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REVIEW ARTICLE

The Neurotoxicity of Drugs Given Intrathecally (Spinal)

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A growing understanding of the neuropharmacology of spinal cord processing of nociceptive input has led to intense interest in the use of spinal drugs in anesthesia and pain management. The direct application of receptor-specific therapeutics at the spinal cord can potentially interrupt specific pain pathways and limit systemic side effects, but this practice also carries the inherent risk of injury to the central nervous system. Thus, the neurotoxicity of spinal drugs is a central safety issue. Spinal cord or nerve root toxicity may manifest itself as histologic, physiologic, or behavioral/clinical derangements after exposure to a spinal drug. Neurohistopathology is broadly classified as neural injury, gliosis, or damage to the myelin sheath, and it also describes inflammatory changes and involvement of the arachnoid cell layers. Physiologic neurotoxicity of spinal drugs includes changes in spinal cord blood flow, disruption of the blood-brain barrier, and changes in the electrophysiology of impulse conduction. Behavioral and clinical signs of neurotoxicity include pain, motor and sensory deficits, and bowel and bladder dysfunction. Ideally, a complete roster of histological, physiologic, and behavioral testing would be performed on spinal drugs in several animal species, followed by safety trials in humans before widespread use. In practice, drugs have taken a variety of roads from conception to application, and often without safety data. In this article, we review available neurotoxicity data on drugs that have a clinical application, classified as spinal local anesthetics, spinal analgesics, or spinal adjuvants.

Spinal Local Anesthetics

The 100-yr history of spinal local anesthetic use in humans has typically involved self-experimentation, followed by widespread application with little or no controlled testing for neurotoxicity. Bier and Hildebrant (1) initially performed spinal anesthesia with cocaine on themselves in 1898, and essentially all of the earliest local anesthetics for spinal anesthesia were introduced in this fashion without toxicity studies. Despite a long history of clinical use, recent interest in neurotoxicity has arisen due to concerns over reports of cauda equina syndrome and transient neurologic symptoms (TNS) from spinal local anesthetics. We review animal data that have been used to assess the neurotoxicity of local anesthetics and summarize data available from human studies.

In 1985, Ready et al. (2) evaluated the neurotoxic effects of single injections of local anesthetics in rabbits. They reported that spinal cord histopathology remained normal and that persistent neurologic deficits were not seen with clinically used concentrations of tetracaine, lidocaine, bupivacaine, or chlorprocaine. However, histopathologic changes and neurologic deficits did occur with higher concentrations of tetracaine (1%) and lidocaine (8%). In this model, extensive neurologic impairment was not necessarily accompanied by equally extensive lesions in the spinal cord and nerve roots, thus demonstrating the need for multiple models to fully assess neurotoxicity.

Recent studies have used desheathed peripheral nerve models, designed to mimic unprotected nerve roots in the cauda equina, to further assess electrophysiologic neurotoxicity of clinically relevant concentrations of local anesthetics (3–5). These models demonstrate that clinically used concentrations of 5% lidocaine and 0.5% tetracaine cause irreversible conduction block, whereas 1.5% lidocaine, 0.75% bupivacaine, and 0.06% tetracaine do not. Electrophysiologic toxicity of lidocaine in these models is concentration-dependent (Figure 1) beginning at 40 mM (approximately 1%) with irreversible ablation of the compound action potential at 80 mM (approximately 2%). Kanai et al. (4) subsequently demonstrated that generation of action potentials was more vulnerable than maintenance of resting membrane potential and that irreversible ablation of action and resting membrane potential by lidocaine seems to be both concentration- and time-dependent.

Effects of local anesthetics on spinal cord blood flow seem benign. Spinal administration of bupivacaine,

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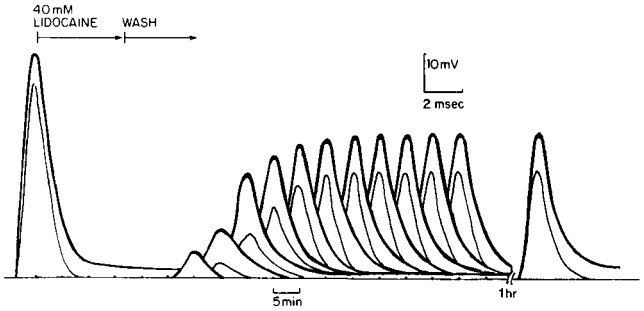

Figure 1. The nonreversible effect of 40 mM lidocaine on the compound action potential (CAP) of frog sciatic nerve. Lidocaine was applied to a stable nerve preparation for 15 min, then washed with frog Ringer's solution for 2 h. Tracings represent CAPs in response to stimuli (1-Hz stimulus = heavy line, 40-Hz stimulus = thin line). Lidocaine 40 mM completely ablated the CAP when applied to the nerve. The 1-Hz CAP response began to return after 10–15 min of washing and reached a new level in 45 min, where it was stable for the subsequent 2 h of observation. The recovered 1-Hz CAP is only 65% of the original. Reprinted with the publisher's permission from Holman SJ. Anesthesiology: hyperbaric dye solution distribution. Anesthesiology 1997;86:969.

lidocaine, mepivacaine, and tetracaine causes vasodilation and increase spinal cord blood flow (6,7), whereas ropivacaine causes concentration-dependent vasoconstriction and reduction in spinal cord blood flow (6). However, the effects of lidocaine on blood flow of *in vitro* peripheral nerve models are more concerning. Myers et al. (8) applied solutions of isotonic sodium chloride solution, 1% and 2% lidocaine with and without epinephrine, and epinephrine alone to isolated rat sciatic nerve and measured changes in blood flow with a laser Doppler flow probe. Blood flow was significantly depressed for all solutions except isotonic sodium chloride solution. Epinephrine by itself significantly reduced nerve blood flow, and, when added to local anesthetic solutions, it reduced blood flow to a greater extent than the reduction caused by local anesthetics alone.

