Comparison of the Particle Sizes of Different Steroids and the Effect of Dilution

A Review of the Relative Neurotoxicities of the Steroids

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Background: Central nervous system injuries after transforaminal epidural steroid injections have been ascribed to occlusion of the blood vessels supplying the spinal cord and brain by the particulate steroid.

Methods: The authors compared the sizes of the particles of the steroids methylprednisolone acetate, triamcinolone acetonide, dexamethasone sodium phosphate, betamethasone sodium phosphate/betamethasone acetate (both Celestone Soluspan®; Schering-Plough, Kenilworth, NJ, the commercial betamethasone; and betamethasone repository, a betamethasone preparation that can be ordered from a compounding company), and betamethasone sodium phosphate. Both undiluted and diluted samples were examined. The samples were examined with a laser scanning confocal microscope, and images were analyzed and measured. The particles were categorized (or tabulated) into groups: 0-20, 21-50, 51-1000, and greater than 1000 μ. Chi-square analyses, with Bonferroni correction, were used to compare the proportion of particles among the undiluted and diluted drug formulations.

Results: Dexamethasone and betamethasone sodium phosphate were pure liquid. The proportion of larger particles was significantly greater in the methylprednisolone and the compounded betamethasone preparations compared with the commercial betamethasone. There was no statistical difference between the commercial betamethasone and triamcinolone, although betamethasone had a smaller percentage of the larger particles. Increased dilution of the compounded betamethasone with lidocaine decreased the percentage of the larger particles, whereas increased dilution of methylprednisolone 80 mg/ml with saline increased the proportion of larger particles.

Conclusion: Commercial betamethasone is the recommended preparation if a nonsoluble steroid is preferred. Dexamethasone is a nonparticulate steroid, but its routine use awaits further studies on its safety and efficacy.

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

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EPIDURAL steroid injections are used for back and neck pain and radiculopathy. It is the most commonly performed procedure in pain clinics. To improve its efficacy, the transforaminal route has been recommended so as to deposit the drug near the nerve root and in the anterior epidural space, at the interface between the herniated disc/foraminal stenosis and the inflamed nerve roots.[1] There have been several reported cases of central nervous system injuries after transforaminal epidural steroid injections.[2-10] One postulated mechanism in these events is occlusion of the segmental artery accompanying the nerve root by the particulate steroid or embolization of the particulate steroid through the vertebral artery.[6,7,11-13] A previous study[7] investigated the particle sizes of the different steroids used in epidural steroid injections but did not investigate the effect of dilution. We investigated the particle sizes of the different steroids to confirm or negate the findings of the previous study and to examine the effect of local anesthetic and saline dilutions on the sizes of the particles. In addition, we compared the particle sizes of commercially available betamethasone and compounded betamethasone. Finally, we compared the vehicles and preservatives of the different steroids and discuss the potential neurotoxicities of these drugs.

Materials and Methods

We compared the particle sizes of the following steroids: a) 80 mg/ml methylprednisolone acetate (Depo-Medrol; Pharmacia-Upjohn, Kalamazoo, MI); b) 40 mg/ml methylprednisolone acetate (Depo-Medrol); c) 40 mg/ml triamcinolone acetonide (Kenalog; Bristol-Myers Squibb, Princeton, NJ); d) 4 mg/ml dexamethasone sodium phosphate (Decadron, American Regent Laboratories, Shirley, NJ); e) 6 mg/ml betamethasone sodium phosphate/betamethasone acetate (Celestone Soluspan®; Schering-Plough, Kenilworth, NJ); f) 6 mg/ml betamethasone sodium phosphate/betamethasone acetate (betamethasone repository; New England Compounding Center, Framingham, MA); and g) 3 mg/ml betamethasone sodium phosphate (New England Compounding Center). The commercially available betamethasone (Celestone Soluspan®) and the compounded betamethasone (betamethasone repository) contain 3 mg/ml betamethasone sodium phosphate and 3 mg/ml betamethasone acetate. We also examined the particle sizes of the undiluted and 1:1, 1:2, and 1:3 dilutions of the particulate steroids by local anesthetic and saline.

