

Dexamethasone Decreases Blood Flow in Normal Nerves and Dorsal Root Ganglia

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Study Design. An experimental physiologic and histologic study of dexamethasone effects on peripheral nerves.

Objective. To characterize the effect of topically applied 0.4% dexamethasone on acute changes in nerve blood flow and subsequent histologic changes in rat sciatic nerve fibers.

Summary of Background Data. Dexamethasone is an anti-inflammatory glucocorticoid used clinically to reduce the neural consequences of inflammation. Several reports of accidental injury to nerves after steroid injections have raised questions about the mechanisms involved in dexamethasone-induced neurotoxic injury.

Methods. Nerve blood flow studies using a laser Doppler flowmeter were conducted in animals with stable temperature and arterial pressure. Dexamethasone 0.4%, 0.1 mL was applied topically to rat sciatic nerve in the following protocol groups: 1) nerve blood flow recording every 5 minutes for 30 minutes, and 2) initial nerve blood flow recording and repeat recording at 4 hours. Three additional animals had 30-minute nerve blood flow recordings in which normal saline was substituted for dexamethasone; these animals were used for control and to assure that the experimental preparation was viable throughout the observational period. Additional groups of two animals each received dexamethasone but were used only for neuropathologic observation at 2, 4, and 6 days after treatment. Neuropathologic studies were conducted on glutaraldehyde-fixed, plastic-embedded tissue.

Results. Application of saline to the exposed sciatic nerves did not significantly change nerve blood flow from baseline values. Nerve blood flow values remained constant throughout the observational period. Dexamethasone, however, significantly reduced nerve blood flow in both the 30-minute and 4-hour groups. Some animals showed an initial transient increase in blood flow before nerve blood flow began to steadily decline to the final values reported. Neuropathologic changes were minimal and consisted only of edema and occasional subperineurial activation of Schwann cells. No demyelination or degeneration was seen.

Conclusion. Dexamethasone causes statistically significant reductions in normal nerve blood flow at 30 minutes and 4 hours after topical application; however, the reduction is on average below the threshold for causing ischemic changes in the structure of peripheral nerve fibers. [Key words: nerve ischemia, inflammation, neuropathy] **Spine 2002;27:581-586**

Dexamethasone is an anti-inflammatory glucocorticoid often used postinjury by infiltration to reduce edema in neurologic tissue and to otherwise mitigate the consequences of neural inflammation.¹⁶ It has been used therapeutically in epidural block.^{9,23} However, the pathophysiologic mechanisms of anti-inflammatory agents on the nerve are largely unknown. Dexamethasone inhibits both cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism, including all downstream metabolites. Dexamethasone has also been reported to decrease upregulation of tumor necrosis factor- α in subcutaneous tissue and to reduce transcapillary permeability in experimental studies with rat gliomas. It is through these mechanisms on cytokine activity and permeability stabilization that the therapeutic effect is thought to occur. However, accidental injuries to nerve after steroid injections are known to be complications of the procedure.^{14,15,17,19,27,29,36,37,40} Nerve injury is a rare complication of dexamethasone injection, and it usually occurs in the context of needle trauma,^{10,15,22,37} although it may also occur in the context of neurotoxic injury.^{27-29,37,40} In addition to dexamethasone, methylprednisolone, hydrocortisone, and triamcinolone are used for near-nerve injection. Methylprednisolone contains polyethylene glycol 40% as a buffer. Hydrocortisone contains benzyl alcohol. It has been shown that these types of buffering agents are themselves neurotoxic.^{8,38}

To further explore the physiologic mechanisms of action, we studied the effect of dexamethasone on rat sciatic nerve and dorsal root ganglia (DRG) blood flow in normal animals. This was done to establish basic values for future studies on its pathophysiologic mechanisms in therapies for low back pain and radiculopathy. In this study we focused on the changes in blood flow to nerve and DRG caused by topical application of dexamethasone. Laser Doppler technology was used to measure acute variations in nerve and DRG blood flow after topical application of a clinically used preparation of dexamethasone. The advantage of this technique is that it permits repeated measures of blood flow over several hours; the disadvantages are that the nerve must be exposed and the animals maintained in a constant physiologic state throughout the recording period. For these reasons we limited our physiologic observations to a period of 4 hours. To determine if there was a residual neuropathologic effect of acute dexamethasone application, histologic analysis was performed on tissue removed from 2 to 6 days after the application of a single