Although experimental studies in animals have provided ample evidence that some local anesthetics in clinically relevant concentrations can injure nerve tissue, the exact mechanisms of injury are unclear. Recent work on neuronal cell lines has attempted to determine the mechanism of local anesthetic neurotoxicity. Johnson and Uhl (9) have shown that direct application of 2.5%–5.0% lidocaine caused a >3-fold increase in intracellular calcium and up to a 20% incidence of cell death during 60 min of exposure in the neuronal cell line. They postulated that the mechanism of neurotoxicity was not likely from sodium channel blockade, because such a block would not lead to an increase in cytoplasmic calcium. Subsequent work in this model determined that 0.5% and 1.0% lidocaine, as well as 0.625% bupivacaine, lead to transient, moderate increases in calcium, probably from the endoplasmic reticulum, without cell death (10). Thus, several different laboratory models have proven that all local anesthetics can be neurotoxic but that lidocaine and tetracaine are potentially more neurotoxic than bupivacaine (Table 1).

Despite the knowledge that all local anesthetics can be neurotoxic in the laboratory model, large-scale surveys of the complications of spinal anesthesia attest to the relative safety of spinal local anesthetics in humans (Table 2). Retrospective (11), prospective (12), and historical studies (13–15) report 0%–0.7% incidence of postoperative neurologic injury in patients undergoing spinal anesthesia. Although lacking a denominator, information from closed-claims databases corroborate these findings (16,17). Thus, the neurotoxic potential of spinally administered local anesthetics has not manifested itself in large-scale studies.

There are few nonepidemiologic clinical studies evaluating the potential neurotoxicity of local anesthetics, and all have focused on electrophysiologic variables after spinal anesthesia. Somatosensory evoked potentials, monosynaptic H-reflex (18), and cutaneous current perception thresholds (19) have been used to evaluate recovery after spinal anesthesia. These measurements have shown complete return to baseline activity after 5% lidocaine spinal anesthesia in very small study populations. Histopathologic or other physiologic data in humans are lacking; thus, information from controlled studies in humans is essentially not available.

Lidocaine

Controversy about the use of single-injection spinal lidocaine began in 1993 when Schneider et al. (20) published four cases of short-lived neurologic symptoms after spinal anesthesia with 5% hyperbaric lidocaine. This was the first report to question the potential for neurotoxicity with standard clinical doses and concentrations of lidocaine after single-injection spinal anesthesia. Subsequent prospective, randomized studies reveal a 4%–33% incidence of TNS after lidocaine spinal anesthesia (Table 3) (21,22). This incidence varies with the type of surgical procedure and is unaffected by baricity or the dilution of lidocaine to 0.5%. Contemporary reports of cauda equina syndrome after continuous lidocaine spinal anesthesia and the potential concentration-dependent neurotoxicity of lidocaine have led several authors to label TNS as a manifestation of subclinical neurotoxicity.

As previously discussed, laboratory work in both intrathecal and desheathed peripheral nerve models has proven that the concentration of lidocaine is a critical factor in neurotoxicity. Because concentrations of lidocaine <40 mM (approximately 1.0%) are not neurotoxic to desheathed peripheral nerve, such dilute concentrations of spinal lidocaine should not cause TNS if the syndrome is caused by subclinical concentration-dependent neurotoxicity. We recently examined whether spinal lidocaine concentrations of <1.0% might

Table 1. Local Anesthetic Toxicity

Local Anesthetic	Animal data			Human data		
	Histologic	Physiologic	Behavioral	Histologic	Physiologic	Clinical
Lidocaine	+	+	+	NA	−	+
Bupivacaine	+/−	−	−	NA	−	−
Tetracaine	+	+	+	NA	NA	+/−
2-Chloprocaine	+	NA	−	NA	NA	NA
Mepivacaine	NA	NA	NA	NA	NA	+/−
Procaine	NA	NA	NA	NA	NA	NA
Prilocaine	NA	NA	NA	NA	NA	−

+ = studies support neurotoxicity, − = studies refute neurotoxicity, +/− = studies are inconsistent, NA = no studies available.

Table 2. Large Epidemiologic Studies of the Neurologic Complications of Spinal Anesthesia

Author/type of study	Patients	Complications
Auroy et al., 1997 (12) /prospective	40,640	7 radiculopathy 5 cauda equina syndrome
Horlocker et al., 1997 (11) /retrospective	4767	6 persistent paresthesia
Aromaa et al., 1997 (17) /closed claims	550,000	5 paraplegia 1 cauda equina syndrome 6 radiculopathy
Dahlgren, 1995 (11) /pro- and retrospective	8,501	4 radiculopathy
Phillips et al., 1969 (14) /prospective	10,440	30 transient paresthesia 2 paresis 2 exacerbation of disc disease
Moore, 1969 (11) /retrospective	11,574	1 paresis
Sadove, 1961 (11) /retrospective	20,000	3 meningitis 1 paraplegia (spinal tumor)
Dripps and Vandam, 1954 (13) /prospective	10,098	71 persistent paresthesia <1 yr 2 foot drop 11 neurologic exacerbation

therefore decrease the incidence of TNS (21). Patients undergoing knee arthroscopy were randomized to receive 50 mg of hyperbaric lidocaine as either a 2.0%, 1.0%, or 0.5% solution. There was no difference in the incidence of TNS (18%) among the three groups. The high incidence of TNS with lidocaine concentrations <1%, despite further dilution in cerebrospinal fluid, seem to lessen the plausibility of a concentration-dependent neurotoxic etiology. Other potential etiologies for TNS include patient positioning, early mobilization, needle trauma, neural ischemia, pooling of local anesthetics secondary to maldistribution by pencil-point needles or the addition of glucose, muscle spasm, myofascial trigger points, and irritation of dorsal ganglia (21). The etiology of TNS is undetermined, and further studies are required to elucidate the underlying mechanism.

In summary, local anesthetics all have the potential to be neurotoxic, particularly in concentrations and doses larger than those used clinically. In histopathologic, electrophysiologic, behavioral, and neuronal cell models, lidocaine and tetracaine seem to have a greater potential for neurotoxicity than bupivacaine at clinically relevant concentrations. Nonetheless, large-scale surveys of the complications of spinal anesthesia attest to the relative safety of spinal local anesthetics.

Spinal Analgesics

There is a complex system of different receptors for the transmission and inhibition of nociception in the spinal cord. These receptors include μ_1-opioid receptors, α_2-adrenergic receptors, muscarinic acetylcholine receptors, γ-amino butyric acid agonist (GABA) receptors, and *N*-methyl-D-aspartate (NMDA) receptors. The neuropeptides substance P and somatostatin function as activators and inhibitors of nociception, respectively, and arachidonic acid metabolites enhance pain transmission (23). Drugs that have been administered spinally in humans are thought to act directly or indirectly within this array of agonists and receptor sites (Figure 2). For each drug, the animal safety data and the human safety data are presented and summarized in Table 4.

