system trauma is control of the so-called secondary injury (i.e., inhibiting lipid peroxidation).<sup>7</sup> Secondary traumatic brain damage is linked to alterations in fundamental neurochemical mechanisms that in turn produce additional vascular and neuronal damage, thus impairing the potential for recovery.<sup>8</sup>

During posttraumatic metabolism, reactive oxygen species are produced as a consequence of mitochondrial dysfunction and as by-products of various enzymatic reactions<sup>8</sup> (Figure 1). These reactive oxygen species are responsible for lipid peroxidation, which plays a crucial role in posttraumatic neuronal degeneration, and have been linked to the prognosis of severe head injury<sup>8</sup> (Figure 2). The degree of reactive oxygen species-mediated oxidative damage is reduced by corticosteroid administration in many experimental models of CNS trauma; this research has led to the hope that glucocorticosteroids could help improve neurologic function.<sup>8</sup> Glucocorticosteroids also reduce cerebral edema formation and modulate the inflammatory response by inhibit-

ing lipocortin production.<sup>9</sup> However, glucocorticoids have actually been shown to potentiate neuronal damage when ischemia is present; the reasoning behind this finding may relate to the fact that corticosteroids make neurons more vulnerable to metabolic insults, such as cerebral hypoxia-ischemia, by exacerbating the excitatory amino acid-calcium cascade.<sup>10</sup> Corticosteroids have also been shown to inhibit remyelination of injured neurons.<sup>9</sup>

Despite the already mentioned advantages and encouraging results in laboratory studies, clinical trials have failed to show a significant effect of glucocorticosteroid administration on neurologic outcome or mortality in humans with head injuries.<sup>6,7</sup> The Brain Trauma Foundation and the American Association of Neurological Surgeons developed a set of guidelines in 1995 for patients with head trauma.<sup>11</sup> In this series of recommendations, glucocorticosteroid administration was not advised for improving outcome or reducing intracranial pressure in humans with severe head injury.<sup>11</sup> In a review of 13 pooled steroid trials, there was an insignificant (1.9%) reduction in deaths.<sup>7</sup> Another review of 2,295 humans with moderate or severe head injury demonstrated no significant difference between corticosteroid and control groups in the rate of the combined endpoint of mortality and severe disability.<sup>12</sup> It has been suggested that failure to demonstrate improved outcome with steroid administration in patients with head trauma is due to bias when recruiting patients into studies<sup>13,14</sup> and

recruitment numbers that are too small to demonstrate small differences in outcome between groups.<sup>12</sup> This issue has recently been addressed in the largest scale investigation published to date, the Corticosteroid Randomization After Significant Head Injury (CRASH) study.<sup>13</sup> The CRASH trial involved over 10,000 patients and was designed to determine the effects of short-term corticosteroid infusion on death and disability following significant head injury. The study demonstrated that the risk of death from all causes, within 2 weeks of severe head trauma, was actually higher in the group treated with corticosteroids than in the placebo group.

Limited experimental evidence of efficacy exists for administering a high-dose methylprednisolone sodium succinate (MPSS) protocol to veterinary patients with severe head injury. Therefore, routine administration of glucocorticoids is not recommended for head injuries; in addition, significant side effects may occur, such as coagulopathies and hyperglycemia (which has an undesirable effect on cerebral edema), together with an

follow acute spinal trauma have been well reviewed.<sup>1</sup>

Although medical therapies for spinal trauma are numerous, experimental studies have suggested that soluble glucocorticosteroids (e.g., MPSS) given within 8 hours of trauma may be beneficial.<sup>16,17</sup> MPSS is a glucocorticosteroid that has free radical-scavenging properties when administered at very high doses.<sup>18,19</sup> The neuroprotective effect of MPSS may also be due to glucocorticoid receptor-mediated inhibition of phospholipase A<sub>2</sub>.<sup>20</sup> However, MPSS has no effect on postinjury concentrations of the products of phospholipase A<sub>2</sub> activation, supporting the hypothesis that the neuroprotective action of MPSS is mediated by free radical scavenging rather than antiinflammatory actions.<sup>21</sup> A multitude of experimental models of acute spinal cord concussion have demonstrated that MPSS has a neuroprotective effect when given at the time of or within minutes after spinal cord injury.<sup>1,20,21</sup> A multicenter study in humans also suggested that MPSS given within the first 8 hours was beneficial.<sup>16,17</sup> In this study, MPSS was given at 30

