Injectable Corticosteroid and Local Anesthetic Preparations: A Review for Radiologists

Corticosteroids and local anesthetics are some of the most commonly administered medications in radiology departments. These medications have marked variability in their formulations, which may increase their adverse event profile for specific procedures. In particular, certain corticosteroid preparations are associated with adverse central nervous system (CNS) sequelae. This is most likely due to distal embolization by particulate formulations. Nonparticulate steroid formulations are not associated with such events. Local anesthetics have severe CNS and cardiac adverse effects if injected intravascularly and have recently been associated with intraarticular chondrolysis if used in large doses. This review discusses these medications with particular emphasis on their established and postulated adverse effects. The administering radiologist should be aware of these potential effects and how best to reduce their occurrence.

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Corticosteroids and local anesthetics (LAs) are some of the most commonly administered parenteral medications in radiology departments. Musculoskeletal and other radiologists administer corticosteroids and LAs routinely as part of their role in the diagnosis and treatment of musculoskeletal disorders.

Common indications for corticosteroid or LA treatment include joint (eg, facet, shoulder, hip, wrist, knee, ankle), bursal (eg, subacromial, iliopectas), tendon sheath, epidural, transforaminal, perineural, interdigital neuroma, and cyst and ganglion conditions. The frequency of such interventional pain management procedures is growing, as evidenced by a Medicare claims study (1) that demonstrated a nearly 100% increase in the frequency of epidural injections between 1998 and 2003.

Corticosteroids are predominately administered because they are proven antiinflammatory agents that provide medium-term relief of symptoms (2–4). LAs can provide not only immediate relief to the patient but also possible medium-term relief of symptoms (2–4). Corticosteroids and LAs routinely as part of their role in the diagnosis and treatment of musculoskeletal disorders.

This article will review the common corticosteroid and LA preparations used in radiology departments, with particular emphasis on their potential for adverse effects and complications.

Corticosteroids

Steroids have variable structures, functions, and sites of effect. In addition to those steroids found in nature, there are many that have been synthetically produced. Steroid molecules differ principally in terms of changes to the functional groups attached to their carbon rings. Natural corticosteroids are formed in the adrenal cortex and are involved in a wide range of physiologic effects. In 1950, the Nobel Prize in Physiology or Medicine was awarded to Philip Hench, Tadeusz Reichstein, and Edward Calvin Kendall for discovering that corticosteroids have important antiinflammatory effects. Corticosteroids can be classified as mineralocorticoids (eg, aldosterone), which control water and electrolyte physiology, and glucocorticoids (eg, cortisol), which control metabolism and inflammation. Due to the powerful antiinflammatory effects discovered by Hench, corticosteroid-like molecules have been synthesized to be used in drug therapy. The efficacy of corticosteroids was dramatically demonstrated when an intramuscular injection of hydrocortisone allowed a patient with rheumatoid arthritis who had been confined to bed to walk again (8).

Corticosteroids and LAs are routinely administered in combination, either in the same syringe or separately during the same procedure. It is important for the administering radiologist to understand the properties of the various pharmaceutical preparations available because there is considerable variability in their effectiveness, duration of action, and potential for severe adverse effects.

Corticosteroid Preparations

The common synthetic corticosteroids used in radiology procedures are derivatives of prednisolone (an analogue of cortisol). All have antiinflammatory potencies per dose unit somewhat greater than that of cortisol. The most commonly used preparations are detailed in Table 1. Methylprednisolone is the methyl derivative of prednisolone, whereas betamethasone, dexamethasone, and triamcinolone are all fluorinated derivatives of prednisolone.

Corticosteroid preparations can be either soluble or insoluble. Most corticosteroid preparations contain corticosteroid esters, which are highly insoluble in water and thus form microcrystalline suspensions. If used in large quantities involves its active moiety entering cells and combining with receptors to alter messenger RNA production, mainly altering the protein annexin-1 (previously called lipocortin-1) (13,14).

Corticosteroids were first used as an intraarticular injectable by Thorn in 1940, but it was Hollander in 1951 who established the practice (15). Hollander successfully treated tens of thousands of patients with a range of conditions that included rheumatoid arthritis, osteoarthritis, bursitis, systemic lupus erythematosus, and gout. In various publications, he described the effects of corticosteroid injections in large joints, small joints, lusae, and tendon sheaths (16–19). These injections were not image guided, and any poor therapeutic response was considered by Hollander as secondary to a failure of the steroid to enter the joint space (17). While Hollander predominately used hydrocortisone, there are now several injectable preparations of corticosteroids available from which the radiologist can choose.

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Corticosteroid preparations can be either soluble or insoluble. Most corticosteroid preparations contain corticosteroid esters, which are highly insoluble in water and thus form microcrystalline suspensions. Dexamethasone preparations,
However, are not esters and are freely soluble in water; hence, the preparation is clear (ie, nonparticulate). The potential advantage of corticosteroid ester preparations is that they require hydrolysis by cellular esterases to release the active moiety and consequently should last longer in the joint than do nonester preparations (20). On the other hand, freely water soluble preparations such as dexamethasone sodium phosphate and betamethasone sodium phosphate are taken up rapidly by cells and thus have a quicker onset of effect but with a concomitant reduced duration of action. Of note, the formulation Celestone Soluspan (Scher- ing, Kenilworth, NJ) contains a combination of betamethasone ester and betamethasone salt and, therefore, may provide a dual action of quick onset and long-acting therapy. However, most clinical studies have not shown a significant difference between Celestone Soluspan and other corticosteroid ester preparations in terms of onset or duration (21,22).