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dose of dexamethasone. We chose this clinically relevant approach to study the pathophysiologic effect of dexamethasone application, rather than an approach involving needle trauma and/or injection of high concentrations of dexamethasone outside the normal clinical range.

■ Materials and Methods

Thirty-four adult female Sprague-Dawley rats weighing 200–250 g were used in this study, which was approved by the animal studies committees of the VA Medical Center and University of California, San Diego.

Anesthesia. Animals were anesthetized by intraperitoneal injection of a solution containing sodium pentobarbital (Nembutal, 50 mg/mL; Abbott Laboratories, North Chicago, IL), diazepam (5 mg/mL; Steris Laboratories, Phoenix, AZ), and saline (0.9%; Steris Laboratories, Phoenix, AZ) in a volume proportion of 1:1:2, respectively. Initially, 0.5 mL of the anesthetic solution was injected and then supplemented with 0.2-mL injections as needed to produce an adequate level of surgical anesthesia throughout the experiment. At the termination of the experiment, the animals were killed by a 0.5-mL intraperitoneal injection of a euthanasia solution (Beuthanasia-D, Schering-Plough Animal Health Corp., Kenilworth, NJ).

Blood Flow in Sciatic Nerve. The left sciatic nerve was exposed by lateral incision of the thigh and reflection of the superficial musculature. The surgery was performed with the use of a stereo operating microscope and microsurgical instruments. Extreme care was taken to avoid injury to the endoneurial circulation. Animals were placed on a heating pad to maintain normal body temperature during both surgery and data collection.

Blood flow in the sciatic nerve was measured with a laser Doppler flowmeter (PeriFlux PF3, Perimed, Stockholm, Sweden), using a 0.5-mm diameter fiber optic probe both to deliver the incident laser energy and to collect the reflected energy from the same site. Care was taken in placing the probe to avoid epineurial vessels; a vessel-free area on the surface of the nerve was always found for the placement of the probe. This provided assurance that the flow measurements represented integrated capillary flow within the fascicle rather than surface epineurial flow from larger vessels either supplying or draining the endoneurial plexus.³¹ The first measurement of blood flow was made after a 15-minute period of stabilization after tissue manipulation was completed and the animals' physiologic status was stable. This value served as the baseline value (100%), and all subsequent recordings of blood flow during the experiment were expressed as a percentage of this value. This technique has been used previously in studies of ischemia and drug toxicity.^{31,32,35}

Blood flow studies in sciatic nerve were conducted in 19 animals with stable temperature and arterial pressure according to the following protocols. Immediately after baseline measurement, normal saline or 0.4% dexamethasone (Decadron, 4 mg/mL; American Pharmaceutical Partners, Inc., Melrose Park, IL) was applied topically on the sciatic nerve in a volume of 0.1 mL. The measurement protocols and animal groupings were as follows: 1) continuous nerve blood flow recording for 30 minutes (normal saline, $n = 3$; dexamethasone, $n = 9$); and 2) initial nerve blood flow recording and repeat recording at 4 hours (saline, $n = 4$; dexamethasone, $n = 4$). Three animals receiving normal saline were used to determine the effect of

long-term exposure of the nerve and the stability of the preparation. Previous studies using this methodology have demonstrated the stability of the technique.³¹

Blood Flow in DRG. The left L5 DRG were exposed by left L5 hemilaminectomy and L5–L6 facetectomy, with great care taken to avoid trauma to the tissue. The exposure was facilitated by suspending the animal from spinal processes to eliminate compression of the inferior vena cava, thereby reducing bleeding in the surgical field. The surgery was performed with the use of a stereo operating microscope and microsurgical instruments.

