Future Considerations for Pharmacologic Adjuvants in Single-Injection Peripheral Nerve Blocks for Patients With Diabetes Mellitus

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Abstract: As the epidemics of obesity and diabetes expand, there are more patients with these disorders requiring elective surgery. For surgery on the extremities, peripheral nerve blocks have become a highly favorable anesthetic option when compared with general anesthesia. Peripheral blocks reduce respiratory and cardiac stresses, while potentially mitigating untreated peripheral pain that can foster physiologic conditions that increase risks for general health complications. However, local anesthetics are generally accepted to be a rare but possible cause of nerve damage, and there are no evidence-based recommendations for dosing local anesthetic nerve blocks in patients with diabetes. This is important because anesthesiologists do not want to potentially accelerate peripheral nerve dysfunction in diabetic patients at risk. This translational vignette (i) examines laboratory models of diabetes, (ii) summarizes the pharmacology of perineural adjuvants (epinephrine, clonidine, buprenorphine, midazolam, tramadol, and dexamethasone), and (iii) identifies areas that warrant further research to determine viability of monotherapy or combination therapy for peripheral nerve analgesia in diabetic patients. Conceivably, future translational research regarding peripheral nerve blocks in diabetic patients may logically include study of nontoxic injectable analgesic adjuvants, in combination, to provide desired analgesia, while possibly avoiding peripheral nerve toxicity that diabetic animal models have exhibited when exposed to traditional local anesthetics.

(*Reg Anesth Pain Med* 2009;34: 445–457)

The underlying mechanisms of insulin resistance in obesity,[1] anesthesia care considerations for patients with diabetes mellitus and/or metabolic syndrome,[2] and chronic pain in the setting of diabetes[3,4] have all recently been reviewed. Interestingly, little has been written regarding the implications of diabetes for peripheral nerve blocks used for surgical anesthesia-analgesia. Nonetheless, increases in the incidence and prevalence of diabetes and metabolic syndrome mean that specialists in regional anesthesia need to reevaluate and potentially improve anesthesia care for diabetic patients undergoing surgery on the extremities. In a recent editorial,[5] a call was issued for a shift in peripheral nerve block research to address (i) the specific perineural pathophysiology associated with hyperglycemia and diabetes mellitus and (ii) the effects of local anesthetics, perineural analgesic adjuvants, and their potential combinations. This editorial[5] also introduced some basic science concepts regarding research models in diabetic neuropathy that may be potentially relevant for creating a model related to peripheral nerve blocks. The editorial was authored in response to a recent publication detailing altered perineural stimulation responses in a dog model with streptozotocin (STZ)–induced hyperglycemia.[6] It is clear that the specific details of research models in diabetic neuropathy are critically relevant for selecting bench science methods that best model peripheral nerve blocks.[5] This translational vignette will first review recent developments in laboratory models of diabetes then discuss the clinical challenges associated with peripheral nerve blocks in diabetic patients, followed by a literature summary (Table 1) regarding the use of adjuvants in peripheral nerve blocks in (heretofore) nondiabetic patients. It will conclude with recommendations for future research.

EVOLVING MODELS OF DIABETES AND POTENTIAL APPLICATIONS

An ''Ideal'' Animal Model for Diabetic Neuropathy

At present, there is no consensus regarding diabetic animal models that best replicate the human condition, neither for endocrinology-metabolism considerations nor for the development of neuropathy. The aforementioned editorial[5] described type 2 diabetes in primates (rhesus monkeys[7]) that are overfed for a protracted period. It seems unlikely that this model will be cost-effective in addressing diabetic polyneuropathy and peripheral nerve blockade.

Diabetic rat strains include BB/W and Zucker diabetic fatty rats[8,9]; there are also nonobese diabetic mouse models that bear the phenotype of severe combined immunodeficiency. These nonobese diabetic/severe combined immunodeficiency animals[10] are derived by selective breeding. As a result of inbreeding, some of these strains have particular characteristics, independent of diabetes, that may complicate implementation as a model of human diabetes.

As noted, there are diabetes-induction models that entail treating normal animals with the pancreatic beta cell toxin, STZ. The effect of STZ is quite rapid, and the potential for preparing littermate animals in a parallel study (ie, treated vs vehicle control) represents significant advantages in experimental design. A wide range of species have been induced diabetic with STZ.[11,12] A disadvantage of STZ is hepatotoxicity and/or nephrotoxicity at higher doses.[13] Importantly, STZ-animal models develop peripheral neuropathy, as demonstrated recently in dogs by Rigaud et al,[6] as well as in the classic rat study by Kalichman

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Accepted for publication November 4, 2008.
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Dr. Williams is supported by departmental sources and by National Institutes of Health grant 1K01DA025146. Dr. Murinson is supported by departmental sources and by National Institutes of Health grant 5K08NS48146. Drs. Grable and Orebaugh are supported by departmental sources.
Reprints will not be available from the authors.