## **Synthetic glucocorticosteroids have multiple physiologic and pharmacologic actions that may be harnessed for multiple benefits in managing specific neurologic diseases.**

increased incidence of infection.<sup>1,6,7,12</sup> Hyperglycemia (>200 mg/dl) has been associated with increased mortality in severely brain-injured humans.<sup>15</sup> The cause of hyperglycemia and the reason for its severity during an ischemic event are unknown and may well be a stress response. Unless a veterinary study demonstrates a benefit of corticosteroid administration in animals with head injuries, a high-dose regimen cannot be advised for canine or feline head trauma.

### **Spinal Trauma**

The most common cause of acute spinal trauma in dogs is thoracolumbar intervertebral disk disease, but this also occurs as a result of external trauma such as vertebral fracture and subluxation.<sup>1</sup> The severity of the spinal cord lesion is influenced by the magnitude of the disk protrusion and its rate of development. The complex sequence of biochemical events initiated by any trauma involves increases in the intracellular calcium content, free radical production, and endorphin-associated ischemia. The vascular and biochemical events that

mg/kg IV as a slow bolus and then at 5.4 mg/kg/hr IV for the next 23 hours as a constant-rate infusion to maintain a high level of the drug in the injured cord for a longer period.<sup>16,17</sup> The clinically detectable benefits were small but significant and involved both long tract and segmental function.<sup>22</sup> These trials also demonstrated that initiating MPSS treatment in patients with incomplete injuries more than 8 hours after injury resulted in a worse outcome.<sup>17,22</sup> It has been proposed that this is the result of glucocorticosteroid interfering with normal regeneration.<sup>1</sup> A more recent clinical trial in humans demonstrated that if treatment with MPSS is initiated within 3 hours of injury, a regimen that continues a maintenance infusion of the drug for 24 hours should be administered.<sup>23</sup> If treatment is initiated between 3 and 8 hours after injury, the infusion should be continued for 48 hours.<sup>23</sup> High doses of MPSS in acute spinal cord injury have been associated with prolonged hospitalization as a result of steroid-related side effects.<sup>1,15-23</sup>

In dogs, it has been suggested that MPSS be given as an initial bolus of 30 mg/kg IV, with additional doses of

15 mg/kg IV at 2 and 6 hours after the initial dose and thereafter every 8 hours for up to 48 hours after the trauma.<sup>1</sup> However, these data have been extrapolated from human and experimental literature because no studies have been conducted to evaluate the efficacy of such a regimen in veterinary patients. The most recent canine experimental study showed that MPSS does not provide a large or significant lasting benefit regarding neurologic preservation or restoration.<sup>24</sup> This study

acute concussive disorders. Spinal cord blood flow and oxygen levels can often be maintained when cord compression occurs slowly; however, the ability of the spinal cord to regulate blood flow to maintain homeostasis is diminished.<sup>26,27</sup> The evident pathology in these cases is predominantly demyelination and axonal swelling, and only late in the course of the disease does the white matter become edematous, which is vasogenic edema.<sup>26</sup> The edema itself is a cause of further compression

## ***CNS trauma has a very complex and well-documented pathophysiology whereby neurologic damage may be progressive because of a secondary injury phenomenon.***

demonstrated a decrease in regional spinal cord blood flow in association with MPSS therapy.<sup>24</sup> The recommended regimen for cats based on experimental feline studies is an initial dose of 30 mg/kg IV followed by 15 mg/kg at 2 and 6 hours and then an IV infusion of 2.5 mg/kg/hr for 42 hours.<sup>19</sup> This regimen has not been clinically evaluated in this species.

If MPSS is administered too quickly to an awake animal, vomiting may occur, as may hypotension, especially in traumatized patients. It is therefore advisable to administer MPSS intravenously for approximately 5 to 10 minutes. Other side effects to consider are those associated with the gastrointestinal (GI) tract.<sup>25</sup> A recent study of dogs undergoing spinal surgery and receiving a single bolus of 30 mg/kg of MPSS followed by a half to full dose 2 to 4 hours later reported that 90% of the dogs developed occult GI hemorrhage.<sup>1</sup> Unfortunately, many patients with spinal injuries that are seen at referral institutions have already been treated with large doses of steroidal or nonsteroidal drugs, which predispose patients to adverse side effects (e.g., GI hemorrhage) and may influence the use and effects of MPSS therapy.