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The unopened vial of the steroid was shaken vigorously 20 times. A 1-ml aliquot was drawn from the vial with a 19-gauge needle, and a drop of the sample was placed on a microscope slide over which a cover slip was placed immediately. Images were collected within 1 min, and two representative pictures were made per steroid. The samples were examined with a Zeiss LSM 510 laser scanning confocal microscope (Carl Zeiss Incorporated, Thornwood, NY), and images were analyzed and measured with Velocity software (Improvision, Boston, MA). Measurements were recorded in a spreadsheet program and arranged according to particle size. Percentages of the particles were calculated by dividing the number of particles within a size range by the total number of particles measured.

We initially grouped the particles according to the following sizes (in microns): 0–10; 11–20; 21–50; 51–100; 101–500; 501–1,000; 1,001–2,500; 2,501–5,000; 5,001–10,000; and greater than 10,000. Chi-square analyses (NCSS 2004, Number Cruncher Statistical Systems, Kaysville, UT) were used to compare the proportion of particles 0-20; 21-50; 51-1,000; and greater than 1,000 μ among the undiluted drug formulations as well as among drugs at equivalent dilutions in local anesthetic and saline. The Bonferroni correction of the criterion for the rejection of the null hypothesis was applied to each test performed so that the overall criterion for rejection of the null hypothesis for each data set was $P < 0.05$.

Results

Dexamethasone sodium phosphate and betamethasone sodium phosphate were pure liquid with no identifiable particles (fig. 1). Methylprednisolone acetate and triamcinolone acetonide were opaque and amorphous in appearance (fig. 2). The commercial betamethasone was rod-like and lucent, whereas the compounded betamethasone was opaque and amorphous (fig. 3). A simplified grouping of the particle sizes of the undiluted and diluted steroids into 0-20; 21-50; 51-1,000; and greater than 1,000 μ is shown in table 1. A more detailed presentation of the distribution of the particles across 0-50 μ, for better comparison of our results with that of Tiso *et al.*,[7] is shown in table 2.

The distribution of particles was significantly different between 80 mg/ml methylprednisolone, 40 mg/ml methylprednisolone, and compounded betamethasone compared with commercial betamethasone ($P < 0.05$), with the percentage of the larger particles greater in the methylprednisolone and compounded betamethasone preparations. There was no statistical difference in the distribution of the particle sizes between the methylprednisolone and compounded betamethasone preparations with triamcinolone. There was also no statistical difference in the distribution of particle sizes between


Fig. 1. **Microscopic appearances of dexamethasone and betamethasone sodium phosphate. There are no identifiable particles in either steroid. An air bubble is shown at the periphery of the slide for contrast generation.**

commercial betamethasone and triamcinolone. However, commercial betamethasone had no particles larger than 500 μ, whereas 3% of particles in triamcinolone were larger than 500 μ and 1% was larger than 1,000 μ. Dilution with either saline or local anesthetic did not affect the distribution of the particles of 40 mg/ml methylprednisolone, triamcinolone, and commercial betamethasone. The increased dilution of compounded betamethasone with lidocaine significantly decreased the percentage of the larger particles (table 1). In contrast, increased dilution of 80 mg/ml methylprednisolone with saline resulted in an increased proportion of larger particles.