Opioids

Hydrophilic Opioids. Dogs and cats exposed to clinically relevant doses of intrathecal morphine for several weeks through indwelling catheters showed no abnormal histopathology of the spinal cord under light microscopy (24,25). Spinal cord blood flow is unaffected by 0.2 mg of intrathecal morphine in dogs (26). Consistent with a lack of histologic or physiologic

Table 3. Incidence of Transient Neurologic Symptoms (TNS) with Spinal Anesthesia in Prospective Randomized Studies

Author	Patients	Drugs used	Incidence of TNS
Pollock et al., 1998 (21)	109 arthroscopy	2.0% Lidocaine	15.8%
		1.0% Lidocaine	22.2%
		0.5% Lidocaine	17.1%
Martinez et al., 1998[a]	200 mixed	5.0% Lidocaine	4%
		5.0% Prilocaine	0%
Liguori et al., 1998[b]	60 arthroscopy	2.0% Lidocaine	22%
		1.5% Mepivacaine	0%
Hampl et al., 1998 (22)	90 gynecology	2.0% Lidocaine	30%
		2.0% Prilocaine	3%
		0.5% Bupivacaine	0%
Pollock, 1996 (21)	100 arthroscopy	0.75% Bupivacaine	0%
		5.0% Lidocaine	16%
		2.0% Lidocaine	22%
	59 inguinal hernia	0.75% Bupivacaine	0%
		5.0% Lidocaine	16%
		2.0% Lidocaine	0%
Hampl, 1996 (22)	50 gynecology	5.0% Lidocaine	31%
		2.0% Lidocaine	40%
Hampl, 1995 (22)	44 gynecology	5.0% Lidocaine + 7.5 glucose	33%
		0.5% Bupivacaine	0%
		5.0% Lidocaine + 2.7 glucose	31%

[a] Martinez-Bourio R, Arzuaga M, Quintana JM, et al. Incidence of transient neurologic symptoms after hyperbaric subarachnoid anesthesia with 5% lidocaine and 5% prilocaine. Anesthesiology 1998;88:624–8.
[b] Liguori GA, Zayas WM, Chrisholm MF. Transient neurologic symptoms after spinal anesthesia with mepivacaine and lidocaine. Anesthesiology 1998;88: 619–23.

neurotoxicity, behavioral effects reported in rats receiving 10–100 μg/kg intrathecal morphine did not include evidence of neurotoxicity (27).

Limited postmortem neurohistopathology studies in patients with cancer after long-term, continuous intrathecal infusions containing morphine failed to definitively implicate the drug (with metabisulfite preservative) in any histopathologic abnormalities (28,29). Electrophysiologic study of spinal morphine is limited to examination of somatosensory evoked potentials, which are unchanged despite intense analgesia (30). No clinical abnormalities attributable to intrathecal morphine were reported in these studies.

Spinal meperidine has undergone no published preclinical animal neurotoxicity testing. In humans, spinal meperidine has been reported as an effective sole drug for surgical anesthesia without noted clinical neuropathology, but no formal neurotoxicity testing has been undertaken (31). Spinal hydromorphone has not been safety tested in animals. A single report describes hydromorphone administered spinally with clonidine in a woman with cancer pain without postmortem evidence of abnormal neurohistopathology (32).

Lipophilic Opioids. In its present preservative-free, commercially available form, fentanyl is commonly administered spinally. However, fentanyl is also notably absent from animal safety testing data. Histopathologic studies of isolated rabbit vagus nerve axons bathed in test solution failed to show evidence of localized neural damage with fentanyl dissolved in isotonic solution. Potential electrophysiologic neurotoxicity was reported with the commercially available hypotonic solution of fentanyl, which caused permanent conduction deficits comparable to water alone (33). *In vivo*, only relatively large doses of fentanyl citrate would be expected to create a hypotonic intrathecal environment.

Controlled human safety data are also minimal with spinal fentanyl. There are no published reports specifically addressing the histologic, physiologic, or clinical evidence of neurotoxicity with spinal fentanyl. No report of persistent neurologic complications was retrieved from a MEDLINE search, despite widespread clinical use of spinal fentanyl.

Sufentanil was administered to cats with indwelling intrathecal catheters for 5 days without distinguishable neurohistopathological abnormalities (27). Similarly, dogs exposed to clinically relevant doses of intrathecal sufentanil for several weeks also showed no abnormal histopathology (24). However, sheep exposed to large (approximately 50 μg) and very large (approximately 200 μg) doses of sufentanil every 6 h for 3 days through intrathecal catheters showed evidence of dose-dependent spinal cord histopathology (34). These findings may reflect a neurotoxic effect at large doses or quite possibly an artifact of the experimental design due to the frequent, large-volume, hypotonic preparation used in this study. No studies of spinal cord blood flow, blood-brain barrier effects, or electrophysiology are available. The rats, cats, and