Various in vitro studies (23–26) have recently demonstrated that there are substantial variations in the size of the crystals in corticosteroid esters preparations. There are also differences in the propensity of different corticosteroid crystals to aggregate into larger particles. In addition, because each pharmaceutical has a different potency, there are varying concentrations of crystals in each to allow equivalent doses between different corticosteroids. These variations are summarized in Table 1. What is important to note is that formulations that contain ester preparations have a relatively larger particulate size. There is, however, considerable variation in the reported particle size for the preparations studied in the literature. The clinical importance of this will be discussed in more detail below.

In addition to the actual steroid, there are several other chemical ingredients in any corticosteroid formulation, including preservatives (commonly, benzyl alcohol) and a drug vehicle (namely, polyethylene glycol). These will also be discussed later.

### Table 1

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Commercial Name</th>
<th>Equivalent Potency (mg)</th>
<th>Solubility*</th>
<th>Maximum Particle Size (μm)</th>
<th>Particle Aggregation</th>
<th>Benzyl Alcohol</th>
<th>Polyethylene Glycol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone acetate</td>
<td>Depo-Medrol, Solu-Medrol, Duralone, Medrolone</td>
<td>4</td>
<td>0.001</td>
<td>&gt;500</td>
<td>Extensive</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>Kenalog</td>
<td>4</td>
<td>0.0002</td>
<td>500</td>
<td>Extensive</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Betamethasone acetate, betamethasone sodium phosphate</td>
<td>Celestone Soluspan, Betject</td>
<td>0.75</td>
<td>Acidic form, “practically insoluble”; sodium phosphate form, freely soluble</td>
<td>0.5</td>
<td>0</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Dexamethasone sodium phosphate</td>
<td>Decadron Phosphate, Adrenocort, Decaject</td>
<td>0.75</td>
<td>Freely soluble</td>
<td>500</td>
<td>35</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

* Information obtained from package inserts for each commercial product.
† Reference 23, 24. Maximum size of a red blood cell is approximately 10 μm.
‡ Value is percent wt/vol.

**Corticosteroid Use**

It is outside the scope of this paper to provide a detailed review of techniques and doses for the multitude of uses for
injectable steroids. Each corticosteroid formulation has a different potency. Table 1 includes the equivalent milligram dose of the various steroids for the purpose of comparison. As can be seen, five times less dexamethasone and betamethasone is required to achieve potency similar to that of methylprednisolone or triamcinolone. The standard approximate corticosteroid doses for intraarticular injections are outlined in Table 2.

The duration of action of corticosteroids can be described by their biologic half-life, pharmacologic half-life, or duration of clinical benefit. While the duration of clinical benefit is the most practical assessment, it is unfortunately the most subjective and differs widely in the literature, without statistically significant differences. For example, in rheumatoid arthritic knee joints, the average duration of benefit is reported to be between 14 and 66 days for triamcinolone (19,27) and between 8 and 56 days for methylprednisolone (28,29). Such wide overlapping ranges are typical and hence difficult to analyze confidently. As previously explained, the ester preparations of a corticosteroid would be expected to have longer half-life, since they rely on the patient’s own hydrolytic enzymes (esterases) to release the active moiety. Although there are very few clinical trials in which a corticosteroid ester is compared with dexamethasone, to date there are no studies of which we are aware that have shown a statistically significant difference between onset, duration, or efficacy (30).

The use of corticosteroid injections to treat neuromas, ganglia, and paralabral cysts is still debated (5). They were first used in this way in 1953 for the treatment of wrist ganglia (31). Since the publication of that article, the data have been conflicting regarding steroid treatment versus aspiration alone. The mechanism of action of how corticosteroids may treat ganglia is unclear. Initially it was thought that ganglia were inflammatory in origin and that steroids would thus be effective. Histopathologic analyses, however, have rarely shown a notable inflammatory component of ganglia, thus indicating that an inflammatory origin is unlikely. A potential benefit possibly arises through a protein catabolic effect, although this is unresolved (32).

Corticosteroids are sometimes administered after admixture with other agents in the same syringe. The potential advantages over a dual-syringe technique would be the reduced chance of inadvertent needle movement during syringe exchange and marginally reduced procedure time. A recent study (24) demonstrated that corticosteroid crystals do not have any greater propensity to aggregate or change size when mixed with lidocaine solution or iodinated contrast material. Thus, it appears safe to coadminister corticosteroids and lidocaine, with the caveat that other LAs have not been formally assessed.

**Contraindications**

There are several known contraindications to the use of corticosteroid injections in musculoskeletal disorders. These are outlined in Table 3. The main concerns are the introduction of sepsis into a joint during the procedure or the exacerbation of sepsis already present within a joint. Thus, local or intraarticular infection is a contraindication to corticosteroid injection. In addition, because corticosteroids inhibit bone healing (33,34), an intraarticular fracture at the time of injection is also a relative contraindication to injection (35). To prevent disease progression, it has generally been advised to minimize the use of injected corticosteroids in markedly unstable joints or in those with severe juxtaarticular osteoporosis.

Worsening of joint instability after corticosteroid injection apparently results from the development of subchondral osteonecrosis and weakening of the capsule and ligaments (36). It is also advised that the number of injections to the same joint or structure be limited to one injection every 6 weeks and/or three injections in 1 year (37). Bacteremia or conditions likely to cause bacteremia (eg, bacterial endocarditis, pneumonia) are generally regarded as contraindications to local corticosteroid injection (38).