Dexamethasone and prednisone have been extensively administered at antiinflammatory doses to control the inflammatory response to disk extrusion as well as to reduce associated edema and improve local spinal cord blood flow.<sup>3</sup> Administering these drugs to patients with chronic disk disease (i.e., protrusion rather than extrusion) is unfounded in the early stages of the disease based on the vastly different pathophysiology that underlies compressive spinal diseases compared with

beyond that of the offending mass. Glucocorticosteroids are effective in treating CNS vasogenic edema and have been shown to be effective in treating spinal cord compression, resulting in return of function without removing the mass.<sup>26</sup> This explains the often dramatic improvement in function with the initiation of glucocorticosteroid therapy occurring in patients with longstanding spinal cord compression.<sup>26,28</sup> However, several points should be emphasized:

- Only short-term antiinflammatory regimens of prednisone should be used. High-dose regimens should not be used following an antiinflammatory regimen when a patient with compressive spinal disease acutely deteriorates because this favors GI ulceration.
- Glucocorticosteroids cannot be advocated for early compressive disease, especially when there is no diagnosis or there are no neurologic signs other than back pain.
- The antiinflammatory effect of steroids can improve the level of discomfort in these patients, encouraging excessive activity levels in animals with spinal disease.
- These patients should be considered for surgical management rather than medical palliation once a diagnosis is made.

## **INFLAMMATORY DISEASES**

### **Infectious Meningoencephalomyelitis**

The common infectious diseases responsible for inflammation of the brain and its structures in dogs are canine distemper virus, rickettsiosis, and fungal and protozoal infections such as toxoplasmosis and neosporosis. In cats, similar infections are detected, but neosporosis

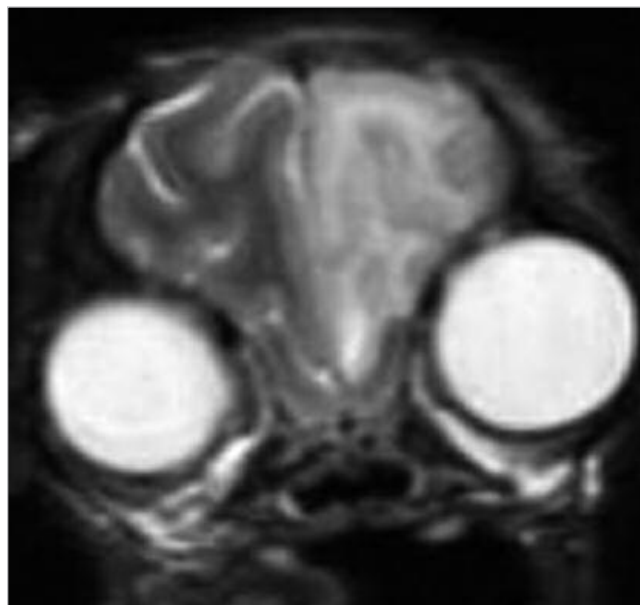
and rickettsiosis are less frequently reported. CNS disease with FIP is also seen in cats. Bacterial infections are uncommon but can follow bacterial otitis media or interna or a systemic septic focus such as prostatitis, particularly if steroids have been used to treat nonspecific clinical signs of these diseases.<sup>29</sup> Distemper is not as common as it used to be because of the success of vaccination programs, but sporadic cases of distemper encephalomyelitis in vaccinated dogs have occurred.<sup>30</sup> With this disease, there may be variable or temporary success in halting neurologic signs in some dogs by administering single, anti-CNS edema doses of dexamethasone (1 to 2 mg/kg IV).<sup>30</sup>

Care should obviously be taken when administering glucocorticosteroids to neurologic patients that may have an infectious disease. The immunosuppressive properties can cause severe extension of the disease; however, the antiinflammatory effects of these drugs can be invaluable when trying to reduce the clinical effects of infectious damage to the CNS. For instance, in the case of rickettsial diseases, although antiinflammatory and immunosuppressive doses of glucocorticosteroids slightly prolong the duration of rickettsemia, they do not increase the severity of the disease in experimentally infected dogs.<sup>31</sup> Treating cases of CNS FIP with glucocorticosteroids would conceivably prevent clinical signs from progressing, but immunosuppression might have the opposite effect and precipitate a worse form of clinical FIP.<sup>32</sup> However, most successful treatments consist of relatively high doses of immunosuppressive and antiinflammatory drugs, including prednisolone (2 to 4 mg/kg/day PO).<sup>32</sup>