Discussion

The central nervous system sequelae from transforaminal epidural steroid injections involve either the brain or the spinal cord (table 3). The cerebral/cerebellar events can be ascribed to trauma to the vertebral artery, vasospasm from the injected dye or steroid, or embolism of the particulate steroid *via* the vertebral artery.[7,13] Trauma to or injection *via* the vertebral artery implies incorrect placement of the needle and inability of the physician to recognize this intraarterial placement.[6] The spinal cord injuries can be ascribed to injury of the
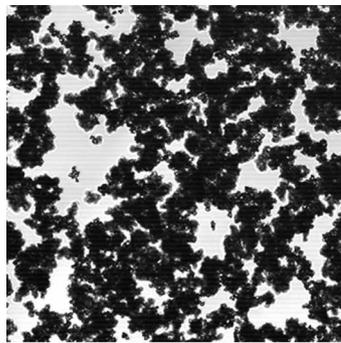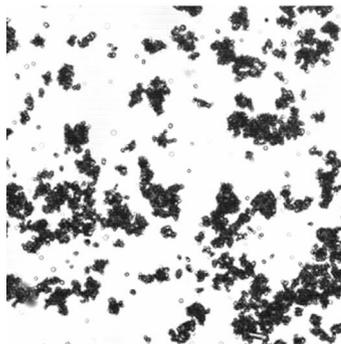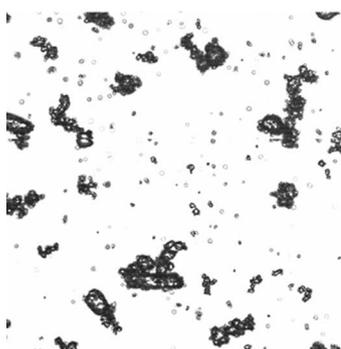
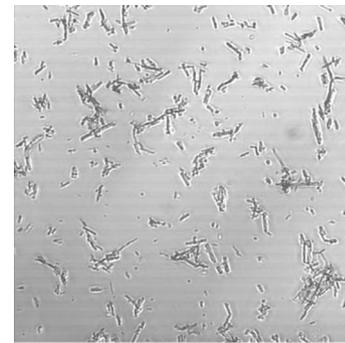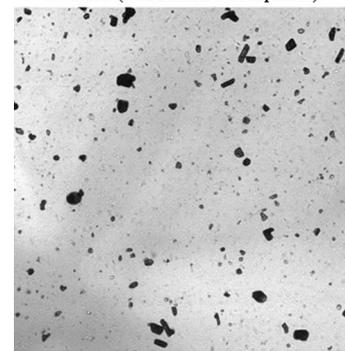Fig. 2. Typical microscopic appearances of 80 mg/ml methylprednisolone and 40 mg/ml methylprednisolone and 40 mg/ml triamcinolone. The particles are opaque and amorphous in appearance.

Fig. 3. Typical microscopic appearances of commercial betamethasone (Celestone Soluspan®; Schering-Plough, Kenilworth, NJ) and compounded betamethasone (betamethasone repository; New England Compounding Center, Framingham, MA). Both preparations contain 3 mg/ml betamethasone sodium phosphate and 3 mg/ml betamethasone acetate. The particles in Celestone Soluspan® are rod-like and lucent, whereas the particles in the betamethasone repository are opaque and amorphous in appearance.

radicular artery accompanying the nerve root, spasm of the radicular artery from the injected radiographic contrast or steroid,[4,7,13] embolism of the particulate steroid,[7,13] or proximal intraneural spread of the injectate.[14] The injection of the contrast medium through a radicular artery that passes to the spinal cord[4] or joins the anterior spinal artery[11] has been demonstrated. The occurrence of adverse events at the lumbar level has been ascribed to intraarterial injection into an abnormally low-lying artery of the Adamkiewicz.[3,10] These adverse events have also been described after injection of local anesthetic[9] and dye,[5] without the steroid. The use of computed tomography, instead of fluoroscopy, does not assure avoidance of the adverse events.[10]

Proximal intraneural spread of the injectate resulting in segmental infarct of the spinal cord has been proposed as a mechanism for the occurrence of paraplegia after intercostal nerve block in patients who underwent general anesthesia.[14] This mechanism can also explain the reported cases of paraplegia after transforaminal epidural steroid injections. Although the published case reports did not mention the presence of pain during the injection, injection into the nerve root is not always painful.[15] The patients may also have been sedated during the procedure. Proximal intraneural spread of the injectate can explain the spinal cord injuries but cannot explain the occurrence of cerebral/cerebellar infarcts after transforaminal epidural steroid injections. The cerebral/cerebellar complications occur mainly through intravascular embolization of the particulate steroid.

Our data, as they pertain to methylprednisolone, triamcinolone, and commercial betamethasone, are in general agreement with the findings of Tiso *et al.*[7] (table 2). Tiso *et al.* did not mention whether they studied the 80-mg/ml or the 40-mg/ml preparation of methylpred-

