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Injectable Corticosteroid and Local Anesthetic Preparations: A Review for Radiologists[1]

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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, iliopsoas), 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). Corticosteroids can additionally be used to treat neuromas, ganglia, and paralabral cysts (5). LAs can provide not only immediate relief to the patient but also possible diagnostic feedback in the elucidation of the source of pain (6,7).

Essentials

- Most corticosteroid preparations contain corticosteroid esters, which are highly insoluble in water and thus form microcrystalline suspensions.
- Corticosteroid transforaminal injections are associated with potential cerebral and spinal cord infarction, likely secondary to distal embolization by the particulate corticosteroid preparation.
- Non-particulate corticosteroid preparations are not associated with embolic type CNS sequelae.
- Local Anesthetics have definite severe CNS and cardiovascular adverse effects if injected intravascularly in large doses.
- Local anesthetics are potentially associated with significant chondrolysis if used in large quantities and/or with vasoconstrictors.

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 pharmaceutic preparations available because there is considerable variability in their effectiveness, duration of action, and potential for severe adverse effects.

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 predominately affect the action of cytokines involved in inflammation (9–11). They lead to down-regulation of immune function (12), inhibiting cell-mediated immunity, reducing cellular accumulation at inflammatory sites and decreasing vascular responses (11,12). Corticosteroids cause these effects through a mechanism that ultimately 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, bursae, 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.

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. Dexamethasone preparations,

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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 (Schering, 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 pharmaceutic 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.

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

Table 1

Common Corticosteroid Injectables

Steroid	Commercial Names	Equivalent Potency (mg)	Solubility*	Maximum Particle Size (μm)†	Particles >10 μm (%)†	Particle Aggregation†	Benzyl Alcohol*	Polyethylene Glycol*
Methylprednisolone acetate	Depo-Medrol, Solu-Medrol, Duralone, Medralone	4	0.001‡	>500	45	Few	Yes	Yes
Triamcinolone acetonide	Kenalog	4	0.0002‡	>500	45	Extensive	Yes	No
Betamethasone acetate, betamethasone sodium phosphate	Celestone Soluspan, Betaject	0.75	Acetate form, "practically insoluble"; sodium phosphate form, freely soluble	500	35	Some	No	No
Dexamethasone sodium phosphate	Decadron Phosphate, Adrenocot, Decaject	0.75	Freely soluble	0.5	0	None	Yes	No

* Information obtained from package inserts for each commercial product.

† References 23, 24. Maximum size of a red blood cell is approximately 10 μm.

‡ Value is percent wt/vol.

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, pharmaceutic 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. Al-

though 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 unproved (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 proce-

dure 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 listed 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 anticoagu-

Table 2

Comparative Table of Typical Dosages for Different Sized Joints

Joint Size	Methylprednisolone Acetate (mg)	Triamcinolone Acetate (mg)	Betamethasones (mL)	Dexamethasone Sodium Phosphate (mg)
Large*	20–80	10–15	1–2	2–4
Medium†	10–40	5–10	0.5–1.0	2–3
Small‡	4–10	2.5–5	0.25–0.5	0.8–1

Note.—Data obtained from package inserts.

* Including knee, shoulder, and ankle. Epidural doses are similar.

† Including elbow and wrist.

‡ Including metacarpophalangeal, facet, and acromioclavicular joints.

Table 3

Contraindications to Corticosteroid Injections

Type of Contraindication	Condition
Absolute	Local or intraarticular sepsis; bacteremia, intraarticular fracture, joint instability
Relative	Severe juxtaarticular osteoporosis, coagulopathy, injection of joint three times that year or within 6 weeks

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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 extraarticular 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 confirms 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 hypothalamus-pituitary-adrenal axis after intraarticular injection of corticosteroids (69–72). Duclos et al (69) demonstrated that seven of 10 male athletes had an abnormally low serum cortisol level after a single intraarticular injection of corticosteroid and that response to adrenocorticotropic hormone stimulation was blunted. This inhibitory effect was seen to persist 14 days later in three of 10 athletes. 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 adrenal crisis in this period after injection. It must be pointed out that inhaled corticosteroids 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 surgery, become severely dehydrated, or expose themselves to severe physical stress within 2 weeks after corticosteroid injection (69).

Several studies have demonstrated a measurable increase in blood glucose level in diabetic patients receiving corticosteroid injections (75–77). The hyperglycemic effect can be seen from 2 to 5 days after injection. Patients with diabetes 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 prospective, 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 placebo, and did not improve symptom relief compared with placebo.