Juxtaarticular osteoporosis was a concern to Hollander, since the use of corticosteroids could potentially decrease bone density, with resultant fracture. It has been argued by some authors (37), however, that this is a regular consequence of synovitis and, thus, that therapy that moderates such synovitis may actually improve juxtaarticular osteoporosis and osteopenia. However, we are aware of no published reports to support this hypothesis.

Joint injection in the presence of coagulopathy or in a patient on anticoagulants is still debated (5). They were first used in this way in 1953 for the treatment of wrist ganglia (31). Since the publication of that article, the data have been conflicting regarding steroid treatment versus aspiration alone. The mechanism of action of how corticosteroids may treat ganglia is unclear. Initially it was thought that ganglia were inflammatory in origin and that steroids would thus be effective. Histopathologic analyses, however, have rarely shown a notable inflammatory component of ganglia, thus indicating that an inflammatory origin is unlikely. A potential benefit possibly arises through a protein catabolic effect, although this is unresolved (32).

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lant therapy is somewhat controversial. While it is prudent that any coagulopathy should be corrected or anticoagulation therapy should be withheld prior to any injection therapy, there is little evidence to suggest that it is a necessary course of action. A small study (39) in which joint and soft-tissue injections were assessed in patients receiving oral anticoagulation therapy did not result in any hemorrhages. Some authors (38), however, still suggest prudence and withholding of oral anticoagulation if the international normalized ratio is greater than 2.

Adverse Effects

The following is a list of the established adverse effects associated with corticosteroid injections: (a) septic arthritis, (b) postinjection “flare,” (c) local tissue atrophy, (d) tendon rupture, (e) cartilage damage, and (f) flushing and increased blood glucose level.

The most feared complication after steroid injection is infection; in particular, a septic joint. With a good sterile technique, however, the incidence of such a complication is as low as 0.01%–0.03% (17,19,40). The most common adverse effect is the postinjection flare, which is a local increase in inflammation that develops within hours and can last 2–3 days. If severe, this flare may be difficult to distinguish from sepsis. If the flare lasts longer than 24 hours, joint aspiration is recommended to exclude infection (37). The prevalence of postinjection flare is 2%–25% (17,19,41) and does not predict a poor response to therapy (19,42,43). The cause of the flare may be due to the previously described microcrystalline steroid esters, which may incite a crystal-induced arthritis (42), or possibly to a chemical within the drug formulation (41).

Local tissue necrosis, calcification, and tendon rupture have been associated with intraarticular injections of the corticosteroid formulation triamcinolone hexacetonide (Aristospan, Novartis, CITY, STATE, COUNTRY). It is for this reason that it is recommended that triamcinolone hexacetonide be used only by experienced radiologists, even though it is a very effective medication with a clinical benefit of up to several months (37).

There has been considerable debate over the past several decades on the risk of articular hyaline cartilage damage with intraarticular injections. The results of animal studies have been inconsistent, with studies in rabbits demonstrating increased cartilage fissures and cysts, reduced proteoglycan and protein synthesis, and reduction of cartilage production by 50% (44,45), while a later study in dogs reported a protective effect (46).

More recent animal studies have assessed biomarkers of cartilage turnover after intraarticular steroid injection. These have demonstrated increased markers of aggrecan turnover and increases in cartilage matrix degradation (47). Results from studies of large patient groups confirm that cartilage loss can occur after repeated corticosteroid injections; however, it is thought that the risk is generally low, with 0.7%–3% of patients who have received multiple injections developing substantial cartilage loss (48). A recent randomized double-blind study demonstrated no deleterious effects on joint space size for a period of 2 years (49). As stated already with regard to juxtaarticular osteopenia, corticosteroids may theoretically help preserve cartilage in the setting of active synovitis. Overall, many investigators believe this benefit outweighs the potential harm (37).

There are a number of soft-tissue adverse effects associated with local injection of corticosteroids: namely, skin atrophy and depigmentation, as well as fat necrosis. These are most noticeable after injection of superficial structures (eg, ganglia, neuromas, tendon sheaths) but can also be seen after an intraarticular injection, presumably due to reflux of corticosteroid along the needle track (50). The mechanisms underlying skin changes are not well elucidated, but several authors (51–54) attribute direct cytotoxicity, altered ground substance, vasoconstriction, and/or the mechanical effects of edema as potential underlying reasons. In addition, decreased type I collagen and glycosaminoglycan synthesis are important factors (55).

Skin depigmentation is an important but underappreciated complication of corticosteroid injection. Such depigmentation is of course most noticeable on dark-skinned patients, and such patients should be informed of such a potential complication prior to injection. It is important to note that it can take up to 2 months for skin effects to manifest. Skin depigmentation normalizes in most patients over a period of 12 months (56). Of interest, there is some evidence that repigmentation is accelerated with exposure to ultraviolet light (56,57).

Cutaneous atrophy is observed clinically as a depressed area of skin, occasionally with hypopigmentation, distended blood vessels, and alopecia. While atrophy usually normalizes over a period of 1–2 years, effects lasting longer than 5 years have been reported (50,58,59). The extent and duration of such skin complications is likely related to the solubility and concentration of the corticosteroid preparation (60). Interestingly, normal saline infiltration has been demonstrated to be a rapid and effective method to treat local and prolonged skin atrophy (61). Of note, methylprednisolone is less associated with these adverse effects than is triamcinolone and, therefore, may be the preferred preparation when injecting superficial structures (50,60).