Table 1. Particle Size Distribution of the Undiluted and Diluted Steroids

Preparation	Dilution	Diluent	No. of particles	Particle Distribution				P Value
				0–20 μm	21–50 μm	51–1,000 μm	>1000 μm	
Methylprednisolone acetate 80 mg/ml	Undiluted		66	63	14	17	6	*
(MPA 80)	1:1	Saline	164	73	11	12	4	0.03
	1:2	Saline	142	58	8	26	8	
	1:3	Saline	174	52	9	32	7	
	1:1	Lidocaine 1%	214	52	17	24	7	0.17
	1:2	Lidocaine 1%	226	63	11	22	4	
	1:3	Lidocaine 1%	224	55	15	28	2	
Methylprednisolone acetate 40 mg/ml	Undiluted		298	64	8	27	1	*
(MPA 40)	1:1	Saline	492	63	9	25	3	0.37
	1:2	Saline	415	67	15	16	2	
	1:3	Saline	281	67	15	17	1	
	1:1	Lidocaine 1%	311	51	20	28	1	0.28
	1:2	Lidocaine 1%	278	62	18	18	2	
	1:3	Lidocaine 1%	281	55	20	24	1	
Triamcinolone acetonide 40 mg/ml	Undiluted		476	79	9	11	1	*
(TRA 40)	1:1	Saline	324	66	10	23	1	0.15
	1:2	Saline	340	72	10	17	1	
	1:3	Saline	241	58	18	23	1	
	1:1	Lidocaine 1%	585	64	14	21	1	0.29
	1:2	Lidocaine 1%	580	63	14	23	0	
	1:3	Lidocaine 1%	376	68	15	17	0	
CLTN Betamethasone sodium	Undiluted		1968	92	6	2	0	*
phosphate/betamethasone acetate	1:1	Saline	519	93	5	2	0	0.29
6 mg/ml (Celestone Soluspan®)	1:2	Saline	560	95	4	1	0	
	1:3	Saline	257	85	12	3	0	
	1:1	Lidocaine 1%	405	93	6	1	0	0.27
	1:2	Lidocaine 1%	588	91	8	1	0	
	1:3	Lidocaine 1%	270	83	15	2	0	
Betamethasone sodium phosphate/	Undiluted		844	68	10	21	1	*
betamethasone acetate 6 mg/ml	1:1	Saline	517	82	8	10	0	0.12
(BTM Rep)	1:2	Saline	699	86	6	8	0	
	1:3	Saline	325	79	9	12	0	
	1:1	Lidocaine 1%	185	51	16	32	1	0.005
	1:2	Lidocaine 1%	108	51	20	29	0	
	1:3	Lidocaine 1%	217	76	11	13	0	

Both CLTN (Celestone Soluspan® [Schering-Plough, Kenilworth, NJ] [betamethasone sodium phosphate/betamethasone acetate, commercial betamethasone]) and BTM Rep (betamethasone repository [betamethasone sodium phosphate/betamethasone acetate, compounded betamethasone]) contain 3 mg/ml betamethasone sodium phosphate and 3 mg/ml betamethasone acetate. Dexamethasone and betamethasone sodium phosphate are liquid with no identifiable particles. Increased dilution of MPA 80 with saline increased the proportion of larger particles. Increased dilution of the BTM Rep with lidocaine decreased the proportion of larger particles.

* Undiluted MPA 80 (80 mg/ml methylprednisolone acetate), MPA 40 (40 mg/ml methylprednisolone acetate), and BTM Rep differ from CLTN, $P < 0.05$.

TRA 40 = 40 mg/ml triamcinolone acetonide.

nisolone. Across the 0- to 50-μ range, we noted a greater percentage of smaller particles compared with that reported by Tiso *et al.* (table 2). There were differences in our results and those of Tiso *et al.* pertaining to dexamethasone and betamethasone sodium phosphate. We noted that dexamethasone and betamethasone sodium phosphate were pure liquid, whereas Tiso *et al.* found small particles in these steroid preparations. We cannot explain the differences in our results; we used a very sensitive microscope (Zeiss LSM 510 laser scanning confocal microscope) and would have detected particles if they had been present. Tiso *et al.* used a Zeiss Axioskop 2 MOT microscope using the Zeiss Plan Neofluar 100× objective (Carl Zeiss Incorporated, Jena, Germany). Their images were taken using a Hamamatsu ORCA-ER

C47242-95 camera (Hamamatsu Photonics Company, Hamamatsu City, Japan), and their measurements were made with the measurements module of Improvision's Openlab 3.1.1 software (Improvision, Boston, MA).