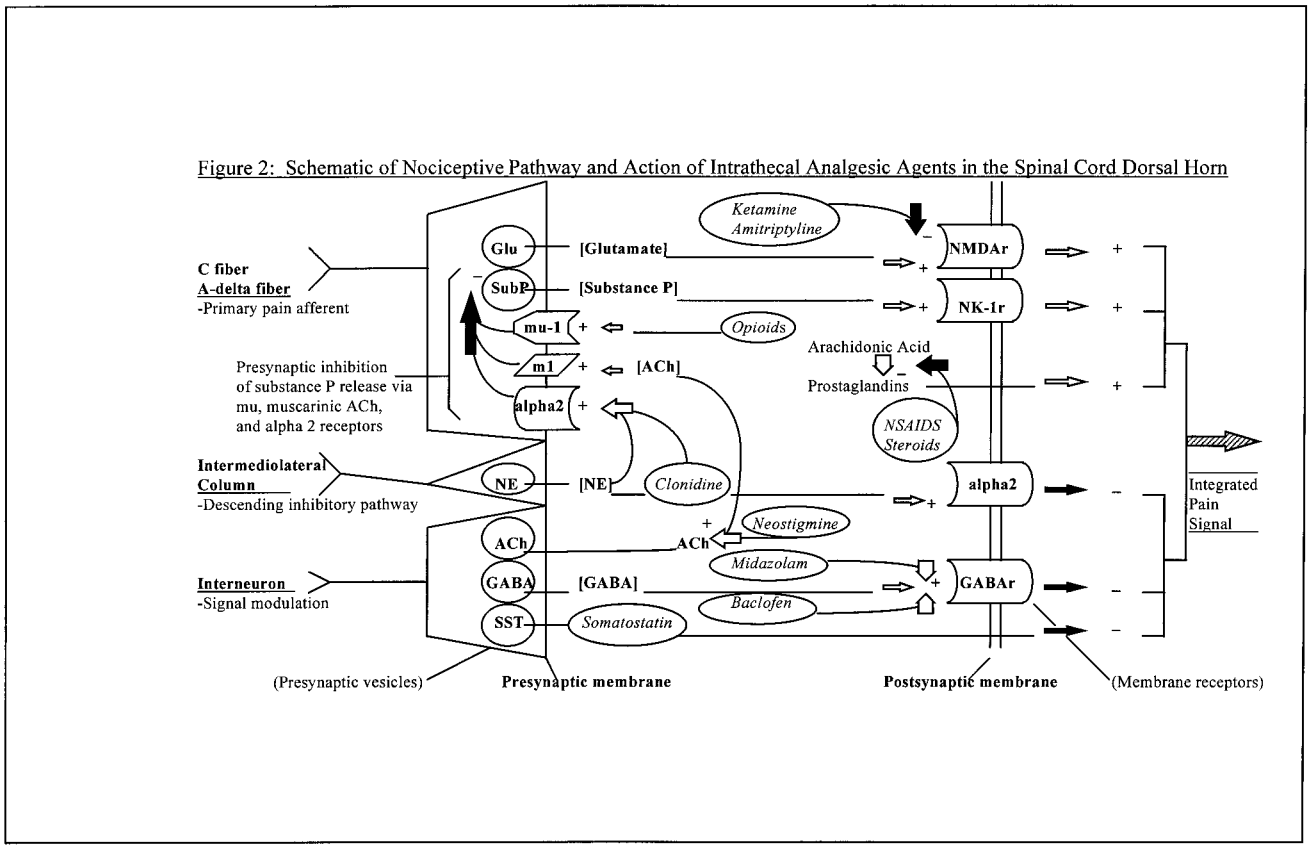

Figure 2. Schematic of mechanisms and sites of actions of spinal analgesics. mu-1 = opioid receptor, m1 = muscarinic type I acetylcholine receptor, ACh = acetylcholine, alpha2 = adrenergic receptor, NE = norepinephrine, GABA = γ-aminobutyric acid, GABAr = GABA receptor, NMDAr = *N*-methyl-D-aspartate receptor, NK-1r = neurokinin 1 receptor, NSAIDS = nonsteroidal antiinflammatory drugs, + and unshaded arrows = activation, − and black arrows = inhibition.

dogs used in the above experiments had no persistent behavioral deficits. The sheep demonstrated dose-dependent agitation and hind-limb motor deficits that resolved spontaneously. There is no formal human neurotoxicity testing of sufentanil, but there are also no clinical reports of neurological impairment from widespread use.

The spinal administration of alfentanil to cats for 5 days and to dogs for several weeks through indwelling intrathecal catheters induced no abnormal histopathology (24). There are no reports of human experience with intrathecal alfentanil. Spinal remifentanil has been studied for efficacy in rats, but no histopathology has been published (35). Rat behavior changes, other than sedation, were not reported, and recovery was not described. There is no published human experience with spinal remifentanil.

Partial Opioid Receptor Agonists. In the sheep experiments with sufentanil noted above, butorphanol given intrathecally as a commercial solution of citrate and tartate salts caused florid histologic and behavioral pathology, whereas nalbuphine in saline was associated with minimal inflammatory histologic changes, mild neuronal changes at large doses, and transient hindlimb weakness (34). No other animal or human data are available.

In summary, laboratory studies and extensive clinical experience with morphine, fentanyl, and sufentanil can reasonably assure the safety of limited intrathecal doses of these drugs. Other opioid agonists or partial agonists are without animal and human safety testing data.

α_2 Receptor Agonists

Clonidine is the predominant spinal α_2-agonist. Extensive preclinical tests in animals produced no neurohistopathologic abnormalities in rats, dogs, sheep, or monkeys. Spinal cord blood flow studies in rats, pigs, and awake sheep reveal perturbations that, on the whole, do not suggest significant decreases under normal clinical circumstances. No behavioral abnormalities suggesting neurotoxicity have been associated with intrathecal clonidine (36).

There has been extensive and graded exposure of humans to spinal clonidine (>968 surgical, obstetrical, and chronic pain patients) with no clinical evidence of neurotoxicity (36). Although no histopathologic or

Table 4. Evidence of Neurotoxicity of Spinal Analgesics

Drug	Animal data			Human data		
	Histologic	Physiologic	Behavioral	Histologic	Physiologic	Clinical
Opioids						
Hydrophilic						
Morphine	−[a]	−	−	−	−	−
Meperidine	NA	NA	NA	NA	NA	NA
Hydromorphone	NA	NA	NA	−[b]	NA	NA
Lipophilic						
Fentanyl	NA	NA	NA	NA	NA	−[c]
Sufentanil	+/−	NA	−	NA	NA	−[d]
Alfentanil	−	NA	−	NA	NA	NA
Remifentanil	NA	NA	NA	NA	NA	NA
Partial agonists						
Butorphanol	+	NA	+	NA	NA	NA
Nalbuphine	+/−	NA	−	NA	NA	NA
α_2-agonists						
Clonidine	−	−	−	−[b]	NA	−
AChE inhibitors						
Neostigmine[e]	−	−	−	NA	NA	−
GABA agonists						
Midazolam	+/−	+	−	NA	NA	−
Baclofen	−	NA	−	NA	NA	−
NMDA antagonists						
Ketamine[f]	+/−	+	+/−	NA	NA	NA
Amitriptyline	−	−	−[g]	NA	NA	NA
Somatostatin	+/−	+	+/−	+/−	NA	NA
NSAIDs						
Ketorolac[h]	NA	NA	NA	NA	NA	NA
Lysine acetylsalicylic acid	+/−	+	+/−	NA	NA	NA
Steroids						
Methylprednisolone[i]	−	NA	−	NA	NA	+/−
Triamcinolone[i]	−	NA	−	NA	NA	+/−