ISSN: 1098-7339
DOI: 10.1097/AAP.0b013e3181ac9e42

TABLE 1. Perineural Multimodal Analgesics, Potential Application for Surgical Anesthesia/Postoperative Analgesia in the Context of Diabetes

Agent	Perineural Clinical Efficacy and Perineural (or Other Neural) Histotoxicology Studies	Potential Value as Perineural Monotherapy or in Combination Therapy With Other Perineural Multimodal Analgesics Listed, and/or Local Anesthetics, Within and Outside the Context of Diabetes	Comment
Epinephrine	Clinically efficacious (prolonging block duration of many local anesthetics); neurotoxicology studies[35]	Traditional agent in nondiabetic contexts Likely should be avoided in diabetes because of microvascular compromise seen in spinal cord in both chronic[36] and early-stage[37] diabetes Endoneurial blood flow is most compromised in the setting of DPN; little apparent perineural benefit and possible detriment in the use of epinephrine in the peripheral nerve blocks of diabetic patients; study in diabetic animal contexts warranted to determine if "test dose" epinephrine poses additional risks to the diabetic nerve; study of multimodal analgesic prolongation is also warranted in nondiabetic contexts, based on effects of buprenorphine combination with epinephrine, mepivacaine, and tetracaine[52,53]	Reviewed extensively as perineural and neuraxial adjuvant[35]
Clonidine	Clinically efficacious: for local anesthetics with the duration of ropivacaine and shorter[38,39,42,43]; prolongs ropivacaine block duration by 25% (ie, from 13 to 16 hrs)[44] Neurotoxicology: well-accepted safety profile epidurally[47] and intrathecally[48] Perineural toxicology: only indirectly studied[49]	Anti-inflammatory properties mediated by α2 agonism (when coadministered with local anesthetics[49]) may theoretically protect the diabetic nerve Research is needed to see if clonidine would offset macrophage-mediated[113] or lymphocyte-mediated[114] inflammation in DPN; the overall safety profile of perineural clonidine to date, along with its antileukocyte effects, may make clonidine a clinically useful adjuvant to local anesthetics in diabetic patients, in an effort to attenuate any inflammatory components of neuropathic conditions; no value as perineural analgesia monotherapy in nondiabetic patients[45] Is used systemically in diabetic patients who are afflicted with cardiac autonomic neuropathy[40]; analgesic efficacy of transdermal clonidine in selected (advanced) diabetic neuropathy patients (ie, sharp or shooting pain) does not seem to be related to changes in sympathetic outflow and/or related to the a2 receptor[50] Case report of analgesia with no motor block (in nondiabetic patients) with perineural clonidine-buprenorphine via sciatic catheter[46]	Analgesic properties mediated by inhibiting I_h cation channel (and not by α2 agonism), enhancing activity-dependent hyperpolarization[41] Further animal research is needed, no clinical reports

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TABLE 1. *(Continued)*

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Dexmedetomidine	No studies of clinical efficacy; perineural toxicology: reported safe at supratherapeutic dose in rat[51]	Warrants consideration similar to clonidine; anti-inflammatory properties in combination with bupivacaine in nondiabetic rat[51] likely mediated by α - 2 agonism Animal research is needed regarding perineural monotherapy or combination with other perineural analgesics	Further animal research is needed, no clinical reports
Buprenorphine	Perineural clinical efficacy[52,53] In nondiabetic patients, prolongs mepivacaine-tetracaine-epinephrine brachial plexus nerve block by 3-fold (from 5–6 hrs to 17–22 hrs)[52,53]; other CNS clinical reports of buprenorphine use: intrathecally[56–62] and epidurally[63–66] No apparent neurotoxicology tissue studies	Is rational to evaluate in diabetic patients and diabetic animals: buprenorphine is metabolized and excreted by the liver (and not the kidney, which is at risk for diabetes-induced end-organ damage)[49] Commonly used in systemic preparations for chronic neuropathic pain,[67] but not specifically documented as such in diabetes Lead author, B.A.W., has used buprenorphine for >6 y, including combinations with clonidine and local anesthetics; anecdotally, it has prolonged analgesia after bupivacaine, levobupivacaine, and ropivacaine blocks, consistent with Candido et al[52,53] reports with mepivacaine-tetracaine-epinephrine Case report of analgesia with no motor block (in nondiabetic patients) with perineural clonidine-buprenorphine via sciatic catheter[46] No published studies of perineural buprenorphine monotherapy; likely limited value as monotherapy due to adverse effects (nausea, pruritis, respiratory depression, etc) in higher doses	Partial μ-opioid receptor agonist and KOR antagonist; uncertain if κ-antagonism is relevant perineurally; STZ-diabetic rats have increased KOR density at the sciatic nerve (compared with nondiabetic rats); analgesic effects of KOR agonism may lead to a novel therapeutic mechanism[115]
Midazolam	Clinical efficacy—studies are limited[68]: midazolam treatment group (n = 20) had faster nerve block onset, longer duration Perineural toxicology: none reported Other neurotoxicology—controversial: 1100 patients received intrathecal midazolam, and no patient complaints[71] Intrathecal midazolam safety (manifesting as no histopathologic changes) reported in a sheep model[72]	Intrathecal efficacy of midazolam via expression of GABA-A receptors in the spinal cord; intrathecal midazolam (coadministered with low-dose bupivacaine) has been used in diabetic patients undergoing foot debridement procedures, with reduced postoperative pain and opioid requirements[70] Intraperitoneal midazolam administration in STZ rat leads to significant reduction in hyperglycemia and hyperlipidemia[69] GABA-A receptor has been implicated as relevant to the pathophysiology of diabetic neuropathy; in STZ rat, exogenous tetrahydroprogesterone interacts with the GABA-A receptor and seems to provide peripheral neuroprotection with respect to nerve conduction	Perineural studies with systemic controls are needed Unknown potential value as perineural monotherapy.