Facial flushing has been reported as an unpleasant adverse effect after intraarticular 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 administration but can occur after any preparation (78). Chilliness, shaking, and headaches can accompany the facial flushing. It is always self-limiting, and its cause is still to be fully elucidated; however, flushing is likely secondary to a histamine-mediated response to the drug (79). If such symptoms persist, consideration should be given to administering diphenhydramine 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 central nervous system (CNS) events occurring secondary to corticosteroid injections. This is most commonly seen with cervical transforaminal corticosteroid injections (81–86), with brain and spinal cord infarction being the most frequent of these uncommon sequelae (87–90). There are additional case reports of paraplegia after selective lumbar transforaminal injection (91). Postulated causes of these negative sequelae include (a) vascular injury causing arterial spasm, trauma, or compression; (b) spinal cord or cerebral embolic infarction after particulate corticosteroid injection into an arterial vessel; and (c) neurotoxicity from the preservative and/or drug vehicle in the steroid 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 different corticosteroid preparations. The size of the corticosteroid particles is likely important, 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. Particles 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 embolization 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-guage needle is approximately 400 µm; however, it is thought that particles, once in the vascular space, can coalesce or precipitate in the blood and form larger particles (24). This theory of particle aggregation in blood has not been demonstrated to date, but corticosteroids are known to have varying propensities to aggregate 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 strengthens the theory that embolic infarction from particulate corticosteroid esters (as opposed to needle-induced vascular injury) is the cause of the reported CNS adverse events. On the other hand, nonparticulate corticosteroids are used much less frequently than are particulate corticosteroids 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 ascending 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 radicular and segmental medullary arteries to the spinal cord (100). A case report by Baker et al (84) describes the opacification of a radicular artery that appears to supply the spinal cord during a transforaminal injection (Fig 2). The procedure was abandoned before corticosteroid injection, 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 corticosteroid emboli is not unique to transforaminal injection. There are multiple reports in the literature of central retinal artery occlusion after retrobulbar or periocular corticosteroid injection (101–104). In many cases, embolic material is actually visualized in small retinal arterioles (101,104).

A recent in vivo animal study (105) assessed the vascular sequelae of particulate steroids. In that study, methylprednisolone was injected directly into the vertebral artery of pigs via a catheter, and the outcome was compared with that in pigs injected with soluble corticosteroids (dexamethasone and prednisolone). Assessment was carried out by direct observation, magnetic resonance imaging, and dissection. The authors demonstrated that all pigs who received methylprednisolone had serious neurologic deficits and required ventilatory support. None of the pigs that received nonparticulate steroids had serious sequelae. While these results do not prove that this is the cause of clinical cases of CNS infarction, they certainly demonstrate the importance of inadvertent passage of particulate steroids into the CNS vasculature and, specifically, that dexamethasone sodium phosphate is safe.

Transforaminal corticosteroid injections can result, extremely rarely, in near instantaneous death, tetraplegia, or paraplegia, with any spinal level being at risk. The precise probability of such complications has not been evaluated at this time. Some centers, notably in France, are designing studies to address this issue (106).

Another potential source of adverse effects is from the preservatives and drug vehicles used in the different formulations
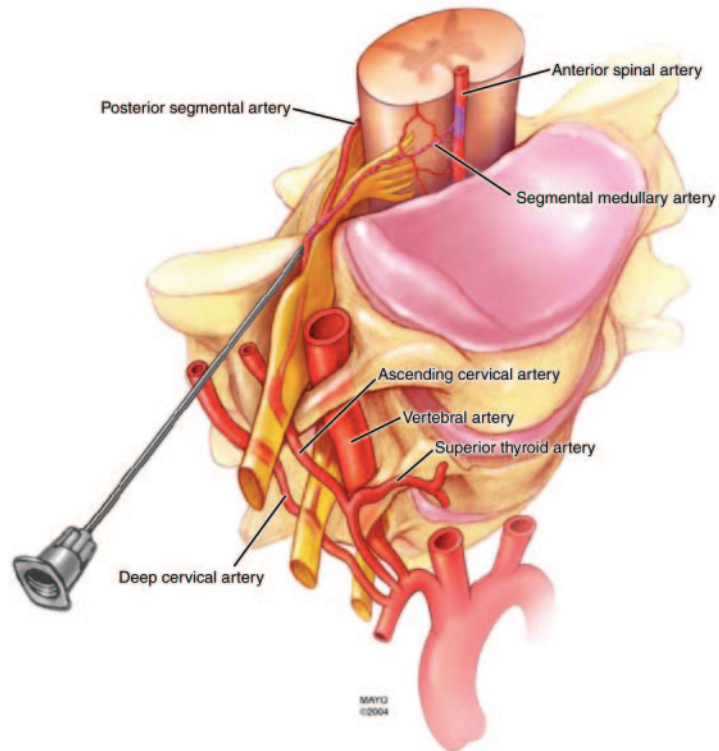
Figure 1