Corticosteroids increase protein catabolism. It has been shown in animal models that intratendinous injection of corticosteroids adversely affects the biomechanical properties of tendons. There is some debate currently on the use of corticosteroids in the treatment of chronic tendon processes (degeneration, tendinosis). Injections may predispose to weakening of tendons and may minimize an inflammatory reaction that aids in the healing process (62). It is relatively well established that intratendinous corticosteroid injection can lead to tendon rupture (63–65). This is likely to occur through the inhibition of tenocyte proliferation (66) and the reduction in the strength of isolated collagen fascicles (67). These observations suggest that peritendinous injections should also be performed with some caution.

Systemic effects of soft-tissue or intraarticular injections do occur but are generally believed to have minimal clinical importance (68). In the past decade, however, there have been a number of
reports of a measurable effect on the hypo-
thalamus-pituitary-adrenal axis after intra-
articular injection of corticosteroids
(69–72). Duclos et al (69) demonstrated
that seven of 10 male athletes had an ab-
normally low serum cortisol level after a
single intraarticular injection of cortico-
steroid and that response to adrenocorti-
cotropic hormone stimulation was blunted.
This inhibitory effect was seen to persist
14 days later in three of 10 ath-
letes. The authors proposed that athletes
should be prohibited from all sporting or
professional activities that have a high
risk of trauma or infection for a period of
2 weeks after treatment, because they
believe there is an increased risk of adre-
nal crisis in this period after injection.
It must be pointed out that inhaled cortico-
steroids are known to cause a similar rate
of adrenal suppression (73), but there are
few cases of adrenal crisis in the literature
(74). Nevertheless, it is important for
the treating radiologist to be aware that
intraarticular corticosteroids do have
variable systemic effects, and patients
should be counseled not to undergo sur-
gery, become severely dehydrated, or ex-
pose themselves to severe physical stress
within 2 weeks after corticosteroid injec-
tion (69).

Several studies have demonstrated a
measurable increase in blood glucose
level in diabetic patients receiving corti-
co Steroid injections (75–77). The hyper-
glycemic effect can be seen from 2 to 5
days after injection. Patients with diabe-
tes should thus be warned to expect an
increase in their blood glucose level at
home.

Corticosteroid injections may be
less effective in patients with diabetes,
as evidenced by results from a prospec-
tive, randomized, controlled trial (76)
of corticosteroid injections in diabetic
patients with trigger finger. The authors
found that corticosteroid injections were
less effective in diabetic patients than in
nondiabetic patients, did not decrease the
surgery rate compared with pla-
cebo, and did not improve symptom re-
 lief compared with placebo.

Facial flushing has been reported as
an unpleasant adverse effect after intra-
articular injection in 15% of patients (78).
Flushing occurs 2–30 hours after injection
and can last 36 hours. It is seen more
commonly after triamcinolone adminis-
tration but can occur after any prepara-
tion (78). Chilliness, shaking, and head-
aches can accompany the facial flushing.
It is always self-limiting, and its cause is
still to be fully elucidated; however, flush-
ing is likely secondary to a histamine-
mediated response to the drug (79). If
such symptoms persist, consideration
should be given to administering diphen-
hydramine to reduce symptom duration
or to switching to another corticosteroid
if further injections are required (80).

Adverse Central Nervous System
Sequelae
In the recent literature there have been a
number of reported cases of adverse cen-
tral nervous system (CNS) events occur-
ring secondary to corticosteroid injec-
tions. This is most commonly seen with
cervical transforaminal corticosteroid in-
jections (81–86), with brain and spinal
cord infarction being the most frequent of
these uncommon sequelae (87–90).
There are additional case reports of para-
plegia after selective lumbar transforami-
nal injection (91). Postulated causes of
these negative sequelae include (a)
vascular injury causing arterial spasm, trauma,
or compression; (b) spinal cord or cere-
bral embolic infarction after particulate
corticosteroid injection into a cerebral
artery; and (c) neurotoxicity from the pres-
servative and/or drug vehicle in the ste-
r oid formulation.

Several authors (81,84,92) agree that
infarctions caused by particulate steroid
emboli are likely the primary cause of the
reported CNS complications. As has been
discussed earlier, there is considerable
variation in the size of particles in differ-
ent corticosteroid preparations. The size
of the corticosteroid particles is likely im-
portant, because it will determine the size
of vessel that is potentially embolized.
Particles larger than a red blood cell but
smaller than an arteriole will have the
greatest propensity to occlude terminal
arterial vessels and cause infarction. Par-
ticles larger than this will likely occlude
larger vessels (arterioles); however,
there is increased likelihood of collateral
blood supply preventing substantial tissue
damage (93). It is for this reason that
small particles in the arterial system can
be the most dangerous, and their use is
typically avoided in interventional embo-
lation procedures (94). Studies in which
cerebral infarction was assessed (95,96)
have demonstrated that microthrombi of
60–100 μm in diameter are capable of
occluding terminal vessels and causing
substantial infarction. As can be seen
from Table 1, the size of corticosteroid
esters is similar to that of agents used in
interventional embolization procedures.
For example, embolization microspheres
are used in sizes ranging from 40 to 1000
μm, depending on the target vessel
(97,98). For additional comparison, a red
corpuscle has a diameter of 4–10 μm.
The diameter of an arteriole ranges from
100 to 500 μm, the diameter of deep and
accessory cervical arteries ranges from
600 to 2600 μm, and that of vertebral
arteries ranges from 3000 to 5500 μm
(24). The inner diameter of a 22-gauge
needle is approximately 400 μm; how-
ever, it is thought that particles, once in
the vascular space, can coalesce or pre-
cipitate in the blood and form larger par-
ticles (24). This theory of particle aggre-
gation in blood has not been demon-
strated to date, but corticosteroids are
known to have varying propensities to ag-
gregate in vitro (Table 1).