A total of 14 adult female Sprague-Dawley rats were used in this part of the study. Similar to the method described above, we measured blood flow in the DRG with a laser Doppler flowmeter in animals with stable temperature and arterial pressure. Immediately after baseline measurement, normal saline ($n = 4$) or 0.4% dexamethasone ($n = 10$) was applied topically in a 0.1-mL volume to the L5 DRG. Blood flow was recorded every 5 minutes thereafter for 30 minutes.

Histology. Additional groups of animals each received the dexamethasone treatment but were used only for neuropathologic observation ($n = 4$). Rats were anesthetized and the sciatic nerve was exposed in the midhigh region. Using a 30-gauge needle, a 0.1-mL volume of 0.4% dexamethasone was injected beneath the sheet of connective tissue that separates the sciatic nerve from overlying muscle, that is, in the epineurial space, and not under the perineurium. This method provides a well-defined perineurial injection without the risk of physical trauma to the nerve.³¹ The rats were allowed to recover, and at 2, 4, and 6 days after application of dexamethasone, a 15-mm-long portion of the sciatic nerve was removed from the region of dexamethasone exposure and immersed in 2.5% phosphate-buffered glutaraldehyde. The central portion of the nerve was then cut into several smaller blocks and postfixed in osmium tetroxide, dehydrated in serial concentrations of alcohol, and embedded in araldite. One-micron-thick histologic sections were cut from each block and stained with methylene blue-Azure II for light microscopy.

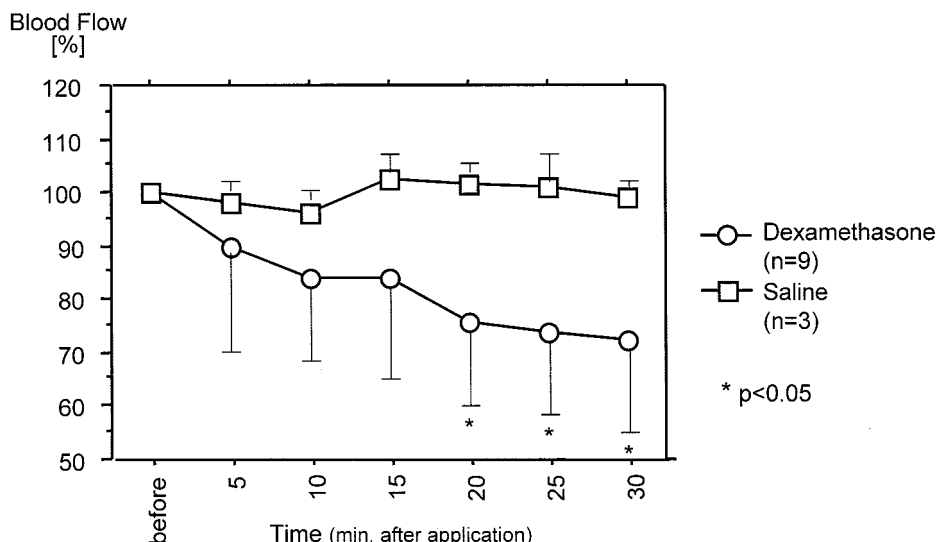
Statistics. Changes of blood flow between the control and experimental groups were analyzed using analysis of variance for repeated-measures followed by Scheffé's *post hoc* analysis. Beginning and ending values were compared and analyzed by paired Student's *t* test. Statistical significance was defined as $P < 0.05$ for all tests. Results are expressed as mean values \pm standard deviation. Because perfusion units are proprietary measures of blood flow, we expressed the data as percentage change from baseline values.³²

■ Results

Blood Flow in Sciatic Nerve

30-minute Measurements. The initial value of blood flow was 64.9 ± 20.0 perfusion units (proprietary measurement unit of the flowmeter) in the dexamethasone group and 71.0 ± 17.0 perfusion units in the saline group. There was no statistical difference between these two initial values. These initial values of blood flow served as a baseline reference (100%). In the saline group the application of saline to the exposed sciatic nerve did not significantly change nerve blood flow from the baseline