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 corticosteroid crystals traveling to the spinal cord. (Reprinted, with permission, from reference 99.)
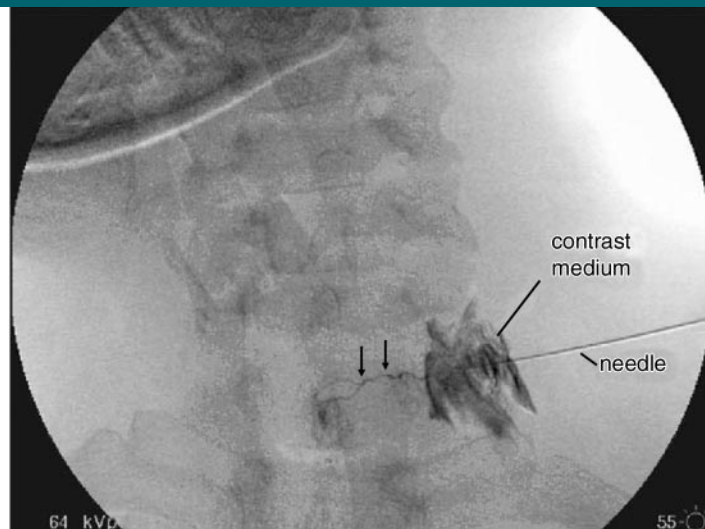
Figure 2

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 transforaminal 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 efficacy of particulate versus nonparticulate corticosteroids for the treatment of cervical and lumbar radicular pain, respectively. Neither of those studies, however, assessed longer term clinical effect.

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 analgesia at the time of a procedure but may also be given for local relief at sites of musculoskeletal discomfort (articular and nonarticular). Mayson et al (114) demonstrated that radiology residents lack knowledge with respect to agents used in radiology departments, including LAs. This section will review LAs for the practicing radiologist.

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 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.

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.

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.

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

Comparative Table of LAs

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

Note.—Information obtained from package inserts.

* pKa = logarithmic acid dissociation constant.

nerve membrane. Protein binding determines the duration of action, and pKa determines onset of action.

The most commonly used LAs in radiology are amides, namely lidocaine and bupivacaine. While lidocaine is the best known amide LA, bupivacaine may be used more commonly in some centers for musculoskeletal procedures.

Lidocaine has a quicker onset but a shorter duration of action than does bupivacaine. Lidocaine is also about half as potent as bupivacaine at inducing local anesthesia (119,120). Ropivacaine, a newer amide LA developed in 1996, is similar in potency to bupivacaine but has fewer cardiotoxic effects (121). As mentioned previously, nearly all these preparations can be formulated or admixed with epinephrine to prolong their duration of action by approximately 50% (122).

LAs are often administered in conjunction with corticosteroids, both as a diagnostic tool but also to provide the patient with immediate relief of symptoms. If symptoms do not resolve after targeted injection, the injected structure is unlikely to be the source of pain. The most commonly administered LA in skeletal procedures is bupivacaine, because it is more potent and has a longer duration of action than does lidocaine. Typical doses of bupivacaine range from 0.5 to 2.0 mL in concentrations of 0.25% or 0.50%, depending on joint size (123,124).

Interestingly, bupivacaine injections have been demonstrated to provide relief from chronic back pain after lumbar facet nerve-root block for a median duration of 15 weeks (123). This is a relatively 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 unknown. Apart from a placebo-type effect, there are a number of postulated mechanisms: suppression of nociceptive discharge (125), blockade of the sympathetic reflex arc (126,127), blockade of axonal transport (128,129), blockade of sensitization, (130,131) and antiinflammatory 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, immediate (<12 minutes) and delayed-type hypersensitivity reactions (48–72 hours) to LAs have been reported (133,134). Local sepsis and coagulopathy are relative contraindications to musculoskeletal LA injections owing to the risk of the introduction of sepsis into a joint or bleeding into a joint. As stated earlier, the risk of intraarticular hemorrhage is very low (39). An additional relative contraindication applies to LA preparations that contain epinephrine or norepinephrine. Such preparations 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 demonstrate 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 maximum doses are, in large part, not evidence based (137). The dose recommendations are meant to prevent the administration 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% lidocaine 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 bupivacaine is approximately 150 mg (2 mg/kg). This equates to 25 mL of 0.5% bupivacaine 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). Because 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 intravascular injection. CNS sequelae include shivering, muscle twitching, tremor, hypoventilation, respiratory arrest, and, finally, generalized convulsions. In an animal 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 convulsions 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 exact dose required for the various LAs to induce convulsions in humans is unknown; however, there are case reports in the literature to act as a guide. Ropivacaine, for example, has been reported to cause CNS toxicity after accidental intravenous injection of doses varying from 75 to 200 mg (143).

The cardiac toxicity related to the use of LAs is initially secondary to sympathetic pathway activation in the CNS. This is then followed by arrhythmias, profound cardiovascular depression, and, finally, cardiovascular collapse (144). Bupivacaine is notably more cardiotoxic than lidocaine and ropivacaine, likely because it is more lipid soluble and protein bound (140).

In the event of a severe adverse reaction to an LA, there are a number of potential treatments. Signs of anaphylaxis include sudden loss of conscious, convulsions, 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 convulsions begins approximately 20 seconds after intravascular administration of lidocaine, 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 af-

ter 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 (Stanford, 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 ortho-

pedic 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).

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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 particulate 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.

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