We found no reports in the literature
of adverse CNS events that were due to
the use of nonparticulate corticosteroids
dexamethasone or pure betamethasone
sodium phosphate) (99). This strength-
en the theory that embolic infarction
from particulate corticosteroid esters (as
opposed to needle-induced vascular in-
jury) is the cause of the reported CNS
adverse events. On the other hand, non-
particulate corticosteroids are used much
less frequently than are particulate corti-
costeroid for transforaminal injections.

It is important for the radiologist to be
aware that critical arteries can be located
posteriorly in the intervertebral foramen
and thus are vulnerable to injection or
injury during a transforaminal injection.
A study by Huntoon (100) found that asc-
ending and deep cervical arterial
branches can enter the external opening
of the posterior aspect of the foramen—
hence, close to the intended target for
transforaminal injection (Fig 1). These
branches can occasionally supply radicu-
lar and segmental medullary arteries to
the spinal cord (100). A case report by
Baker et al (84) describes the opacifica-
tion of a radicular artery that appears to
supply the spinal cord during a transfo-
raminal injection (Fig 2). The procedure
was abandoned before corticosteroid in-
jection, and the patient experienced no ill
effects. This confirms that it is possible to
inject a radicular artery by using standard
fluoroscopy-guided techniques.

Of note, the phenomenon of cortico-
steroid emboli is not unique to transfo-
raminal injection. There are multiple re-
ports in the literature of central retinal
artery occlusion after retrobulbar or peri-
ocular corticosteroid injection (101–104).
In many cases, embolic material is actu-
ally visualized in small retinal arterioles
(101,104).

A recent in vivo animal study (105)
assessed the vascular sequelae of par-
ticulate steroids. In that study, meth-
lyprednisolone was injected directly
into the vertebral artery of pigs via a
catheter, and the outcome was com-
pared with that in pigs injected with
soluble corticosteroids (dexamethasone
and prednisolone). Assessment was
carried out by direct observation, mag-
netic resonance imaging, and dissec-
tion. The authors demonstrated that all
pigs who received methylprednisolone
had serious neurologic deficits and re-
quired ventilatory support. None of the
pigs that received nonparticulate ste-
roids had serious sequelae. While these
results do not prove that this is the
cause of clinical cases of CNS infarction,
they certainly demonstrate the impor-
tance of inadvertent passage of particu-
late steroids into the CNS vasculature
and, specifically, that dexamethasone
sodium phosphate is safe.

Transforaminal corticosteroid injec-
tions can result, extremely rarely, in near
instantaneous death, tetraplegia, or parap-
legia, with any spinal level being at risk.
The precise probability of such complica-
tions has not been evaluated at this time.
Some centers, notably in France, are de-
signing studies to address this issue (106).

Another potential source of adverse
effects is from the preservatives and drug
vehicles used in the different formulations

Figure 1: Diagram demonstrates potential mechanism of spinal cord infarction caused by transforaminal
injection of corticosteroid crystals traveling to the spinal cord. A radicular artery is located posteriorly at the
foramen that, in some patients, may contribute arterial supply to the spinal cord. Diagram illustrates cortico-
steroid crystals traveling to the spinal cord. (Reprinted, with permission, from reference 99.)

Figure 2: Fluoroscopic contrast medium—enhanced spot image obtained during routine transforaminal
injection. Radiopaque contrast medium is seen opacifying a radicular artery (arrows) that appears to supply
the spinal cord. (Reprinted, with permission, from reference 83.)
of corticosteroids. Benzyl alcohol is the most commonly used preservative, and there is some debate over its adverse effects. A number of neurotoxic effects have been described including demyelination, neural degeneration, and paraplegia (107–109). This compound is found in formulations of methylprednisolone, triamcinolone, and dexamethasone (Table 1). Because the adverse CNS sequelae reported with corticosteroids occur quite soon after injection, it is thought that this preservative cannot explain the majority of events in the literature.

Polyethylene glycol is a drug vehicle used in many formulations (Table 1). This chemical has been shown to reversibly decrease the action potentials of neural fibers, which could potentially cause adverse effects after intraarterial injection (110). However, no clear link has been established. Indeed, some authors (111,112) now believe that polyethylene glycol has no neurotoxic effects at commercially available concentrations.

As there are no reported cases of CNS sequelae from the use of nonparticulate corticosteroids, many authors suggest that all transfemoral procedures should use such preparations to reduce adverse event rates (24,99,113). Unfortunately there are many fewer data on clinical efficacy for such formulations. In addition, such preparations would be expected to have a reduced duration of action. Importantly, some studies (21,113) have found no difference in immediate action. Importantly, some studies (21,113) have found no difference in immediate action, and is less potent than cocaine. Since then, multiple synthetic LAs have been developed, notably lidocaine in 1943 and bupivacaine in 1957.

LAs act mainly through inhibition of sodium-specific ion channels on neuronal cell membranes. This prevents the development of an action potential in the neuron, thus inhibiting signal conduction.