For bacterial diseases in humans, dexamethasone administered at 0.15 mg/kg 15 to 20 minutes before initiating antimicrobial therapy for up to 4 days seems to lower intracranial pressure, CNS inflammation, and neurologic sequelae.<sup>33</sup> A meta-analysis of randomized, controlled clinical human trials conducted from 1988 to 1997 showed a beneficial effect of adjunctive dexamethasone therapy in bacterial meningitis cases and suggested a protective effect if the drug was given before or with parenteral antibiotics.<sup>34</sup> Unfortunately, no clinical trials have been conducted to evaluate the efficacy of steroidal therapy in canine or feline bacterial CNS disease, and so guidelines can be extrapolated only from human data, which may not be appropriate.

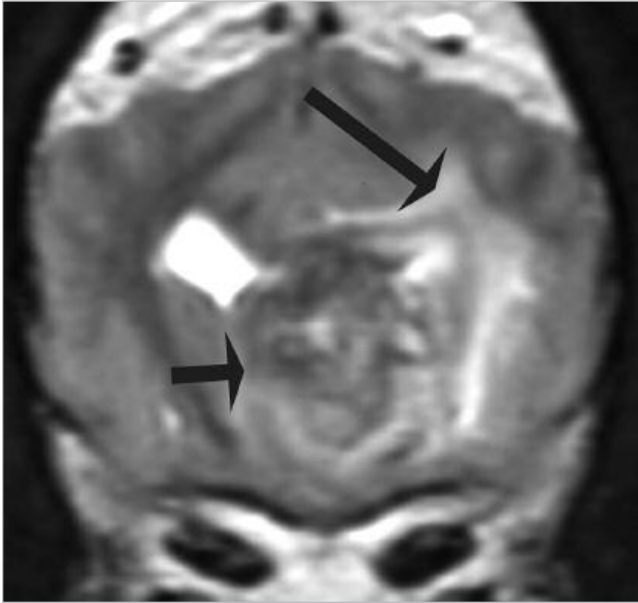
### Granulomatous Meningoencephalomyelitis

Granulomatous meningoencephalomyelitis (GME) is the most well-documented sterile inflammatory disease



**Figure 3.** Transverse T2-weighted magnetic resonance cerebral scan of a 3-year-old female Maltese at the level of the frontal lobes. The dog presented with seizure activity and dementia. The diffuse hemispheric hyperintensity is suggestive of an inflammatory lesion and was confirmed to be necrotizing meningoencephalitis at the postmortem examination.

of the nervous system, although the precise cause remains unknown. The characteristics of the lesions seen in patients with GME suggest a possible immunologic basis for the disease, although it may not be one disease entity.<sup>35</sup> Large perivascular accumulations of mononuclear cells, predominantly CD3+ lymphocytes, are often detected in the parenchyma and meninges of the brain and spinal cord.<sup>35</sup> Adult small-breed dogs (especially poodles and terriers) are predisposed to this condition. Signs consist of acute or chronic onset of ocular, focal, or multifocal neurologic deficits or signs of meningitis; focal GME is described as having an insidious onset with a slowly progressive course, whereas the disseminated form manifests with acute onset and rapidly progressive signs.<sup>35</sup> Definitive diagnosis is difficult without histopathologic assessment of cerebral lesions following biopsy; however, in confirmed cases, signs often dramatically improve with an initial dose of prednisone (1 to 2 mg/kg [preferably PO] bid).<sup>35</sup> The dose should be tapered gradually to establish the minimal effective dose. The prognosis for permanent recovery is poor, and the overall response rate is variable.<sup>36</sup> The survival time for dogs with GME treated with corticosteroids ranges from 7 to longer than 1,000 days.<sup>35</sup>



**Figure 4.** Transverse T2-weighted magnetic resonance cerebral scan of a 7-year-old boxer at the level of the lateral ventricles and the parietal lobes. The scan demonstrates a large, poorly demarcated mass of heterogeneous intensity (*short arrow*) with surrounding edema through the white matter (*long arrow*).