		velocity, thermal nociceptive thresholds, and intraepidermal nerve fiber density[100] GABA-A receptors in the periphery at the temporomandibular joint space in (nondiabetic) rat,[116] in sensory axons of normal and regenerating rat peripheral nerves,[117] and in axons of mammalian peripheral nerve trunks.[118]	
	Rat spinal cord neuronal death (electron microscopy)[73] Intracisternal injection of midazolam in rabbit showed cord pathology (greater than lidocaine or saline) by light microscopy and changes in the blood-brain barrier[74] Rabbit spinal cord lesions (vascular and histopathologic) after midazolam with and without preservative[75] Neonatal rabbit spinal cord lesions after epidural injections of commercially available (acidic) midazolam and saline, while normal pH saline did not cause changes[76]		
Tramadol	Perineural efficacy: in nondiabetic patients, efficacious when combined with mepivacaine[82,83] but not levobupivacaine[81] No difference with sufentanil or clonidine adjuvants when combined with ropivacaine[84]; no effect during perineural coadministration of tramadol (1.5 mg/kg) with prilocaine 1.5% (40 mL) for brachial plexus block; prilocaine with clonidine (1.5 μg/kg) had longer duration motor-sensory block[85] Other CNS efficacy: in clinical contexts of regional anesthesia and analgesia, tramadol was not efficacious intrathecally in transurethral prostate surgery[80]; perineural histotoxicology: indirect study only; in rat, it produces reversible blockade, with no effect on somatosensory potentials at 48 hrs[78]; nerves not examined microscopically	Allergic reactions may be of concern: rash may be problematic[102]; may be focally antibacterial[119] Rat models have shown that tramadol enhances insulin sensitivity[120]; in diabetic patients, its systemic use is likely limited as monotherapy because adverse effects commonly prohibit long-term use[40]; study needed to determine if also true with perineural use	Stimulates serotonin release intrathecally and inhibits norepinephrine reuptake; weak μ-agonist; in vitro, blocks voltage-gated sodium channels[77]; this effect is not opioid receptor related[78] Blocks sodium channels similar to lidocaine, while blocking potassium channels more potently than does lidocaine[79] No injectable form available in North America
Dexamethasone	Limited efficacy study (when coadministered with aqueous local anesthetic)[91] Lidocaine axillary nerve block duration increased 2.4-fold (98–130 mins with plain lidocaine vs 242–310 mins with dexamethasone 8 mg added, for sensory-motor blocks, respectively)[86]; however, underpowered, no systemic control, and dexamethasone preparation not disclosed Two other nerve block studies in which dexamethasone was used but not part of the specific aim[90] or was used in nonstandardized local anesthetic mixtures[89]	Warrants extensive study in nondiabetic patients In nondiabetic patients, unknown value as monotherapy, likely promising when coadministered with local anesthetics; likely no role in the perineural treatment of diabetic patients; in nondiabetic patients, other corticosteroids (specifically methylprednisolone) specifically inhibit C-fiber transmission[103] Although anti-inflammatory properties seem intuitively to be desirable, the effects of perineural dexamethasone on supporting cells (eg, Schwann cells) require proper evaluation before healthy patients would consent to appropriate prospective clinical study	Perineural dexamethasone requires proper neurotoxicology testing in vitro and in an animal model in vivo of peripheral nerve (both nondiabetic and diabetic animals), both as monotherapy and in combination therapy; routine neuraxial use clinically awaits further studies on its safety and efficacy[104] Dose-finding studies are desperately needed for nondiabetic patients; even then, it seems unlikely that dexamethasone would achieve a place in perineural therapy for diabetic patients