In conclusion, there is wide variation in the preparations of corticosteroids that affect onset, efficacy, duration of action, and adverse effects profile. A good understanding of these important factors is critical for the radiologist in deciding on the most appropriate therapy for the patient.

Local Anesthetics

LAs inhibit nerve excitation and/or conduction to cause local analgesia and/or paralysis. They are among the most commonly administered pharmaceutics in radiology departments. Anesthetics are administered primarily to induce cutaneous anesthesia obtained at epidural blocks and bupivacaine in 1957.

The first clinically administered LA was cocaine. Cocaine was extracted and isolated from coca leaves in the 1860s (115). This naturally occurring LA is, however, relatively toxic and has caused notable abuse and addiction issues. The first synthetic LA, procaine (Novocaine), was developed in 1904, but it has a delayed onset of action, short duration of action, and is less potent than cocaine. Since then, multiple synthetic LAs have been developed, notably lidocaine in 1943 and bupivacaine in 1957.

LAs can be divided into those that are esters (eg, cocaine and procaine) and those that are amides (lidocaine, bupivacaine, ropivacaine). The ester preparations of LAs are associated with a risk of severe allergic reactions secondary to the breakdown product paraaminobenzoic acid (116). True allergic reactions are much less common with amide preparations (117).

The relative potencies of different LAs are reviewed in Table 4. It is important to note that while increasing the dose of administered LA increases the degree of anesthesia and duration of action, the time of onset of anesthesia is unchanged.

In conclusion, there is wide variation in the preparations of corticosteroids that affect onset, efficacy, duration of action, and adverse effects profile. A good understanding of these important factors is critical for the radiologist in deciding on the most appropriate therapy for the patient.

While all neurons are sensitive to LAs, smaller-diameter neurons are blocked better than are larger neurons, and thus pain sensation (small myelinated axons) can be blocked but sensation relatively preserved.

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It is relatively common for a vasoconstrictor, typically epinephrine, to be added to LA formulations. This decreases the rate of vascular absorption, allowing more anesthetic to reach the neuron and improve potency. For example, the addition of epinephrine to 0.5% bupivacaine increases the depth and duration of local anesthesia obtained at epidural blocks (118).

LA Preparations

The most commonly administered LAs are reviewed in Table 4. The physiochemical properties that influence the activity of LAs include lipid solubility, protein binding, and the acid dissociation constant pKa. Lipid solubility is the primary determinant of intrinsic LA potency: The more lipophilic the preparation, the more easily it penetrates the

### Table 4

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Relative Potency</th>
<th>Protein Binding (%)</th>
<th>pKa Value*</th>
<th>Lipid Solubility</th>
<th>Onset</th>
<th>Duration of Action (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine hydrochloride</td>
<td>Novocain</td>
<td>1</td>
<td>5.8</td>
<td>8.9</td>
<td>1.7</td>
<td>Moderate</td>
<td>30–60</td>
</tr>
<tr>
<td>Lidocaine hydrochloride</td>
<td>Xylocaine</td>
<td>2</td>
<td>55</td>
<td>7.8</td>
<td>25</td>
<td>Rapid</td>
<td>80–120</td>
</tr>
<tr>
<td>Bupivacaine hydrochloride</td>
<td>Marcaine</td>
<td>8</td>
<td>96</td>
<td>8.1</td>
<td>346</td>
<td>Longest (2–10 min)</td>
<td>180–360</td>
</tr>
<tr>
<td>Ropivacaine hydrochloride</td>
<td>Naropin</td>
<td>6</td>
<td>95</td>
<td>8.1</td>
<td>115</td>
<td>Moderate</td>
<td>140–200</td>
</tr>
</tbody>
</table>

* pKa = logarithmic acid dissociation constant.
The use of LAs. A clinical history of hyper-

sensitization, (130,131) and antiinflam-
ausal transport (128,129), blockade of

discharge (125), blockade of the sympa-

tic effect, there are a number of postulated

drugs is bupivacaine, because it is more

potent and has a longer duration of action

than does lidocaine. Typical doses of bu-
pivacaine range from 0.5 to 2.0 mL in con-

centrations of 0.25% or 0.50%, de-
pending on joint size (123,124).

Interestingly, bupivacaine injections have been demonstrated to provide re-

lief from chronic back pain after lumbar facet nerve-root block for a median du-
ration of 15 weeks (123). This is a rela-
tively unexpected finding because the anesthetic effect of bupivacaine lasts for

no more than 6–7 hours (Table 4). The mechanism of how such relatively long-
term relief is provided by LAs is un-

known. Apart from a placebo-type ef-

fect, there are a number of postulated

mechanisms: suppression of nociceptive discharge (125), blockade of the sympa-

thetic reflex arc (126,127), blockade of axonal transport (128,129), blockade of

sensitization, (130,131) and antiinflam-

matory effects (132).

There are few contraindications to

the use of LAs. A clinical history of hyper-
sensitivity reaction to any amide-type LA

is a contraindication. A true anaphylactic

allergy is extremely rare; however, imme-
diate (<12 minutes) and delayed-type hypo-
sensitivity reactions (48–72 hours) to

LAs have been reported (133,134). Local

sepsis and coagulopathy are relative con-

traindications to musculoskeletal LA in-

jections owing to the risk of the introd-

uction of sepsis into a joint or bleeding into

a joint. As stated earlier, the risk of intra-

articular hemorrhage is very low (39). An

additional relative contraindication ap-

plies to LA preparations that contain epi-
nephrine or norepinephrine. Such prepa-

rations may produce severe prolonged

hypertension in patients also receiving

monoamine oxidase inhibitors or tricyclic

antidepressants (135). Such a risk is low,

but because these medications demon-

strate some systemic absorption from

joints, the potential risk does exist during

intraarticular injection (136).