+ = studies support neurotoxicity, − = studies refute neurotoxicity, +/− = studies are inconsistent, NA = no studies available.
AChE = acetylcholinesterase, GABA = γ-amino butyric acid, NMDA = *N*-methyl-D-aspartate, NSAIDs = nonsteroidal antiinflammatory drugs.
[a] Large-dose, high-concentration, long-term spinal morphine may be neurotoxic.
[b] Neurohistopathology performed on a single cancer patient.
[c] Fentanyl safety based on clinical experience, not formal neurotoxicity testing.
[d] Sufentanil associated with transient muscle rigidity with epinephrine; safety based on clinical use only.
[e] Neostigmine formulated with or without methyl- and propylparabens.
[f] Ketamine preserved with benzethonium chloride or chlorbutanol.
[g] Sedation and seizure followed by death in one animal receiving an intrathecal cervical superclinical dose.
[h] Ketorolac contains 10% alcohol solvent.
[i] These depot steroid preparations contain 3% polyethylene glycol and <1% benzyl alcohol.

physiologic studies have been reported, clonidine seems to be a safe spinal drug in humans.

Acetylcholine Esterase Inhibitors

Neostigmine indirectly produces a muscarinic agonist effect by inhibiting acetycholinesterase and has been shown to cause analgesia in animal and human experiments. Neurohistopathological analysis of rats and dogs after long-term intrathecal neostigmine (with and without paraben preservatives) administration reveal no spinal cord toxicity (37,38). Neostigmine does not affect spinal cord blood flow in sheep (37), and there were no behavioral changes suggesting neurotoxicity reported in the above animal studies.

Phase I safety assessments in human volunteers have been performed for both preservative-free (50–750 μg) and paraben-containing hyperbaric preparations (10–100 μg) of spinal neostigmine without clinical evidence of neurotoxicity (40,41). Although the human experience with spinal neostigmine is limited, clinical trials performed thus far have not reported any evidence of neurologic sequelae.

γ-Amino Butyric Acid Agonists

Midazolam. Unlike other benzodiazepines, midazolam is soluble in an aqueous solution when buffered to approximately pH 3.5. At physiologic pH, midazolam becomes lipophilic, facilitating tissue penetration. These characteristics have made midazolam the most extensively studied spinal benzodiazepine. Neurotoxicity studies in animals have yielded conflicting results. Four initial rat studies with intrathecal catheter

Table 5. Comparative Animal and Human Toxicity Data of Common Spinal Adjuvants

	Animal data			Human data		
	Histologic	Physiologic	Behavioral	Histologic	Physiologic	Clinical
Epinephrine	−	−	+/−	NA	NA	−
Phenylephrine	NA	−	−	NA	NA	+
Glucose	−	−	+/−	NA	NA	−
Sodium bisulfite	+	NA	+	−	NA	−
Ethylenediaminetetraacetate	+	NA	+	−	NA	−
Parabens	−	+/−	+/−	NA	NA	NA
Chlorobutanol	NA	NA	+	NA	NA	NA
Benzethonium chloride	NA	NA	−	NA	NA	NA
Glycine	NA	NA	+	NA	NA	NA
Polyethylene glycol	NA	−	NA	NA	NA	NA

+ = studies support neurotoxicity, − = studies refute neurotoxicity, +/− = studies are inconsistent, NA = no studies available.

implantation using 0.15 mg/kg for 15 days (two studies) or isolated exposures to 0.1–0.3 mg/kg of midazolam (two studies) prepared in saline solution showed no neurotoxic reactions on light or electron microscopy (42). However, a subsequent study in rabbits after a single 0.1 mg/kg intrathecal injection of midazolam reported that three of nine animals (33%) showed spinal cord histopathologic changes 8 days after exposure (43). The diffuse nature of the histopathologic abnormalities that uncharacteristically extended from cervical to lumbar sections, the presence of significant and persistent diastolic hypotension in the treatment group, and the delayed postmortem tissue fixation all suggest a possible systemic source of artifact in the three affected animals. To investigate these contrasting results, a state-of-the-art study on the rat was performed using light microscopy, electron microscopy, cell morphometry, and transcardial tissue fixation after daily intrathecal administration of approximately 0.3 mg/kg midazolam for 20 days (44). The spinal cords showed strong evidence of neuronal death and cellular abnormalities, even on light microscopy, in most midazolam-treated rats. Of note, a hypotonic commercial preparation of midazolam was used in contrast to the isotonic saline preparation used in all previous reports. Hypotonicity results in permanent nerve injury in isolated nerve preparations (33) and has been implicated in the neurotoxicity of spinal sufentanil in sheep (45). Although hypotonicity may be the etiology of the reported abnormalities, intrinsic neurotoxicity of spinal midazolam is a consideration.

No animal studies on spinal cord blood flow or electrophysiology have been reported. The effect of midazolam on blood-brain barrier integrity was investigated in the above-described study on rabbits and showed compromise in three of nine animals (43). Despite some histopathologic evidence of neurotoxicity, no significant behavioral abnormalities have been reported in any of the animal neurotoxicity studies of intrathecal midazolam.

There are no histologic or physiologic studies of humans exposed to spinal midazolam, although there are seven small reports of intrathecal midazolam for anesthesia and pain management. Within this limited human experience, there are no reports of clinical neurologic deficit, even after prolonged continuous intrathecal use in four patients with chronic benign pain syndromes (46).

Midazolam neurotoxicity is controversial. Although the commercial midazolam solution seems to be neurotoxic in rats, hypotonicity of the solution may be culpable, rather than the drug itself. Midazolam in saline does not seems to be neurotoxic in the rat, but it may be toxic in the rabbit. There are insufficient studies in humans to determine the risk of neurotoxicity with spinal midazolam.