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TABLE 1. *(Continued)*

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	Several studies involving dexamethasone added to free base bupivacaine microspheres[91–95] Neurotoxicology: dexamethasone causes minimal peripheral nerve damage when compared with hydrocortisone or triamcinolone[96] Temporarily decreases perineural blood flow, but with no ensuing neuropathology[97] Intrathecally, continuous dexamethasone (rat) showed low doses to be safe, but higher doses to be associated with increased infection risk and focal meningeal necrosis[97]	One clinical use in diabetic patients has been reported, called *retrograde venous perfusion*; dexamethasone 4 mg is combined with antibiotics, buflomedil, and heparin in normal saline, and this mixture is injected into a dorsal foot vein in an effort to treat diabetic foot ulcers in patients with neuropathy; this practice, although apparently successful in treating stated foot ulcers,[121] does not necessarily seem to be a part of mainstream diabetic foot care practice	

CNS indicates central nervous system.

and Calcutt[14]; this latter study reported that sciatic nerve blocks with procaine and lidocaine lead to nerve injury in this model.

Streptozotocin diabetes-induction models, despite limitations, are still in widespread use. Inducing diabetes in the rat with STZ has been a generally accepted method of studying diabetic neuropathy in rodent models,[15] but this model of inducing short-term hyperglycemia and STZ-induced neuropathy, along with STZ-induced behavioral changes, has been criticized. This is because in association with the risks of other end-organ toxicity with STZ, STZ can induce altered mental status and produce other systemic effects in treated animals, making interpretation of nociceptive testing difficult. In either case, since 1992,[14] no dose-response curves for nerve block safety with any other local anesthetics have been established either in diabetic animal models or diabetic patients.

Kalichman et al[16] also studied neuropathy induced by galactosemia (characterized by hyperglycemia without hypoinsulinemia). Subsequent studies with this model showed that histopathologic changes in experimental galactose neurotoxicity matched the histopathologic changes found in sural nerve biopsies of humans with diabetic neuropathy.[17] To our knowledge, no sciatic nerve blocks, or any nerve blocks with any local anesthetics, have ever been reported using the animal model of galactose neuropathy (induced in healthy rat or induced in the STZ-diabetic rat). Whether this model may prove useful in the study of local anesthetic and analgesic adjuvant toxicity remains to be seen.

More recently, genetic manipulation with Cre/lox techniques has been used to create transgenic mice with selective disruption of various genes related to insulin signal transduction. Because mice with complete loss of insulin receptors die shortly after birth, the selective genetic manipulation approach has been essential for understanding the role of the insulin receptor in various organs. To date, disruptions of insulin receptor in liver, muscle, and fatty tissue have been investigated; animals with liver insulin receptor knockout develop a syndrome with impaired glucose tolerance and other features of diabetes. Despite these important advances, little has been reported regarding whether the selective knockout animals develop peripheral neuropathy,[18,19] and as mouse models, sciatic nerve testing with nerve blocks would seem less likely to resemble that of the human condition (when compared with rat).

At this juncture, the benefits derived to date from studies of STZ-hyperglycemic/diabetic animals seem to outweigh concerns about limitations of the STZ model system. Despite this, clinical perineural complications with local anesthetic nerve blocks do not yet seem to match the severity that would have been projected by the 1992 rat study by Kalichman and Calcutt[14] involving procaine- and lidocaine-induced perineural neurotoxicity. At present, clinical wisdom matches the classic statements of Selander[20]: "Correctly administered local anesthetics of clinical concentrations are safe, but animal data indicate that al local anesthetics are potentially neurotoxic." Given the complexities of the pathophysiology of diabetic neuropathy (described in the following section) and the complexities of deriving an animal model (summarized described in this section), it seems ill-advised to "accept" local anesthetics as the only potential anesthetic-analgesic perineural option if other known perineural analgesic adjuvants are demonstrated to be nontoxic in animal models.

Histopathology in Diabetic Neuropathy

Chronic sensorimotor distal symmetric polyneuropathy of diabetes (diabetic peripheral neuropathy [DPN]) is characterized by a loss of myelinated and unmyelinated fibers observed in

transverse nerve sections.[21] Axonal pathology is prominent in DPN, whereas myelin remodeling is rare. Axonal degeneration, decreased regenerative activity, secondary loss of Schwann cells, breakdown of Schwann cell tubes, and misdirection of regenerating fibers could all be responsible for defective regeneration.[21] Multifocal forms of diabetic neuropathy are usually attributed to ischemic injury. Pathologically, changes are seen in both large and small nerve blood vessels, but large vessel changes are likely due to atherosclerosis and not directly involved in the pathogenesis of DPN. Small vessel changes include thickening of the basement membranes of endoneurial capillaries.