Known or Potential Adverse Effects

It is important for the radiologist to be

aware of the maximum safe dose of an

LA. Present recommendations for maxi-

mum doses are, in large part, not evi-

dence based (137). The dose recommenda-

tions are meant to prevent the admin-

istration of a toxic dose of an LA. In

Europe, the maximum dose of lidocaine is

200 mg (or 3 mg per kilogram of body

weight). This equates to 20 mL of 1% lido-

caine or 10 mL of 2% lidocaine. In the

United States, the maximum dose is 300

mg. If epinephrine is used with lidocaine, then the maximum dose increases to 500

mg in both Europe and the United States

(137). The maximum safe dose of bupi-

vacaine is approximately 150 mg (2 mg/

kg). This equates to 25 mL of 0.5% bu-
pivacaine or 50 mL of 0.25% bupivacaine.

The maximum safe dose for ropivacaine

is 375 mg. These doses, however, do not

take into account the site of injection. For

example, similar plasma concentrations of

lidocaine are obtained after a 300-mg intercostal block, a 500-mg epidural

block, a 600-mg brachial plexus block, and a 1000-mg subcutaneous infiltration of

the leg (138,139).

The most well-known and established

adverse effects from LAs are CNS and

cardiac toxicity after intravascular or un-

wanted intrathecal injection (140). Be-

cause the CNS is more sensitive to the

effects of LAs than is the cardiovascular

system, CNS sequelae are usually the first

indication of systemic toxicity after intra-

vascular injection. CNS sequelae include

shivering, muscle twitching, tremor, hy-

poventilation, respiratory arrest, and, fi-

nally, generalized convulsions. In an ani-

mal model, bupivacaine had a markedly

lower threshold dose to induce generalized convulsions than did the other amide

LAs (lidocaine and ropivacaine) (141). In

fact, that study demonstrated that the
dose of lidocaine needed to induce con-

vulsions was four times higher than that

of bupivacaine (141). Ropivacaine is

more toxic to the CNS than lidocaine but

less toxic than bupivacaine (142). The ex-

act dose required for the various LAs to

induce convulsions in humans is un-

known; however, there are case reports

in the literature to act as a guide. Ropiv-

caine, for example, has been reported to

cause CNS toxicity after accidental intra-

venous injection of doses ranging from 75
to 200 mg (143).

The cardiac toxicity related to the use

of LAs is initially secondary to sympa-
thetic pathway activation in the CNS. This

is then followed by arrhythmias, pro-

found cardiovascular depression, and, fi-
nally, cardiovascular collapse (144). Bu-
pivacaine is notably more cardiotoxic

than lidocaine and ropivacaine, likely be-

cause it is more lipid soluble and protein

bound (140).

In the event of a severe adverse reac-
tion to an LA, there are a number of po-
tential treatments. Signs of anaphylaxis

include sudden loss of consciousness, con-

vulsions, and cardiovascular collapse. These

signs can be seen at variable times after

administration, depending on the site of

injection (soft tissue vs vascular) and on

the agent administered. The onset of con-

vulsions begins approximately 20 seconds

after intravascular administration of lido-

caine, as compared with 7 seconds for

bupivacaine (141). If advanced cardiac

life support treatment fails to treat the

reaction, a lipid emulsion (eg, Intralipid

20%; Baxter Healthcare, Deerfield, Ill)

should be administered intravenously

(145). This may reverse LA toxicity by

extracting lipophilic LAs from plasma and
tissues and by counteracting any myocardial inhibition (146). If this fails, consideration should be given to cardiopulmonary bypass (147).

In addition to CNS and cardiac toxicity, LAs can, on rare occasions, cause clinically important skeletal muscle toxicity (148,149). All LAs in experimental settings are myotoxic in clinical concentrations, with a dose-dependent rate of toxicity (150–152). Bupivacaine is characterized with a high rate of myotoxicity, as compared with ropivacaine and lidocaine (152–154). While necrotic changes predominate in LA-exposed myocytes, bupivacaine seems to uniquely induce myocyte apoptosis (149). The pathogenesis of LA myotoxicity is highly complex and incompletely understood. It appears that a fast and permanent increase in intracellular calcium levels is the most important mechanism (149).

The clinical effect of LA-induced myotoxicity remains controversial. There are only a few case reports of myotoxic complications in patients. Muscle weakness and malfunction have been described after continuous peripheral blockade, infiltration of wound margins, and peri- and retrobulbar blocks (151,155,156). While experimental evidence of myotoxicity is strong, in the clinical setting it is relatively rare. This is likely because of rapid and complete recovery with complete tissue regeneration. The radiologist should be aware, however, that this type of toxicity may be seen in this class of agents.

**LA Effect on Articular Cartilage**

Authors of several publications (157–161) have demonstrated that LAs (lidocaine, bupivacaine, and ropivacaine) are toxic to chondrocytes. This issue has been raised recently in the radiology literature by Kamath et al (162). The initial evidence was seen in cases of severe chondrolysis in patients who had undergone continuous intraarticular infusion of bupivacaine at arthroscopy (163). Subsequently, a number of in vitro studies (157–161) have been performed to better assess any effects.