Figure 1. Changes in sciatic nerve blood flow. Baseline values of blood flow were defined as 100%, with subsequent data compared with this value. Note that the blood flow in the sciatic nerve from animals in the control group that had saline applied to the exposed sciatic nerve changes very little over the 30-minute observation period. Animals receiving dexamethasone, however, had reduced blood flow that was statistically different from the saline group 20–30 minutes after application.



values throughout the 30-minute recording period (Figure 1). Thirty minutes after application of saline, nerve blood flow was $99.3 \pm 3.5\%$ of the baseline value (Figure 2). However, in the dexamethasone group nerve blood flow was significantly reduced 20–30 minutes after application of dexamethasone ($P < 0.05$) (Figure 1). Some animals showed an initial transient (10-minute) increase in blood flow before nerve blood flow began to steadily decline to the final values given. The nerve blood flow 30 minutes after application of dexamethasone was $72.3 \pm 19.9\%$ of the baseline value (Figure 2). By paired statistical analysis, it was determined that this value was significantly less than the baseline value ($P = 0.003$).

4-hour Measurements. The nerve blood flow 4 hours after application of dexamethasone was $74.5 \pm 13.5\%$ of the baseline value (Figure 3). By paired statistical analysis it was determined that this value was significantly less than the baseline value ($P = 0.033$).

Blood Flow in DRG

30-minute Measurements. The initial value of blood flow was 80.4 ± 9.1 perfusion units in the dexamethasone group and 75.5 ± 13.1 perfusion units in the saline group. There was no statistical difference between these two initial values. These initial values of blood flow served as a baseline reference (100%). In the saline group application of saline to the exposed DRG did not significantly change nerve blood flow from the baseline values throughout the 30-minute recording period (Figure 4). Thirty minutes after application of saline, nerve blood flow was $102.5 \pm 4.0\%$ of the baseline value (Figure 5). However, in the dexamethasone group DRG blood flow

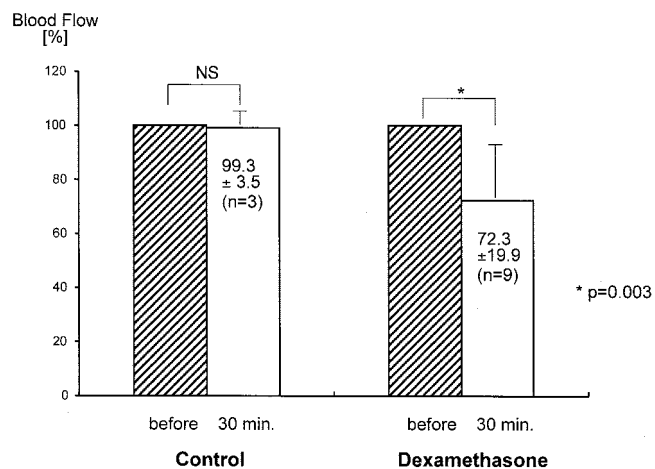


Figure 2. Blood flow in the sciatic nerve. Comparison of beginning values and values 30 minutes after application of either saline (control) or dexamethasone to the sciatic nerve. Note the significant reduction in the dexamethasone-treated group.