Taxonomy of Diabetic Neuropathy

It is important to recognize that diabetic neuropathy is heterogeneous, including generalized symmetric polyneuropathies (sensory, sensorimotor, and autonomic) and focal-multifocal neuropathies (cranial, truncal, focal limb, proximal motor, and chronic inflammatory demyelinating neuropathy).[22] In addition, diabetic neuropathy can be found in association with other treatable etiologies, such as chronic inflammatory demyelinating polyneuropathy, B_{12} deficiency, hypothyroidism, and uremia.[22] We will restrict this review to the most common peripheral subtype[22]: chronic sensorimotor distal symmetric polyneuropathy (DPN). It is generally the case that DPN affects small nerve fibers before affecting larger fibers. As a consequence, numbness, pain, and autonomic dysfunction are common early manifestations of DPN.

Proposed Mechanisms of DPN

There are 3 leading pathophysiologic processes[23,24] associated with DPN that will be discussed here: (i) the polyol pathway, (ii) microvascular alterations, and (iii) glycosylation end-product theories.

The polyol pathway plays an important role in diabetic neuropathy, in part because glucose uptake in peripheral nerves is less dependent on insulin than in other tissues. Instead, high nerve glucose concentrations prompt aldose reductase to initiate the polyol pathway, converting glucose into sorbitol. Although aldose reductase activation reduces the available cofactor, nicotinamide adenine dinucleotide phosphate, ultimately leading to less available nitric oxide and glutathione, the accumulation of perineural sorbitol and fructose inhibits membrane channel activity involving myoinositol, leading to reduced sodium/potassium ATPase activity. This attenuation of ionic flux reduces the propagation of action potentials. Meanwhile, the loss of glutathione reduces the nerve's ability to offset oxidative stress, as the reduction of nitric oxide leads to both reduced antioxidant activity and impaired vasodilation (via impaired smooth muscle relaxation), yielding chronic perineural ischemia.[23,24] Aldose reductase inhibitors, which are intended to reduce perineural sorbitol levels, have been protective against neuropathy in animal models (including the STZ-diabetic rat) but have generally not been successful in humans,[24] although some next-generation aldose reductase inhibitor trials are ongoing.[22]

Alteration in perineural microvasculature is the next mechanism with relevance for DPN. Pathologic changes in diabetic nerves include capillary basement membrane thickening, endothelial cell hyperplasia, and neuronal ischemia and infarction.[23] Loss of focal vascular supply and associated diminished endoneurial blood flow and endoneurial oxygen tension correlate with the extent of nerve injury.[24] Endoneurial capillaries, specifically, are more severely injured than are capillaries in the epineurium, skin, and muscle.[24] Therefore, endoneurial vasculature seems to be of greater concern than epineurial vasculature with respect to DPN. It follows that the avoidance of intraneural injection, given the precarious nature of endoneurial blood flow in diabetes, would be an appropriate primary goal in the care of patients at risk for DPN, whether diabetic or "prediabetic"[3,25] (ie, patients with impaired glucose tolerance but not yet diagnosed with diabetes).

Glycosylation end-products have also emerged as an important contributor to the pathophysiology of DPN. These end-products (i) result from chronic intraneuronal and intracellular hyperglycemia and (ii) are deposited intraneurally and perineurally. These deposits slow nerve conduction and worsen the potential for oxidative stress.[23]

It should be clear that the mechanisms of DPN are quite complex; excellent reviews are available.[4,21,26–30] Two other specific classifications of neuropathic etiology in diabetic patients should be considered when these patients present for peripheral orthopedic surgery. In particular, these are the *inflammatory neuropathies* and the *compressive neuropathies*. These conditions may coexist with diabetes, and compressive neuropathies have increased incidence in diabetic patients. The inflammatory neuropathies include radiculoplexus neuropathies (which are typically painful and asymmetric) and chronic inflammatory demyelinating neuropathy (which is symmetric, but not typically painful).[21] Compressive neuropathy conditions include those involving the median nerve, ulnar nerve, and common peroneal nerve at the fibular head. These compressive conditions have as a common feature repetitive use and/or injury.[21]

CLINICAL CHALLENGES OF PERIPHERAL NERVE BLOCKS IN DIABETIC PATIENTS AND LABORATORY MODELS

A recent case report highlighted the technical challenges associated with peripheral nerve blocks in diabetic patients.[31] In this report, 2 patients showed neither paresthesiae nor motor responses during sciatic nerve stimulation with electrical current less than 2.4 mA, although both patients were successfully blocked with ultrasound guidance. This concept of difficult neurostimulation in diabetes/hyperglycemia is corroborated by a recent animal study in dogs that were rendered hyperglycemic with STZ. In this study, a sciatic twitch response was elicited and maintained at a threshold electrical current of 0.5 mA. This twitch response–electrical current relationship was uniformly associated with intraneural injection.[5,6]

Another case report described a patient with subclinical polyneuropathy (not related to diabetes) who experienced nerve damage after a femoral perineural ropivacaine infusion.[32] In this report, the patient received a continuous perineural infusion (10 mL/hr of ropivacaine 0.2%) after total knee arthroplasty and experienced persistent quadriceps weakness, hyposensitivity of the medial thigh, and an ablated patellar tendon reflex.[32]

There has been a clinical data review addressing neuraxial anesthesia outcomes in diabetic patients[33] and another report of decreased postoperative insulin resistance when epidural anesthesia and analgesia were used (only when these patients have preoperative insulin resistance).[34] However, to our knowledge, there have been no formal patient outcome reviews related to peripheral nerve blocks in diabetic patients.