### Necrotizing Meningoencephalitis

Necrotizing meningoencephalitis is a chronic progressive disorder that has been documented in various forms in pugs, Maltese, and Yorkshire terriers<sup>37</sup> (Figure 3). Clinically and pathologically, this disease is identical in pugs and Maltese; it affects dogs of both genders and any age, causing an onset of seizure activity and generalized forebrain dysfunction, although a few animals may exhibit brain-stem signs. The cause of this disease is unknown, although the predominantly mononuclear inflammation identified typically on CSF analysis suggests a viral cause.<sup>37</sup> Histologic examination, which is the only way to definitively diagnose this disease, can confirm typical necrotizing lesions of the cerebrum with disseminated meningitis, choroiditis, and cerebral encephalitis.<sup>37</sup> There are several notable differences to the presentation of this disease described in Yorkshire terriers, including the fact that they seem to manifest the disease as a chronic, slowly progressive dysfunction of the fore- and hindbrain (often with cranial nerve signs) and the lesions in the CNS are multifocal in the cerebral white matter and brain stem. Administering steroids has not been shown to have an effect on the clinical course of the disease in any of these breeds,

although some patients may temporarily improve with administration of prednisone (1 to 2 mg/kg/day).<sup>37,38</sup>

### Steroid-Responsive Meningitis–Arteritis

Steroid-responsive meningitis–arteritis has been reported frequently in large-breed dogs—often younger than 2 years of age. Clinical signs are those characteristically seen in patients with meningitis, including fever, cervical pain, hyperesthesia, and pleocytosis of the CSF.<sup>39</sup> Increased serum and CSF IgA levels have been documented in this disease and are diagnostically helpful, although the causes of their intrathecal production remain unknown. Attempts to isolate an etiologic agent have been unsuccessful; therefore, an immunologic cause is suspected. A small proportion of affected dogs may also have idiopathic immune-mediated polyarthritis. Affected dogs characteristically show dramatic improvement in clinical signs when treated with immunosuppressive doses of corticosteroids.<sup>39</sup> It is recommended to administer prednisone at 4 mg/kg PO q24h or IV for 48 hours, then 2 mg/kg PO q24h for 1 to 2 weeks, tapering to 1 mg/kg q24h until the CSF is normal.<sup>37,39</sup> The glucocorticosteroid dose can be slowly tapered over several months. Long-term therapy is necessary in most cases, and relapses may occur as the steroid dose is tapered. However, the prognosis for resolution and at least a 2-year remission of clinical signs with appropriate therapy is excellent in over 50% of cases.<sup>37,39</sup> The elevated serum and CSF IgA levels do not decrease to normal values during prednisolone treatment, but pleocytosis can correlate with the clinical signs.<sup>37</sup>