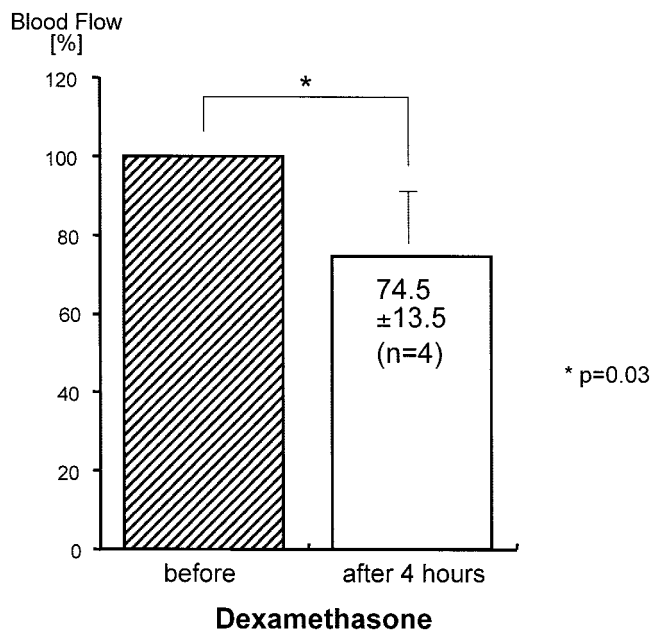
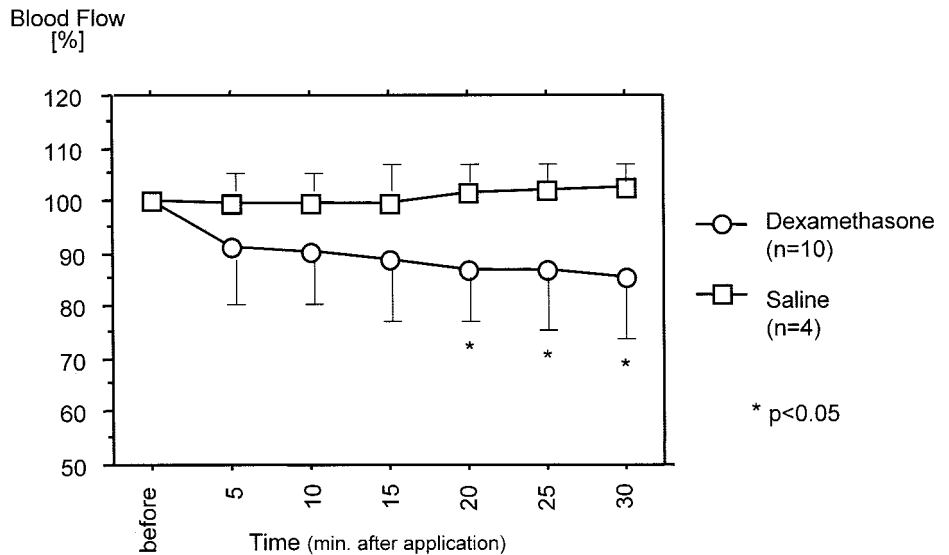


Figure 3. Blood flow in the sciatic nerve. Comparison of beginning values and values 4 hours after application of either saline (control) or dexamethasone to the sciatic nerve. Note the significant reduction in the dexamethasone-treated group.

Figure 4. Changes in DRG blood flow. Baseline values of blood flow were defined as 100%, with subsequent data compared with this value. Note that the blood flow in DRG from animals in the control group that had saline applied to the exposed DRG changes very little over the 30-minute observation period. Animals receiving dexamethasone, however, had reduced blood flow that was statistically different from that of the saline group 20–30 minutes after application.



was significantly reduced 20–30 minutes after application of dexamethasone at all time points measured ($P < 0.05$) (Figure 4). The DRG blood flow 30 minutes after application of dexamethasone was $85.6 \pm 12.1\%$ of the baseline value (Figure 5). By paired statistical analysis, it was determined that this value was significantly less than the baseline value ($P = 0.004$).

The reductions in sciatic nerve blood flow after application of dexamethasone was greater than the reductions in DRG blood flow, and there was statistical difference between the values at 25 minutes after drug application ($P < 0.05$).

Histology

Sciatic nerves were studied by light microscopy with unexposed contralateral tissue used as control. Neuro-pathologic changes were minimal and consisted only of edema in one animal and occasional subperineurial activation of Schwann cells in two animals at 2 days. No

significant changes were seen at 4 or 6 days. No demyelination or degeneration was seen (Figure 6).