Baclofen

Spinal spasticity, which is thought to result from disinhibition of motor horn cells after upper motor neuron damage, can be treated with baclofen. Baclofen is a stable analog of GABA and interacts primarily with the inhibitory GABA-B receptors in lamina 2 of the dorsal horn (Figure 1). Twenty-eight dogs exposed to chronic spinal delivery of either saline, clinical, or supraclinical doses of baclofen showed no neurohistopathologic changes. Cats exposed to intrathecal baclofen for 8 days likewise showed no abnormal spinal cord histopathology (47). No studies on spinal cord blood flow, blood-brain barrier effects, or electrophysiology have been published with regards to intrathecal baclofen. Neither dogs, cats, nor monkeys showed behavioral evidence of neurotoxicity (25).

There are no published human studies evaluating histopathologic or physiologic neurotoxicity of baclofen. Spinal baclofen was infused in seven subjects for 3–22 mo without clinical evidence of neurotoxicity (48). An extensive review of cases involving intrathecal baclofen overdose did not note any long-term sequelae (49). Based on animal studies and considerable

clinical experience, spinal baclofen is not likely to cause neurologic damage.

N-Methyl-D-Aspartate Antagonists

Ketamine. Animal studies examining the neurotoxicity of ketamine generally support its safety, with the exception of some poorly explained findings. Studies performed in monkeys, baboons, and rabbits after single-dose intrathecal ketamine injections (0.3–0.6 mg/kg) with and without benzethonium chloride preservative did not uncover histopathologic evidence of neurotoxicity (50,51). In contrast, two other rat studies reported histopathologic evidence of neurotoxicity with spinal ketamine. One study found vacuolization of the ganglion cells in posterior nerve roots in 3 of 33 rats that died immediately on injection of preservative-free ketamine (52). However, it is difficult to ascribe these findings to ketamine neurotoxicity given the uncertain circumstances of demise. Similarly, another rat study with single intrathecal injections of 2.5 mg of ketamine hydrochloride with the preservative benzethonium chloride reported that two of six rats had radicular demyelination injury at sites distant from the injections on histological examination (53). However, more than half of the animals in the ketamine treatment group either died after rapid injection (two rats) or had single hindlimb paralysis after injection (four rats), which puts the validity of the results in question.

No animal studies have been published on the effect of spinal ketamine on spinal cord blood flow or electrophysiology. Rabbits showed a pattern of blood-brain barrier compromise differing significantly from that of saline-injected control rabbits after single 3-mg injections of ketamine with chlorbutanol (43) but not with preservative-free ketamine (50).

The neurotoxicity of spinal ketamine is largely untested in humans, despite a few case series reporting ketamine use for spinal anesthesia and analgesia (54). Taken together, the rat, rabbit, and primate studies with intrathecal ketamine support its safety if used without a preservative. A small preliminary human experience suggests that the anesthetic is well tolerated. However, the commercially available preparation of ketamine contains an untested preservative (benzethonium chloride) and cannot be recommended for intrathecal use in humans.

Amitriptyline. Preclinical animal testing of intrathecal amitriptyline is limited to a physiologic assessment in adult sheep (55). A range of intrathecal doses (0.25, 1, or 5 mg) with a maximal dose representing approximately 25–50 times the anticipated human dose did not reduce spinal cord blood flow. No behavioral abnormalities were reported except for transient agitation with the injection of 5 mg of amitriptyline. The injection of 5 mg of amitriptyline into the cervical intrathecal space sedated the animals for 10–60 min, whereas 10 mg produced intense sedation and seizure, followed by death from uncertain causes in one animal. Long-term exposure and neurohistopathologic studies are reported to be in progress (55). The determination of amitriptyline neurotoxicity awaits further investigation.

Somatostatin

In rats, intrathecal somatostatin (SST) produced marked, dose-dependent neurotoxic responses at or near doses required to produce analgesia (56) with similar findings in cats and mice (57). SST administered in similar doses to guinea pigs, in contrast, did not provoke significant neurohistopathological changes (58). Spinal SST in rats had significant vasoconstrictive effects in the spinal cord and brain, leading to reduced blood flow, increased vascular permeability, and compromised blood-brain barrier (59). No spinal cord blood flow changes were seen in the guinea pig. Significant behavioral changes were noted in the rat, cat, and mouse experiments, but not in the guinea pig experiments. Species differences in the neurotoxic susceptibility to SST may explain these differences, but there is evidence for neurotoxicity in several animal species.

In humans, spinal SST has been offered to terminally ill patients. Four patients with intractable cancer pain were studied after daily injections of spinal SST. Postmortem histopathology was undertaken on the spinal cords of two patients. One showed moderate degeneration of some dorsal roots within the cauda equina, whereas the other demonstrated no histopathologic changes. Clinical signs of neurotoxicity were not discussed (60).

In summary, SST has been shown to be neurotoxic in rats, mice, and cats at doses comparable to those that confer analgesia. In humans, relatively small doses of SST have been anecdotally reported to variably relieve pain in the absence of overt neurologic sequelae. Based on this demonstrated record of neurotoxicity in several animal species, spinal SST should be considered a last-line analgesic only in the terminally ill patient.

Nonsteroidal Antiinflammatory Drugs

Prostaglandins are involved in the spinal cord facilitation of pain processing, and spinal nonsteroidal antiinflammatory drugs (NSAIDs) can abolish wind-up behavior in animals (61). Although the analgesic efficacy of spinal ketorolac has been established, no animal neurotoxicity studies have been published (61). However, the 10% alcohol solvent used for commercial preparations is potentially neurotoxic, and commercial ketorolac should not be used spinally.

Lysine acetylsalicylic acid (L-ASA) dosed intrathecally has been shown to be antinociceptive and has

been tested in the rat for neurotoxicity with conflicting results. Although limited technically by a >50% spinal cord trauma rate related to needle puncture, one rat study reported radicular demyelination injury in one of the seven undamaged rats (14%) who received intrathecal L-ASA (53). In contrast, neither histopathologic abnormalities nor a persistent decrease in spinal cord blood flow were seen in another rat study with large daily doses of L-ASA for at least 14 days (62). The initial study described aggressive behavioral changes in rats after the spinal injection of L-ASA, leading to death from combat. The subsequent study did not report behavioral findings. Although the second report supports the safety of intrathecal L-ASA, the single instance of radicular demyelination, and especially the behavioral disturbances noted in the earlier study, are disturbing and require clarification.