Tiso *et al.* did not tabulate particles larger than 50 μ. They commented, "particle size approached 100 μ in some cases." In contrast, we noted particles larger than 1,000 μ. We cannot explain the differences between our results and those of Tiso *et al.* The steroid particles precipitated quickly, and this probably resulted in the development of the large "particles." We captured representative images immediately, whereas Tiso *et al.* captured their images within 5 min. Although very sensitive, it is possible that our computerized measurements could not separate the individual particles and counted aggre-

Table 2. Percentage Distribution of the Particle Sizes of the Steroids

Size (μ)	MPA 80	MPA 40	TRA 40	CLTN	BTM Rep	BSP	DEX
0–10	60 (49)	53	71 (37)	82 (48)	61	0 (93)	0 (15)
11–20	3 (11)	11	8 (28)	9 (28)	7	0 (6)	0 (15)
21–50	14 (31)	8	9 (31)	6 (23)	10	0 (1)	0 (67)
>50	23 (9)	27	12 (4)	3 (1)	22	0	0 (3)

Tiso et al.'s[7] results are shown in parentheses. They did not state whether the methylprednisolone that they examined was 80 or 40 mg/ml. Tiso et al. noted particles in betamethasone sodium phosphate and dexamethasone, whereas we did not observe any.

BTM Rep = betamethasone repository (betamethasone sodium phosphate/betamethasone acetate, compounded betamethasone); BSP = betamethasone sodium phosphate; CLTN: Celestone Soluspan® (Schering-Plough, Kenilworth, NJ) (betamethasone sodium phosphate/betamethasone acetate, commercial betamethasone); DEX = dexamethasone sodium phosphate; MPA 80 = 80 mg/ml methylprednisolone acetate; MPA 40 = 40 mg/ml methylprednisolone acetate; TRA 40 = 40 mg/ml triamcinolone acetonide.

gates of particles as one particle. We saw active aggregation of the particles immediately, as soon as the solution was "spotted" on the slide. Only one investigator (T.L.C.), who was experienced in these studies, performed all our measurements. Our results are probably closer to clinical situations than those of Tiso et al., as aggregation of the particulate steroids occurs after precipitation.

Dexamethasone is devoid of particles. It has little or no mineralocorticoid activity, similar to methylprednisolone, triamcinolone, and betamethasone.[16] The increased glucocorticoid activity of dexamethasone and betamethasone (table 4) can theoretically result in greater increases in blood glucose compared with methylprednisolone and triamcinolone. If a nonparticulate steroid is preferred for transforaminal epidural steroid injection, then dexamethasone may be used because the other nonparticulate steroid, betamethasone sodium phosphate, is short-acting and not commercially available. However, soluble steroids are rapidly cleared from the spinal canal, theoretically resulting in a short duration of effect.[17] The intrathecal injection of soluble steroids in animals resulted in convulsions.[17–19] Definitive studies on the efficacy of dexamethasone in epidural steroid injections are also lacking. A recent study by Dreyfuss et al.[20] showed less, but not statistically significant, efficacy of dexamethasone compared with triamcinolone. The study by Dreyfuss et al. is not definitive; a limited number of patients were studied ($n = 30$), there was no randomization, different pain rating scales were used before and after the steroid injection (visual analog pain scale before the injection and verbal integer scale at the 4-week follow-up), and follow-up was by telephone interview. Dreyfuss et al.[20] did not plan their study as an efficacy study but wanted to evaluate whether there was a basis for promoting a safer nonparticulate steroid. They concluded, "slightly lesser yield of dexamethasone is worth the theoretical reduction in risk of spinal cord injury, stroke, or death." More definitive studies are needed to investigate not only at the efficacy of dexamethasone but also its dose-response characteristics and neurotoxicity, if it has any.