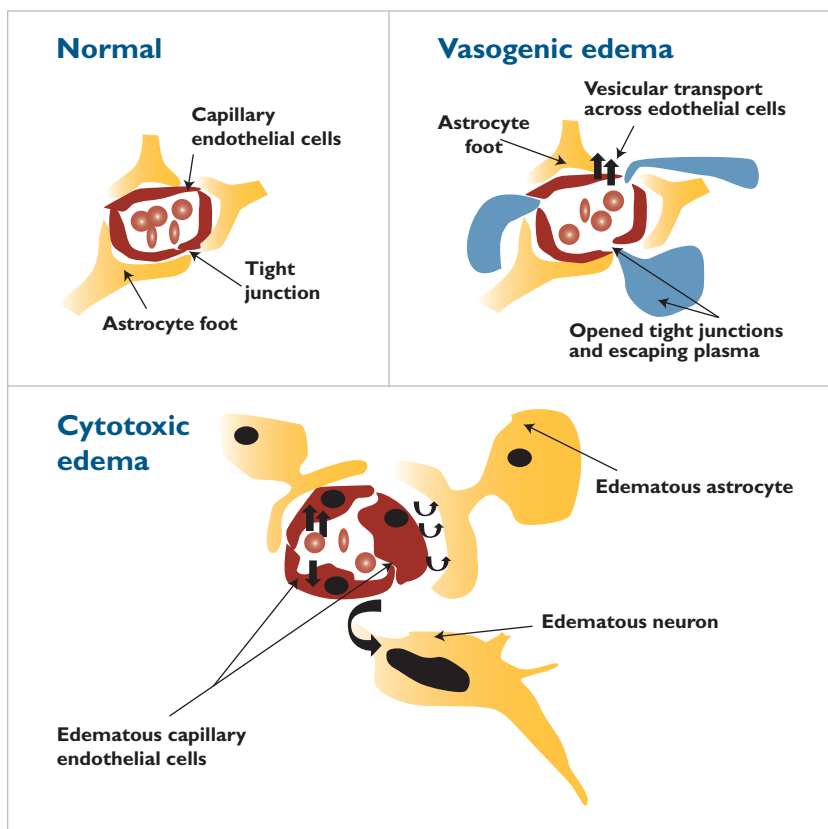
### NEOPLASTIC DISEASES

Although glucocorticosteroid therapy is deemed as only minimal supportive care for all types of brain tumors in the nervous system, it can often be necessary and helpful. The aim of such treatment is directed at controlling the secondary conditions of acquired hydrocephalus and peritumoral edema as well as reducing associated intracranial pressure<sup>40,41</sup> (Figure 4). Glucocorticosteroids given at antiinflammatory doses can reduce CSF production as well as vasogenic edema and blood supply to the tumor within 24 hours.<sup>42</sup> Glucocorticoids are believed to reduce tumor-associated vasogenic edema (Figure 5) by decreasing the pathologically increased capillary permeability of the blood–brain barrier.<sup>42</sup> Glucocorticosteroids presumably act directly on endothelial cells, reducing their permeability as well as shrinking normal brain tissue, thus reducing overall

intracranial pressure.<sup>43</sup> In humans with brain tumors, there is no rigid schedule for administering high-potency steroids; the drugs are just administered at bedtime to suppress headaches and focal signs and are more successful for the former. Although some clinicians prefer methylprednisolone, dexamethasone is the glucocorticosteroid administered most often to neuro-oncologic patients at empirically chosen antiinflammatory doses initially and up to four times daily.<sup>42</sup> There is no reported consistently effective glucocorticosteroid regimen in veterinary medicine, although we administer a parenteral antiinflammatory dose of dexamethasone after an imaging diagnosis of neoplasia is made while the patient is still under anesthesia; this is routinely followed by antiinflammatory doses of daily prednisone or dexamethasone. Dexamethasone has been preferred because of its low mineralocorticoid activity, which decreases the chance of fluid retention. There have also been studies suggesting that dexamethasone may lower patient risk of infection and impairment of the coagulation system compared with other steroids.<sup>42</sup>

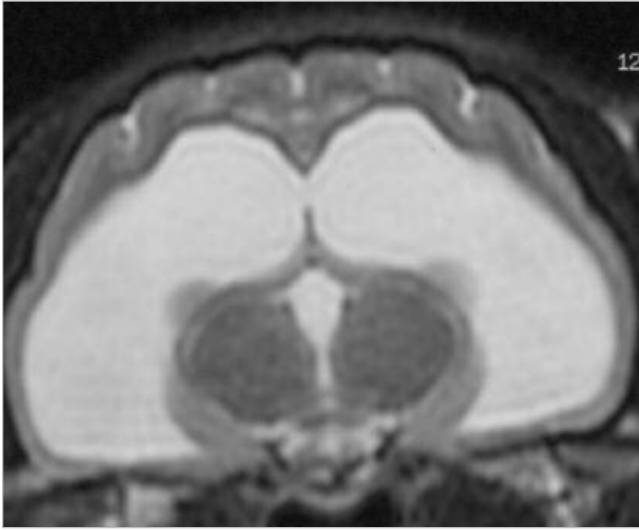
Clinical signs improve in many patients with neoplastic disease when steroids are administered. There are not much data concerning the survival of dogs or cats with brain tumors that have received only steroids as palliative therapy. Results of one study indicated a mean and median survival of 81 days and 56 days, respectively, following diagnosis via computed tomography of primary brain tumors in eight dogs.<sup>44</sup> Six of the eight dogs in this study died or were euthanized within 64 days of brain tumor diagnosis. In another study, survival times from initial clinical signs of the brain tumor to necropsy varied from 1 day to 405 days, with a mean survival time of 53 days.<sup>45</sup> When intracranial meningiomas were specifically evaluated recently, the median survival time from diagnosis following steroidal therapy was 119 days.<sup>46</sup>

Glucocorticoids can be administered at least 1 week before intracranial surgery in brain tumor patients to reduce cerebral edema and thereby facilitate cerebral retraction for improved exposure.<sup>47</sup> Although clinical