In summary, there is insufficient evidence for safety of spinal administration of NSAIDs in either animals or humans.

Steroids

Corticosteroids affect spinal cord pain processing, in part by interfering with the formation of inflammatory mediators (Figure 2). A recent study with chronic intrathecal administration of triamcinalone and methylpredisolone in rats did not detect histologic or behavioral signs of neurotoxicity (63). Corticosteroids are commonly administered epidurally in humans as depot steroids, which implies a finite risk of intrathecal injection, and depot steroids saw intentional intrathecal use before an international controversy regarding the safety of this practice. A recent literature review emphasizes the lack of objective evidence that intrathecal methylprednisolone, administered at widely spaced intervals, causes clinically significant lumbar arachnoiditis (64). In contrast, there are numerous anecdotal claims that suggest that intrathecal methylpredisolone is the cause of arachnoiditis and prolonged neurologic sequelae in humans. Currently available preparations of methylprednisolone and triamcinolone contain polyethylene glycol and benzyl alcohol (see Spinal Adjuvants).

Even in the absence of concrete evidence of neurotoxicity, it seems prudent that steroids not be administered intrathecally to humans until the current controversy is resolved. However, should a "wet tap" occur during epidural needle placement for intended epidural steroid injection, replacing the epidural needle at an adjoining interspace and injecting a standard dose of steroid epidurally, especially using the common 1:10 dilution of depot steroids (and, thereby, their preservatives) in saline or local anesthetic solutions, would seem highly unlikely to endanger the patient.

Spinal Adjuvants

Spinal drugs are commonly combined with vasoactive additives to prolong duration, and/or with glucose to adjust baricity, or possibly formulated with an antioxidant, preservative, or excipient. Despite the widespread use of adjuvants, there is little controlled, prospective research attesting to their safety.

Epinephrine

Epinephrine is often used to prolong spinal anesthesia and to increase block intensity. Three areas of concern surround possible epinephrine-induced spinal cord toxicity: direct tissue toxicity, reduced spinal cord blood flow secondary to vasoconstriction, and pH effects.

In animals, two studies have unsuccessfully sought histopathologic evidence of epinephrine-induced spinal cord injury. Single injections of epinephrine in doses of 0.3–0.75 mg caused rabbits to convulse, then fully recover. After the animals were killed, spinal cord cellular changes were not different from those observed after tetracaine or saline injection (65). Multidose, long-term intrathecal epinephrine in rats caused no clinical signs of neurologic injury, nor were mild histopathologic changes different from those in the saline control group (66).

How epinephrine affects spinal cord blood flow is controversial. Clinically relevant doses of intrathecal epinephrine alone do not adversely affect spinal cord blood flow in dogs, but they do significantly reduce dural blood flow (67), which may explain epinephrine's ability to prolong the duration of some local anesthetics. When administered along with spinal lidocaine, tetracaine, or mepivacaine, epinephrine tends to prevent the increase in spinal cord blood flow seen with these local anesthetics, thereby resulting in no net change in spinal cord blood flow (7).

Whereas the spinal administration of epinephrine alone or in combination with local anesthetics does not seem to reduce spinal cord blood flow or cause neurotoxicity, some peripheral nerve studies reveal different results. In rats, for instance, epinephrine alone produces dose-dependent reductions in peripheral nerve blood flow. More worrisome, epinephrine plus 2% lidocaine synergistically decreases peripheral nerve blood flow by 60% (68). These results may imply that spinal nerves compromised by disease or hypotension are at higher risk from a combination of epinephrine and lidocaine than from either drug alone. However, the applicability of animal peripheral nerve studies to human spinal cord pathophysiology is unclear.

Premixed local anesthetic/epinephrine solutions intended for epidural use are formulated with a low pH (approximately 4.5) to prolong shelf-life. Adding fresh

epinephrine to 20 mL of epidural local anesthetic solutions does not significantly change pH (69). Epinephrine added to spinal anesthetic mixtures may constitute up to 20% of their volume, but it is unclear how pH is affected. Regardless, various epinephrine concentrations added to 1 mL of 7.5% dextrose in water (pH 2.60–3.29) do not significantly affect spinal cord blood flow (70).

No human clinical or postmortem studies specifically address the issue of epinephrine-induced spinal cord toxicity. Although a recent editorial has questioned the continued use of epinephrine with lidocaine spinal anesthesia (71), large-scale prospective (14) and retrospective (11) clinical surveys have not suggested a link between neurologic complications and intrathecal epinephrine. For example, in Dripps and Vandam's (13) report of patients with minor neurologic sequelae after lumbar puncture, only 5 of 17 received epinephrine. Similarly, 16.6% of spinal anesthetics in Horlocker et al.'s (11) review contained epinephrine, but none of six patients with neurologic complications received it. The absence of scientific rigor limits conclusions drawn from these and similar surveys; nevertheless, their large patient numbers suggest that spinal epinephrine is extremely safe.

In summary, there is no animal or human evidence documenting epinephrine-induced neurotoxicity.

Phenylephrine

No animal studies address direct spinal cord histopathology secondary to phenylephrine. Instead, as with epinephrine, most studies are concerned with the possibility of spinal cord ischemia consequent to phenylephrine-induced vasoconstriction. Phenylephrine either does not reduce spinal cord blood flow in dogs (67) or reduces it to a clinically insignificant extent (72). It does cause dural vasoconstriction (67), which suggests a mechanism for prolonging local anesthetic duration. Rhesus monkeys given intrathecal lidocaine and phenylephrine show no clinical or behavioral signs of neurotoxicity (73).

In humans, phenylephrine was used as an adjuvant to tetracaine in 16.5% of 11,574 spinal anesthetics reported by Moore and Bridenbaugh (74) but was not specifically implicated in any postoperative complications. Transient leg and buttock pain after tetracaine spinal anesthesia was reported to occur more frequently when phenylephrine was added, although it is unclear whether this represents neurologic injury (75).

Although poorly studied, there are no animal data to suggest that phenylephrine is neurotoxic or that it significantly reduces spinal cord blood flow in animals. However, human data suggest that it may increase the risk of transient neurologic symptoms after tetracaine spinal anesthesia.