Discussion

Steroids or combinations of a local anesthetic and a steroid are generally used to treat peripheral mononeuropathy^{11,18,20,30,37} and radiculopathy.^{5,6,13} Devor et al reported that ectopic neural discharge originating from experimentally induced neuromas is inhibited by locally applied corticosteroids, whether they are administered at the time of nerve injury or after abnormal neural activity has become established.¹² Hong et al demonstrated in animals with experimentally induced compression neuropathy that local steroid injection at the site of nerve compression may facilitate the recovery of nerve conduction block but not the recovery of a demyelinating le-

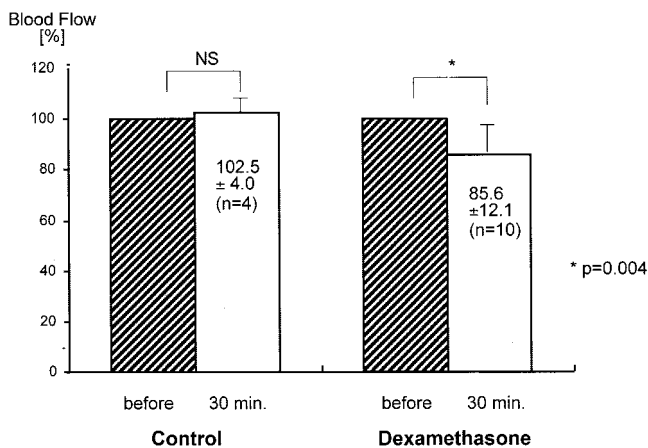


Figure 5. Blood flow in DRG. Comparison of beginning values and final values 30 minutes after application of either saline (control) or dexamethasone to DRG. Note the significant reduction in the dexamethasone-treated group.

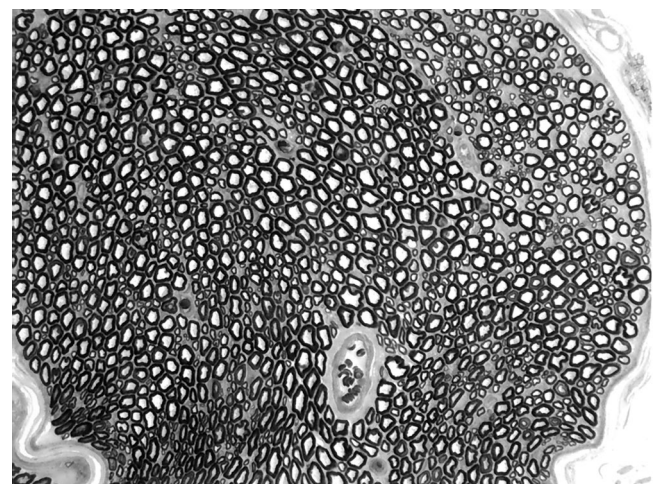


Figure 6. Histology section from plastic-embedded rat nerve removed 2 days after acute application of dexamethasone. Only minor pathologic changes are seen. Although there is no axonal degeneration or demyelination, edema is seen in the subperineurial space (especially in the upper right quadrant of the micrograph) and in perivascular spaces.

sion.²¹ However, steroid injection is known as a technique that may be complicated with accidental injury of peripheral nerve.^{14,15,17,19,27,29,37,40} Also, transient increased sciatic pain and paresthesias are reported after epidural steroid injections,^{1,2,4} despite the fact that the injection is intended to improve neuropathies with these features. The cause of this phenomenon is not known. The mechanism of nerve damage has been attributed to direct needle injury to the nerve, direct neurotoxic effect, ischemia, scarring, and allergic phenomenon. Wood et al⁴¹ found diffuse axonal degeneration, demyelination, and endoneurial fibrosis in about half of the rat sciatic nerves after local multiple injections of either methylprednisolone or vehicle. These neuropathologic changes, especially axonal degeneration, have been directly related to pain.³³ Mackinnon et al²⁸ reported that intrafascicular injection of triamcinolone hexacetonide produces irreversible injury to the fibers in histologic studies, whereas dexamethasone produced minimal damage and methylprednisolone affected the nerve to an intermediate degree. They concluded that steroid agents have a direct neurotoxic effect on the peripheral nerve tissue but that it is seen only when the drugs are injected intrafascicularly into the nerve bungle. This, of course, should always be avoided in clinical practice. Although the pathophysiologic mechanisms of anti-inflammatory agents on the nerve are largely unknown, it has been reported that methylprednisolone reduces early vascular permeability increases in spinal nerve roots induced by epidural application of nucleus pulposus.⁷ This positive therapeutic result may be an indirect effect of the agent on inflammatory cytokine activity or a direct effect on vascular smooth muscle.