Given the existing gaps in the clinical science of an epidemiologically prominent disease state, translational research is required. In the remainder of this article, we review a variety of adjuvant agents with potential for translational studies of diabetic neuropathy.

RELEVANT PERINEURAL ANALGESIC ADJUVANTS AND COMPATIBILITY WITH THE DIABETIC DISEASE STATE

Epinephrine

Epinephrine remains one of the most common perineural adjuvants, likely even in diabetic patients. Epinephrine (5 μg/mL) was used in the lidocaine nerve blocks at the popliteal fossa described in the diabetic case reports of Sites et al[31] cited previously. Epinephrine as perineural and neuraxial adjuvant was reviewed extensively by Neal.[35] Based on this review, it seems apparent that (i) neuraxial epinephrine may increase the theoretical risk of spinal cord ischemia in patients with compromised spinal circulation, as may occur with diabetes; (ii) peripheral perineural epinephrine in combination with local anesthetics may reduce peripheral perineural blood flow to a threshold associated with nerve damage in patients with compromised vascular integrity due to diabetes; and (iii) epinephrine worsens animal nerve injury in the setting of physical nerve damage or local anesthetic neurotoxicity.[35] Given that endoneurial blood flow is compromised in the setting of DPN, there seem to be little perineural benefit and possible detriment in the use of epinephrine in the peripheral nerve blocks of diabetic patients, and this is supported by neuraxial histologic and applied physiologic study as well (Table 1).[36,37] However, there have likely been millions of diabetic patients who have received adjunctive epinephrine without any apparent injury; epinephrine remains a commonly used adjunct to detect potential unwanted intravascular injections during nerve block placement.

Alternative Adjuvants

There has been recent interest in studying alternative perineural analgesics with previous reports of regional analgesia in other contexts (eg, neuraxial) and in diabetic contexts. These alternative adjuvants include clonidine,[38–50] dexmedetomidine,[51] buprenorphine,[52–67] midazolam,[68–76] tramadol,[77–85] and dexamethasone/other corticosteroids (Table 1).[86–97] Novel perineural multimodal analgesics introduce the potential to produce or enhance analgesia, thus reducing (i) systemic opioid analgesic requirements after surgery and (ii) potential neurotoxicity of local anesthetics that have been documented in STZ-diabetic rat models.[14] All of these drugs described previously are commercially available as injectables and are approved for use as parenteral injectables in humans (although tramadol is neither available nor approved as an injectable in the United States). Other than local anesthetics, these adjuvants (including clonidine) have not been approved for peripheral nerve block, and none of them have ever been formally tested (perineurally) in diabetic animal models, let alone diabetic patients. Although nothing prevents a clinician from using these agents for this purpose, it should be emphasized that such off-label use requires the clinician to defend his/her practice based on the factors mentioned and beyond the availability of the compound in an injectable form. Although multimodal combinations of perineural analgesics may theoretically reduce the risks associated with local anesthetic nerve toxicity in the diabetic state (eg, if lower doses of all agents are used vs a large dose of any single monotherapy), research is needed to determine whether the multimodal concept may, in fact, increase the toxic risk of local anesthetics on the susceptible nerve.[§]

Following this logic, preliminary study of perineural analgesic adjuvants in diabetic animal models should answer several key questions. Specifically, are such adjuvants (i) antinociceptive, (ii) more motor sparing than are local anesthetics, (iii) reversible in their antinociceptive and motor-proprioceptive block effects, and (iv) histologically safe upon microscopic examination of harvested nerve? If any such adjuvants do not meet these criteria as monotherapy and/or as combination (with each other and/or with local anesthetics), then it would be illogical to further evaluate the mechanism of a perineural adjuvant that has already been tested in humans in the absence of animal safety evidence. After these initial questions are answered, more resource support would be logically directed to mechanistic evaluation of adjuvants (and combinations) that seem to be fundamentally safe in the diabetic animal model (eg, STZ rat). Given this explanation, the adjuvants of greatest apparent immediate interest will be considered one at a time.