**Figure 5.** Representation of astrocytes and endothelial cells of the capillary wall in the normal state, vasogenic edema, and cytotoxic edema. Heightened permeability in vasogenic edema is due partly to a defect in tight endothelial junctions but mainly to active vesicular transport across endothelial cells. The bottom diagram represents cellular (cytotoxic) edema showing swelling of the endothelial, glial, and neuronal cells at the expense of the extracellular fluid space of the brain.

data confirming the efficacy of this regimen are lacking in veterinary medicine, we have been comfortable extrapolating the perioperative indications and steroid regimen from the human literature. If adequate surgical decompression of the brain tumor is achieved, the steroid dose can be tapered rapidly and discontinued within the first week or two after surgery. Some patients require steroid maintenance because a large volume of tumor remains, tumor occupies the brain stem, or drug dependence has resulted from long-term use. Patients that no longer require glucocorticosteroids after surgery may need them during or after radiation therapy. Reactive edema may occur during irradiation, which may cause transient clinical deterioration.<sup>47</sup> The lowest dose of glucocorticoids that maintains patients at their maximum level of comfort and function should be used.<sup>47</sup>



**Figure 6. Transverse T2-weighted magnetic resonance cerebral scan of a 2-year-old domestic shorthaired cat.** The image depicts bilateral symmetric, lateral ventricle enlargement with third ventricular enlargement compatible with hydrocephalus.

This is ordinarily determined by decreasing the dose until signs increase or become apparent and then increasing the dose until they subside. If deterioration is secondary to tumor growth or treatment-induced effects, the glucocorticosteroid dose may have to be increased to keep the patient comfortable.

Far fewer recommendations are available for administering steroids to patients with spinal tumors; although glucocorticosteroids are clearly indicated in treating cord and nerve root compression, neither an optimal dose nor the best schedule has been defined.<sup>47</sup> Current recommendations for veterinary patients with neoplasia affecting the spinal cord are extrapolated from the human literature and include starting at high anti-inflammatory doses and tapering to effect.

## HYDROCEPHALUS

*Hydrocephalus* is the term commonly used to describe abnormal dilation of the ventricular system within the cranium (Figure 6). Ventricular dilation occurs in dogs and cats because of a wide variety of intracranial disease processes, often resulting in a form of stenosis of the mesencephalic aqueduct or obstruction of the CSF drainage pathways.<sup>39</sup> Hydrocephalus can result in clinical signs from loss of neurons or neuronal function, alterations in intracranial pressure, or associated pathophysiologic effects of intracranial disease.<sup>48</sup> For example,

hydrocephalus may result in interstitial edema (i.e., increased water content of the periventricular white matter) because of movement of CSF across the ventricular walls. This may be secondary to increases in white matter hydrostatic pressure or decreases in periventricular white matter blood flow.<sup>48</sup>

Medical therapy for this condition does not usually provide long-term resolution of clinical signs unless a specific cause can be identified and resolved with treatment.<sup>49</sup> Glucocorticosteroids can be administered to decrease CSF production, thereby limiting intracranial pressure and further neurologic injury.<sup>48</sup> Prednisone (0.25 to 0.5 mg/kg PO bid) is recommended.<sup>48</sup> The dose should be gradually reduced at weekly intervals to 0.1 mg/kg every other day.<sup>48</sup> The dose should be continued for at least 1 month and then discontinued if possible. Alternatively, dexamethasone may be administered at 0.25 mg/kg PO q6–8h. The dose can be gradually reduced over 2 to 4 weeks. Some animals can be adequately managed with long-term glucocorticosteroid administration at low doses. If no clinical benefits are observed within 2 weeks or if side effects develop, other forms of therapy (e.g., surgery) should be considered.

## CEREBROVASCULAR DISEASE

Cerebrovascular disease is defined as an abnormality of the brain attributable to a disturbance in its blood supply.<sup>49–52</sup> This can be diagnosed with the aid of imaging techniques that are now more commonly available, such as computed tomography and magnetic resonance imaging.<sup>50–52</sup> A stroke is a focal neurologic deficit of sudden onset resulting from a cerebrovascular accident.<sup>52</sup> In dogs, the cause of strokes can be classified as infarction (subsequent to blood vessel obstruction and ischemia) or hemorrhage (often secondary to blood vessel rupture).<sup>52</sup> Cerebral ischemia is reduction although not necessarily cessation of blood flow to a level incompatible with normal function; the impairment may be global or regional.<sup>52</sup> Ischemia, viewed simplistically as hypoxia plus hypoglycemia, affects the most sensitive elements in tissue and, if severe, persistent, or both, perturbs all components. Severe ischemia, which in the CNS produces necrosis of neurons and glial elements, results in an area of dead tissue called an *infarct*. Much of the brain swelling following an ischemic event is due to cytotoxic edema, which is related to cell membrane dysfunction<sup>49</sup> (Figure 5).