Glucose

Glucose is added to many spinal anesthetics to increase baricity. Sacral pooling of microcatheter-delivered hyperbaric spinal anesthetics may be associated with the cauda equina syndrome (76). A further concern is that glucose causes marked hypersmolarity, which may itself be neurotoxic. Animal and human studies have largely exonerated glucose as a major contributor to neural injury. Histologic spinal cord examination in rats and sheep exposed to intrathecal 5% glucose with neostigmine failed to demonstrate neuronal damage (38). However, studies in diabetic rats do raise the possibility that altered glucose metabolism may contribute to local anesthetic-induced nerve damage (77). Glucose 7.5% does not cause sensory impairment after 5% lidocaine in the rat (78), nor does it affect the compound action potential in desheathed bullfrog nerves (5). Several human studies have indirectly considered the role of glucose in the development of transient neurologic symptoms after spinal anesthesia, but none has implicated it as a causative substance (75). Thus, most animal and human studies attest to the safety of spinally administered glucose in concentrations $\leq$7.5%.

Antioxidants, Preservatives, and Excipients

Many drugs intended for epidural use (such as steroids, opioids, and 2-chloroprocaine) contain antioxidants or preservatives or are formulated with vehicles known as excipients. Problems can arise when these drugs are unintentionally deposited in the subarachnoid space. Furthermore, some preservative-containing drugs, such as morphine, are chronically infused into the subarachnoid space of cancer patients, where adjuvants could conceivably cause neural injury.

Antioxidants. Antioxidants are added to local anesthetics to prolong shelf-life. Sodium bisulfite gained notoriety in the early 1980s when it was associated with neural deficits after the unintentional subarachnoid injection of 2-chloroprocaine. Sodium bisulfite alone is toxic in several animal models; however, the combination of sodium bisulfite 0.2% and low pH was ultimately implicated as causing neurotoxicity (79).

Largely in response to concerns over sodium bisulfite, disodium ethylenediaminetetraacetate (EDTA) was introduced as an antioxidant/chelator for 2-chloroprocaine preparations. In a rat model, EDTA ($\geq$1.5 mM) causes behavioral and histologic evidence of neural injury, which is preventable by pretreatment with $CaCl_2$ (80). Chloroprocaine containing EDTA has been associated with transient, severe back pain after epidural administration (81). This phenomenon should be distinguished from the neural injury seen with unintentional intrathecal dosing of chloroprocaine with sodium bisulfite described above and does not imply neurotoxicity.

The postmortem examination of patients receiving long-term spinal infusions of preservative-containing morphine contributes to our knowledge of the neurotoxic potential of antioxidants in humans (29). These patients received cumulative doses of sodium metabisulfite 3–1050 mg and up to 105 mg of EDTA over 3–275 days, in concentrations 5–240 times lower than those associated with neurotoxicity in animal models. The authors attributed no new clinical or neuropathologic deficits to the intrathecal administration of these antioxidants. However, care must be taken when interpreting such uncontrolled data, especially because many of the lesions attributed to tumor invasion, chemotherapeutic drugs, or radiation have also been observed in animal models of EDTA toxicity (80).

Preservatives. Preservatives are often added to local anesthetic and opioid preparations dispensed in multidose containers, and they are less commonly added to drugs intended for single use. High-concentration methylparaben (up to 0.1%) caused suppression of compound action potentials in rabbit vagus nerve, but the animals recovered completely after washout. On subsequent section and electron microscopy, there was no evidence of histopathologic changes (82). Similarly, sheep and rats exposed to paraben-containing intrathecal neostigmine show no evidence of neural damage on histologic examination (38). Small-scale human volunteer studies have not reported behavioral evidence for toxicity with spinal administration of paraben-containing solutions of neostigmine (41). These findings suggest that parabens are safe when administered spinally in the small doses associated with preservative use.

Ketamine has been formulated with one of two preservatives: chlorobutanol or benzethonium chloride. Commonly available preparations include the latter. Spinal chlorobutanol has been shown to be toxic in rabbits (43), whereas intrathecal benzethonium chloride causes no neurohistologic changes in baboons (50). There are no formal human studies examining these preservatives.

Benzyl alcohol is a common antibacterial substance found notably in depot steroid preparations at $\leq$1% concentration. It is common practice to dilute depot steroids 1:10 before epidural injection. However, alcohols are neurotoxic at sufficient concentrations, and proper safety studies should precede their intrathecal use as preservatives in humans.

Excipients. Excipients are used as vehicles in the preparation of some pharmaceuticals. Remifentanil is formulated with a glycine excipient. This combination is associated with dose-dependent, reversible motor impairment when administered spinally to rats via a continuous infusion. The mechanism of action is undefined, and there are no human studies (35).

Polyethylene glycol (PEG) is used as an excipient for depot steroid preparations. Methylprednisolone and triamcinolone preparations usually contain 3% PEG. Concerns have been raised over potential neurotoxicity if commercial preparations containing 3% PEG were injected intrathecally in humans. Experiments with rabbit sheathed and desheathed nerve preparations revealed no significant neurolysis or slowed conduction velocities in concentrations up to 40%. Histopathologic studies of the nerve preparations were not performed, and there are no human neurotoxicology studies (83).

Thus, despite concerns with past preparations, most antioxidants, preservatives, and excipients seem to be safe for human use. Nevertheless, a note of caution seems appropriate, as antioxidants, preservatives, and excipients are the least well studied of all spinal adjuvants.

Summary

Overall, most spinal drugs in clinical use have been poorly studied for spinal cord and nerve root toxicity. Laboratory studies indicate that all local anesthetics are neurotoxic in high concentrations and that lidocaine and tetracaine have neurotoxic potential in clinically used concentrations. However, spinal anesthesia (including lidocaine and tetracaine) has a long and enviable history of safety. Spinal analgesics such as morphine, fentanyl, sufentanil, clonidine, and neostigmine seem to have a low potential for neurotoxicity based on laboratory and extensive clinical use. Most antioxidants, preservatives, and excipients used in commercial formulations seem to have a low potential for neurotoxicity. In addition to summarizing current information, we hope that this review stimulates future research on spinal drugs to follow a systematic approach to determining potential neurotoxicity. Such an approach would examine histologic, physiologic, and behavioral testing in several species, followed by cautious histologic, physiologic, and clinical testing in human volunteers and patients with terminal cancer refractory to conventional therapy.

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