There has been no report describing the effect of dexamethasone on rat sciatic nerve and DRG blood flow in normal animals. Our study in normal rat sciatic nerve and DRG indicates that there is a significant effect of dexamethasone in reducing nerve blood flow. The mechanism of this response is not clear. It has been reported that epinephrine and/or local anesthetics applied to the surface of the epineurium decrease nerve blood flow and produce subperineurial demyelination,³¹ and this may be attributed to sympathetic vasoconstriction of the innervated epineurial vessels. The frequency of epinephrine use in epidural and steroid injections, however, is thought to be rare.^{3,23} The influence of other pharmacologic agents on arteriolar caliber is not always predictable and can even be bimodal.²⁴ For example, Johns et al have shown that lidocaine produces vasoconstriction at low doses and vasodilation at high doses²⁵ but that bupivacaine produces only a dose-related microvascular constriction.²⁶ Several mechanisms may be responsible for these changes, including a direct neural effect on sympathetic fibers and alterations of local calcium concentration. Endothelium-derived relaxing factor, a potent vasodilator produced and released locally by endothelial cells, also has a role in these drug-induced changes in vascular caliber.²⁷ For these reasons it is often difficult to predict the vascular effect of combined therapeutic agents and their adjuvants.

Nevertheless, extensive clinical experience with steroids and local anesthetics suggests that their therapeutic use is of value and that their ischemic potential is not of significant concern in the usual clinical setting.

However, it is clear that reduction of nerve blood flow can produce ischemic injury in subperineurial nerve fibers. Devascularization of the epineurium in rat peripheral nerve causes a 58% reduction in nerve blood flow and subsequent subperineurial demyelination.³² The average reduction in nerve blood flow observed in this study is less than the 58% reduction previously shown to cause nerve fiber pathology. The lack of demyelination and axonal injury in the current study is consistent with the understanding of this ischemic threshold for nerve fiber injury. However, in the current study we did observe edema and Schwann cell activation in some animals as indications of preliminary or minimal manifestations of neuropathologic change due to ischemia and/or toxic injury to nerve fibers. Schwann cell activation is associated with upregulation of cytokine production and is observable morphologically as an increase in the volume and apparent hydration of Schwann cell cytoplasm.³⁴ Schwann cell activation and endoneurial edema are early changes in the pathogenesis of many painful neuropathies but may appear and resolve without other pathologic or neurologic consequences.^{33,39} Some animals showed approximately 50% reduction in nerve blood flow, but we were not able to associate this deficit with nerve injury because our methodology precluded direct, paired correlation of blood flow and histology in individual animals. Thus, it is possible that the local application of dexamethasone on the nerve can cause ischemic injury in selected animals, and this problem may be exacerbated in sick animals or in situations in which other agents causing nerve ischemia may be combined with dexamethasone. A combination of ischemic injuries will likely result in nerve fiber injury.

■ Conclusion

The current study demonstrates that application of dexamethasone to the sciatic nerve and DRG decreases blood flow in these tissues at 30 minutes and 4 hours after acute application. Although the measured deficit in blood flow was modest in normal animals relative to the threshold for ischemic injury, it is possible that dexamethasone in combination with vasoconstrictive adjuvants, such as lidocaine and epinephrine, would have a pathophysiologic role in nerve damage after its therapeutic application.

■ Key Points

- Dexamethasone causes reduced blood flow in normal nerve.
- Dexamethasone causes reduced blood flow in normal dorsal root ganglia.
- The reduced blood flow is at the threshold for ischemic injury

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