Initially, Chu et al (157) demonstrated that 0.5% bupivacaine was cytotoxic to bovine articular chondrocytes after only 15–30 minutes of exposure. This same group (159) demonstrated in 2007 that lidocaine (1% and 2%) had dose- and time-dependent cytotoxic effects on bovine cartilage but that the effects were less than those they had reported previously with bupivacaine. It is important to note that these experiments were designed to simulate large-volume (30–60 mL) intraarticular injections of LA prior to arthroscopic surgery or continuous LA joint infusion after arthroscopy. Chu et al (158) recently repeated their initial experiments, but this time they used human articular cartilage to show that 0.25% and 0.50% bupivacaine are cytotoxic to human chondrocytes. They also demonstrated that the intact articular surface (as opposed to cell cultures) has a partially protective effect (158). A team from Stanford University (San Francisco, Calif) (161) recently demonstrated that exposure to 0.25% bupivacaine or 1% lidocaine for less than 48 hours had minimal effect on chondrocyte viability, however 0.5% bupivacaine and all epinephrine-containing LA formulations demonstrated significantly increased chondrocyte apoptosis. Last, a study by researchers in San Francisco, Calif, demonstrated that while 0.5% ropivacaine was toxic to cultured chondrocytes, it was significantly less toxic than 0.5% bupivacaine; this difference was especially the case when assessing the effects on intact cartilage (160). Those researchers concluded that ropivacaine may be a safer alternative to bupivacaine for intraarticular analgesia. Of note, ropivacaine costs two to three times more than bupivacaine ($6.20 vs $2.30 for equivalent dose).

It must be highlighted that the Stanford group demonstrated a significant increase in chondrocyte toxicity with the use of lidocaine and bupivacaine formulations that contained epinephrine at all doses and exposure times. Interestingly, they believe that this finding may be secondary to the significantly lower pH in these formulations (161). Thus, epinephrine-containing formulations of LAs should not be used in intraarticular injections.

All the above-reported studies were designed to assess the effect on cartilage by the large volumes of LA used in orthopedic practices. Since there are few case reports of clinically significant chondrolysis after a single intraarticular injection and because this technique has been used for decades, the results suggest that any clinically significant effect is mild but that further clinical research is warranted. Intraarticular injections of LAs are unlikely to expose chondrocytes to the concentrations used for in vitro experiments owing to the dilutional effects of joint fluid and active synovial absorption (158). Studies have shown that LAs are naturally absorbed from the joint, with absorption peaking within the 1st hour (164,165). Importantly, 0.125% bupivacaine, a potential joint concentration after a single 0.25% bupivacaine injection, does not appear to markedly affect chondrocyte viability (158).

While the toxic effect from LAs may be minimal, it is important for the radiologist to be aware that chondrocyte exposure to high concentrations of LA for prolonged periods is cytotoxic. The mechanisms underlying this effect are still to be elucidated. There are several proposed theories of how LAs are cytotoxic to chondrocytes, including (a) increased intracellular nitric oxide, (b) increased reactive oxygen species, and (c) mitochondrial transmembrane potential disruption (159,160,166). Of note, corticosteroids have been shown to ameliorate the expression of inducible nitric oxide systems in cultured chondrocytes; therefore, the concurrent administration of corticosteroids at the time of LA injection may counteract the chondrocytotoxic effect (167).

Most local anesthetics are vasodilators at clinical doses, and for this reason a vasoconstrictor, namely epinephrine, is added to reduce the rate of drug absorption and hence increase the duration of anesthetic effect (168). The introduction of ropivacaine has prompted interest because it is less neuro- and cardiotoxic than other long-acting LAs. More recent evidence, as outlined earlier, also suggests it is less chondrocytotoxic than bupivacaine. What is less well known is that ropivacaine has vasoconstrictor activity as well. Indeed, the addition of epinephrine to ropivacaine has been shown to have no beneficial effect (169–171).
Moreover, ropivacaine alone has been shown to cause vasoconstriction in multiple vascular beds including the skin, cerebral arteries, and mesenteric arteries (169,172–175). In addition, a vasoconstrictive effect was noted clinically in patients who received epidural analgesia with ropivacaine (176).

Patients undergoing transforaminal nerve root injections typically receive a corticosteroid and an LA. As described in the corticosteroids sections, the needle position used for these procedures can be extremely close to vessels that potentially supply the spinal cord and/or brain. As concluded previously, the use of particular corticosteroids should be avoided in such procedures, to reduce the risk of spinal or cerebral infarction. Because ropivacaine is vasoconstrictive, it could be postulated that intravascular or perivascular injection for a transforaminal injection may cause significant vasoconstriction of arterioles supplying the CNS, thus increasing the risk of CNS infarction. This suggests that ropivacaine should not be used in transforaminal injections or injections near vessels that supply organs with limited ability to form collateral vessels or to cope with short-term ischemia.

In summary, LAs have variable pharmacologic characteristics, depending on the formulation administered. It is important for the practicing radiologist to be aware of their adverse effects, especially the potential for chondrocyte toxicity.

Conclusions

Corticosteroids and LAs have marked variability in their formulations, which may increase their adverse event profiles for specific procedures. Radiologists should be aware of these potential effects and how best to reduce their occurrence.

References


REVIEW: Injectable Corticosteroids and Local Anesthetics

MacMahon et al.