Methylprednisolone and triamcinolone are the com-

Table 3. Adverse Central Nervous System Events after Transforaminal/ Selective Nerve Root Injections

Author	Site	Injectate	Needle	Event
Brouwers et al.[2]	C6–C7	0.5 ml triamcinolone + 0.5 ml 0.5% bupivacaine	22 G	C3 quadriplegia (spinal cord infarct)
Rozin et al.[6]	C7	80 mg methylprednisolone + 0.75% bupivacaine (3 ml total)	25 G Quincke	Death (brainstem hemorrhage)
Tiso et al.[7]	C5–C6	80 mg triamcinolone + 2 ml 0.25% bupivacaine	25 G Quincke	Cerebellar infarct
Karasek et al.[9]	C6–C7	0.8 ml 2% lidocaine	Unknown gauge	Paralysis of extremities × 20 min
McMillan et al.[5]	C5–C6	2 ml iopamidol	22 G	Cortical blindness × 3 wk (edema of occipital cortex)
Houten et al.[3]	L3–L4, L4–L5	12 mg betamethasone + 0.25% bupivacaine (3 ml total)	25 G spinal	L1 paraplegia (spinal cord edema)
	L3–L4	40 mg methylprednisolone + 1 ml 1% lidocaine + 0.2 ml isovue	20 G spinal	Low thoracic paraplegia (spinal cord edema)
	S1	40 mg methylprednisolone + 1 ml 1% lidocaine	22 G spinal	T10 paraplegia
Huntoon et al.[8]	L1	40 mg triamcinolone + 5 ml 0.12% bupivacaine	25 G and 22 G Quincke	T10 paraplegia (spinal cord infarct)
Somayaji et al.[10]	L2–L3	40 mg triamcinolone + 1 ml 0.5% bupivacaine	21 G spinal	L2 paraplegia (spinal cord infarct)

The magnetic resonance imaging findings in the "Event" column are in parentheses. The patients reported by Huntoon et al.[8] and Houten et al.[3] underwent lumbar spine surgeries. The case reported by Somayaji et al.[10] was performed under computed-tomography guidance.

G = gauge.

Table 4. Comparison of the Different Steroids in Terms of Glucorticoid Potencies, Component Vehicles, and Preservatives

Steroid	Relative glucocorticoid potency*	Vehicle	Preservatives		
		PEG	Benzyl alcohol	Methylparaben	Sodium bisulfite
Methylprednisolone	5	+	+	−	−
Triamcinolone	5	±†	+	−	−
Betamethasone	33	−	−	−	−
Dexamethasone	27	−	−	+	+

All the steroids in table 4 have minimal mineralocorticoid activity.

* Relative milligram potency to hydrocortisone. † Triamcinolone acetonide does not contain polyethylene glycol (PEG), whereas triamcinolone diacetate does; both contain benzyl alcohol. Triamcinolone diacetate has been recently discontinued in the United States.

monly used steroids for epidural injections. The popularity of methylprednisolone is supported by controlled studies that showed its short-term efficacy in interlaminar[21-23] and transforaminal[24] epidural steroid injections. Although we are not aware of controlled studies of triamcinolone, its frequent use[2,7,8,10] may be related to its excellent antiinflammatory effect, low potential for sodium retention, and ability to remain in suspension for a long time.[25] No study has directly compared the efficacy of the different steroids in epidural injections.

Recent controlled studies on transforaminal epidural steroid injections used betamethasone.[26,27] There has been a recent shortage of commercial betamethasone, which led pain medicine practitioners to order compounded betamethasone. We decided to compare both commercial and compounded betamethasone to determine whether there is a difference between the two preparations. We were surprised to see that the two preparations were different not only in their appearance but also in the proportion of the sizes of the particles. There are probably differences in the way these drugs are compounded to give rise to these differences. We studied a compounded preparation of betamethasone from one compounding company, and our findings may not reflect the particle sizes from other compounding companies.

Betamethasone sodium phosphate is the short-acting component of commercial and compounded betamethasone and can be ordered separately from compounding companies. Betamethasone sodium phosphate is a pure liquid and contains no particles but is short-acting, and there are no studies that have evaluated the efficacy of this drug in transforaminal epidural steroid injections.

In an elegant anatomic study, Huntoon[13] noted that the vertebral, ascending cervical, and deep cervical arteries supplied segmental medullary vessels. These findings were confirmed by Hoeft *et al.*[28] Huntoon found that the ascending and deep cervical arteries were within 2 mm of the path of the needle that is inserted for cervical transforaminal epidural steroid injections. Finally, he noted that the outer diameter of the vessels ranged from 3 to 5.5 mm for the vertebral arteries, 0.6 to 1.2 mm for the ascending cervical arteries, and 0.8 to 2.6 mm for the deep cervical arteries.[13]

The particles of the steroids larger than 1,000 μ are more than adequate to completely occlude the ascending cervical and deep cervical arteries and to partially occlude the vertebral artery. Particle sizes larger than 1,000 μ cannot theoretically enter the vessel. Because the solution is usually shaken before it is injected, it is possible that the steroid particles coalesce and precipitate to form the large particles after the steroid has entered the blood vessel. The medium-sized particles (51–1,000 μ) can enter and partially occlude the vessels. Smaller particles (10–50 μ) may not be able to occlude the arteries. However, these smaller particles can occlude the arterioles and capillaries, causing tissue damage. It is therefore possible that any particulate steroid can occlude the distal portions of the arteries.