Clonidine and Dexmedetomidine

Clonidine (molecular weight of the hydrochloride salt = 266 and $pK_a = 8.2$) is an α2-adrenoreceptor agonist in the central nervous system that has been well reviewed.[38,39] Dexmedetomidine[51] is generally considered to be more specific than is clonidine as an α2 agonist. We will focus primarily on clonidine, however, because of its longer-term use in routine clinical care as a perineural adjuvant. Clonidine's epidural and intrathecal histologic safety in animal models is accepted. We are not aware of any formal toxicology studies of clonidine at the level of the diabetic peripheral nerve. Although the prolongation of local anesthetic effect by clonidine is not currently attributed to α2 agonism, the perineural injection of clonidine has been shown to prevent chronic pain responses in an induced chronic pain model (rat sciatic nerve ligation) via α2 agonist effects. Specifically, focal macrophages at the site of injury have been shown to express α2 receptors, and the agonist activity at these receptors by clonidine leads to a shifted balance of proinflammatory and anti-inflammatory cytokines (ie, more anti-inflammatory transforming growth factor β1, less proinflammatory interleukin 1β, and less tumor necrosis factor α).[49] The overall safety profile of perineural clonidine to date, along with its antileukocyte effects, may make clonidine a particularly useful adjuvant to local anesthetics in clinical practice in the interim, in both diabetic and nondiabetic patients, in an effort to attenuate any inflammatory components of neuropathic conditions. A logical threshold for diabetic patient perineural dosing would seem to be 1 μg/kg, although lesser dose would seem to reduce the risk for systemically mediated hypotension, for which diabetic patients with autonomic neuropathy may be at particular risk.

[§]Formal study of previously-tested perineural adjuvants seems logical despite the lack of defined perineural mechanisms of action. The logic is that most patient-tested chronic systemic treatments for painful DPN enter phase 3 trials without analgesic mechanisms having been formally defined.[98] The reasons cited for this occurrence are similar to what our specialty encounters daily. A robust animal model is described, and the marketplace sees the success of a drug (eg, the now-generic gabapentin as DPN therapy) with an equivocal mechanism for efficacy. The pharmaceutical industry then focuses considerable effort on developing new therapies that are highly selective in their actions, although other generic but effective drugs can have many different actions that can contribute to pain relief (eg, tricyclic antidepressants). Meanwhile, randomized controlled clinical trials become subject to increasing resource allocation, sophistication, and regulation; the resources simply become too limited to better identify specific basic science mechanisms of action before human testing (eg, pregabalin testing in neuropathic and nonneuropathic pain states in humans). Such trials were not explicitly mechanism oriented but were sufficiently large in scope, while being sufficiently similar in design (eg, earlier gabapentin and subsequent pregabalin study designs) and covered such a broad range of conditions that they have allowed important insights applicable to clinical trial design and mechanism-oriented research.

Buprenorphine

Buprenorphine is an opioid receptor μ-agonist and κ-antagonist with a 2-phase pK_a of 8.42 and 9.92 and a molecular weight of 504. Buprenorphine has both systemic effects as an analgesic and an antihyperalgesic,[54,55] although the exact mechanisms of the multiple modalities of buprenorphine analgesia and antihyperalgesia remain unknown.[67] Neither perineural nor nociceptive mechanisms have been identified with respect to buprenorphine's peripheral mechanism of action, to our knowledge, other than presumed μ-agonist activity. Buprenorphine, along with being a partial μ-opioid receptor agonist, is a known κ-opioid receptor (KOR) antagonist. We are not aware of any formal neural tissue toxicology studies relevant to regional anesthesia that have been done for buprenorphine, although its clinical use has commonly been reported neuraxially (Table 1). Buprenorphine is emerging as an important therapeutic option in the chronic systemic treatment of neuropathic pain, based on recent reviews, with positive evidence with oral, transdermal, intravenous, and intrathecal use.[67] Buprenorphine has not been formally studied as a sole perineural analgesic; however, we recently reported 2 cases of motor-sparing sciatic block efficacy when combined clonidine and buprenorphine were administered in a saline diluent.[46] Buprenorphine has not been studied perineurally in diabetic patients, to our knowledge. Buprenorphine is a rational drug to test in a diabetic animal model because it is metabolized and excreted by the liver (and not the kidney, which is at risk for diabetes-induced end-organ damage).[99] Interestingly, an OVID MEDLINE search (by author B.A.W., accessed September 17, 2008) combining *buprenorphine* (3281 citations) and *diabetic neuropathies* (10,042 citations) yielded an "empty set."

Midazolam

Midazolam is a benzodiazepine, the base of which having a molecular weight of 326 and a pK_a of 6. As of this writing, there is only 1 clinical study of midazolam as a perineural analgesic adjunct in brachial plexus blocks.[68] Midazolam is a physiologically rational drug to test in a diabetic animal model (Table 1). The intrathecal efficacy of midazolam relies on the expression of γ-aminobutyric acid (GABA) A receptors in the spinal cord, and these receptors have also been shown to exist in the periphery (Table 1). The argument of intrathecal effect does not support its clinical use for peripheral nerve blocks. The use of midazolam as a regional anesthetic adjunct (neuraxial, perineural) has been quite controversial (Table 1). If perineural midazolam is to be studied at the bench, it seems reasonable to consider animal models other than rabbit, given the apparent intrathecal clinical safety (in patients[71]) and intrathecal in vivo safety (in sheep model).[72] Of note, the GABA-A receptor has been implicated recently as relevant to the pathophysiology of diabetic neuropathy (Table 1).[100] To date, we are not aware of any basic studies using midazolam as perineural analgesic monotherapy in either nondiabetic or diabetic subjects.