Cerebrovascular accidents are characterized clinically by peracute or acute onset of focal, asymmetric, and

nonprogressive brain dysfunction.<sup>49</sup> Worsening of edema (associated with secondary injury phenomenon) can result in progression of neurologic signs for 24 to 72 hours. Hemorrhage may be an exception to this description, and patients may present with a more progressive onset. Clinical signs usually regress after 24 to 72 hours; this is attributable to diminution of the mass effect secondary to hemorrhage and reorganization or edema resorption.<sup>49</sup>

Administering glucocorticosteroids does not have a positive effect on cytotoxic edema, can alter the size of the infarction or hemorrhage, and probably does not decrease intracranial pressure.<sup>49</sup> Although steroids are often administered to decrease cerebral edema, their benefit in cerebrovascular disease is questionable.

## SUMMARY

Glucocorticosteroids have multiple physiologic and pharmacologic effects that can be therapeutically beneficial in CNS diseases. Although patients with many neurologic diseases (e.g., cerebrovascular diseases) may benefit from steroidal therapy, there is no substantial clinical evidence for administering this therapy to patients with these diseases. Many of the regimens for administering steroids in neurologic disease have been transcribed from human clinical trials, and there are no similar trials in veterinary medicine. A definitive diagnosis is always required for specific steroidal therapy to be maximally beneficial to patients without a risk of side effects; however, because this is not often possible, the likely benefits must be weighed against potential detriments.

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## ARTICLE #3 CE TEST



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### 1. Where are glucocorticoid receptors located in target cells?

- |              |                   |
|--------------|-------------------|
| a. cytoplasm | c. nucleolus      |
| b. nucleus   | d. Golgi's bodies |

### 2. In relation to aldosterone, how much mineralocorticoid activity do synthetic glucocorticoids possess?

- |                 |                  |
|-----------------|------------------|
| a. less than 1% | c. 50%           |
| b. 11%          | d. more than 71% |

### 3. Reactive oxygen species produced immediately after head trauma are responsible for

- a. hypoglycemia.
- b. hypoxemia.
- c. lipid peroxidation.
- d. hyperglycemia.

### 4. It has been recommended that soluble glucocorticoids should be administered within \_\_\_ hours after spinal trauma in humans.

- |      |       |
|------|-------|
| a. 8 | c. 15 |
| b. 9 | d. 18 |

### 5. One of the predominant pathologic changes early in the course of spinal cord compression is

- a. cytotoxic edema.
- b. neuron cell body swelling.
- c. interstitial edema.
- d. demyelination.

### 6. What is the predominant cell type in the perivascular lesions of granulomatous meningoencephalitis?

- a. neutrophils
- b. CD3+ lymphocytes
- c. eosinophils
- d. mast cells

### 7. What is the proposed main mechanism of action of glucocorticoids in reducing tumor-associated vasogenic edema?

- a. cerebral vasoconstriction
- b. reduction of local intracellular calcium buildup
- c. reduction of endothelial cell permeability
- d. reduction of reactive oxygen species concentrations

(text continues on p. 228)

**Administering Corticosteroids in Neurologic Diseases***(continued from p. 220)*

- 8. What is the mean survival period of dogs with nonspecific cerebral neoplasia (after clinical signs appear) if treated with steroids alone?**
- a. 5 days
  - b. 59 days
  - c. 175 days
  - d. 275 days
- 9. Glucocorticoids purportedly help reduce clinical signs associated with hydrocephalus by**
- a. increasing CSF absorption.
  - b. decreasing cerebral perfusion pressure.
  - c. causing cerebral vasoconstriction.
  - d. decreasing CSF production.
- 10. What type of edema, if any, is commonly associated with cerebral ischemic events?**
- a. interstitial
  - b. vasogenic
  - c. cytotoxic
  - d. none of the above