In epidural steroid injections, the steroids are usually diluted to decrease the concentration of benzyl alcohol and polyethylene glycol[29] and to improve the spread of the drug.[30] Pain medicine practitioners use either local anesthetic or saline, and we wanted to evaluate whether the particle size distribution was affected by dilution, at what dilution, and with what diluent. We found that dilution did not decrease the size of the particles except in compounded betamethasone, in which increasing dilutions with the local anesthetic decreased the proportion of the larger particles. Interestingly, increased dilution of 80 mg/ml methylprednisolone with saline resulted in the increased proportion of larger particles.

The question of neurotoxicity of the steroids arises from the vehicle polyethylene glycol and the preservative benzyl alcohol in the steroid preparation. Polyethylene glycol concentrations greater than 20% have been shown to reversibly decrease the compound action potentials of the A, B, and C fibers.[29] Benzyl alcohol has been implicated in a case of flaccid paraplegia that lasted 16 months.[31] Methylprednisolone contains 3% polyethylene glycol and 0.9% benzyl alcohol, whereas triamcinolone acetonide contains benzyl alcohol only. Triamcinolone diacetate (Aristocort Intralesional®; Astellas Pharma US, Deerfield, IL; and Sandoz Pharmaceuticals Corporation, Princeton, NJ), which contains both polyethylene glycol and benzyl alcohol, was recently discontinued in the United States. Dexamethasone and com-

mercial betamethasone do not contain either polyethylene glycol or benzyl alcohol (table 4). Compounded betamethasone can be ordered in two preparations: one that is preservative-free and another that contains benzyl alcohol. Other vehicles or preservatives in the steroids that can cause potential problems are methylparaben and sodium bisulfite. Of the steroids that we examined, dexamethasone contains methylparaben and sodium bisulfite, compounds that have been implicated in allergic reactions to local anesthetics.[32]

Animal studies of steroid neurotoxicity included the epidural, intrathecal, and intraneural injections of the steroid preparations. Epidural injection of triamcinolone diacetate and its vehicle, and the vehicle itself, in cats showed minimal inflammatory changes that were similar to the changes after no injection or after the epidural injection of lidocaine.[25] The epidural injection of methylprednisolone acetate in rabbits did not cause microscopic changes in the meninges and spinal cord.[33] Serial intrathecal injections of methylprednisolone sodium succinate and triamcinolone diacetate in rats resulted in spinal cord histology that was similar to saline injections.[34] The extrafascicular injection of steroids into rat sciatic nerves did not produce any damage, whereas intrafascicular injection resulted in varying degrees of nerve injury: dexamethasone caused minimal damage, and methylprednisolone acetate and triamcinolone acetonide caused intermediate changes.[35] There has been no comparable animal study on betamethasone or dexamethasone.

Central nervous system adverse events have not been reported after interlaminar epidural steroid injections. Any of the particulate steroids can therefore be used with this approach. For the transforaminal approach, commercial betamethasone is the preferred particulate steroid in terms of the size of its particles. Triamcinolone has a smaller percentage of larger particles than methylprednisolone and compounded betamethasone and can be used if commercial betamethasone is not available. The recommended precautions should be observed when performing transforaminal epidural steroid injections. These precautions include aspiration before injection and the use of blunt needles, flexible extension tubing, and real-time imaging.[11,12,36] If the pain medicine practitioner prefers a nonparticulate steroid because of possible arteriolar occlusion and tissue damage even with the smaller particles, then dexamethasone can be used. Although we have demonstrated that dexamethasone is nonparticulate, practitioners should use caution in moving toward routine use of this steroid until further studies clarify its safety and efficacy.

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