Tramadol

Tramadol, with a molecular weight of 300 and a pK_a of 9.4, stimulates serotonin release intrathecally and inhibits norepinephrine reuptake. It is a weak μ-agonist, with respect to its opioid receptor activity, and has other receptor and channel activities (Table 1). In contexts related to diabetes, tramadol is available as a systemic drug for the treatment of painful DPN,[40] understanding that adverse effects commonly prohibit long-term use of tramadol in this population. To date, no specific oral analgesic or combination has yet emerged as the initial therapy of choice for painful DPN.[101] Local skin reactions (rash) were problematic when subcutaneous tramadol was compared with subcutaneous prilocaine.[102]

Corticosteroids, With Specific Attention to Dexamethasone

Anesthesiologists desire greatly to increase the duration of single-injection nerve block analgesia. Where this desire becomes potentially deleterious was illustrated in a letter to the editor[87] and a subsequent reply.[88] Methylprednisolone 40 mg (commonly used in epidural steroid injections) was reported as being useful in prolonging brachial plexus (axillary block) analgesia by about 7 hrs.[87] A reply to this letter eloquently stated that one of the characteristics of methylprednisolone for epidural steroid injection is the neurolytic effect of the preservative diluent, benzyl alcohol, the effects of which go unnoticed in patients with existing nerve damage related to chronic low back pain.[88]

It is a common clinical practice for pain clinicians to add dexamethasone to their peripheral nerve blocks. This is probably because methylprednisolone has been shown to specifically inhibit C-fiber transmission.[103] Pain practitioners likely use dexamethasone quite commonly because it is a pure liquid (ie, nonparticulate) steroid. However, its routine use awaits further studies on its safety and efficacy.[104]

A decade ago, authors called for a halt to intrathecal steroid use based on a review of intrathecal pharmacology in the clinical context; these authors described spinal cord toxicity with methylprednisolone[105] and recommended no further intrathecal steroid use until proper animal safety studies are performed. The preservatives and vehicles in steroid preparations are primary concerns with respect to safety of nerve tissue (neuraxial or peripheral), and generally speaking, polyethylene glycol is a bigger problem than the small amount of benzyl alcohol in a steroid preparation. Preservatives and vehicles have been carefully reviewed elsewhere.[104,106] If dexamethasone is preservative-free, this does not "absolve" it from being rigorously tested in the animal models described before being routinely studied and/or recommended in patients. In either case, the use of perineural dexamethasone in diabetic patients should be considered ill-advised at best, given the hyperglycemic response that accompanies steroid use in diabetes. Steroids used as analgesic adjuvants in diabetic patients are controversial, if not contraindicated, not only for their neurotoxic effect (linked to preservative component) but also because steroids induce hyperglycemia and result in the need to modify insulin doses for several days (which are well-known sequelae after single epidural injection in the pain clinic).

Given the descriptions above, it seems illogical to endorse any perineural steroid adjuvant until there are proper, current safety studies (as monotherapy and in combination with local anesthetics) involving primary sensory neurons (not necessarily from a diabetic animal) in vitro and in a validated diabetic animal model in vivo (such as the rat sciatic nerve).

Dexamethasone, the preparation of which being marketed as a preservative-free solution of dexamethasone sodium phosphate at 10 mg/mL, is packaged at pH 7.0 to 8.0 and has a molecular weight of 516. Citations regarding the perineural use of dexamethasone with aqueous and microsphere local anesthetic preparations are given in Table 1. There have been no reports of the coadministration of dexamethasone with ropivacaine. Discussion of dexamethasone formulated within local anesthetic microspheres and liposomes for peripheral nerve blocks is beyond the scope of this translational vignette.

In historical basic research (rat model),[96] dexamethasone was reported to cause minimal peripheral nerve damage when compared with other steroids such as hydrocortisone or triamcinolone (which cause more damage). More recently (2002), dexamethasone was shown to temporarily decrease perineural blood flow, but with no ensuing neuropathology.[97] Intrathecally, continuous infusions of dexamethasone in rats showed low doses to be safe, but higher doses to be associated with increased infection risk and focal meningeal necrosis. To summarize, there are limited (if any) modern safety data regarding the intrathecal, epidural, and perineural routes of administration for dexamethasone in nondiabetic contexts.[104] Our impression is that dexamethasone requires proper neurotoxicology testing in vitro and in an animal model in vivo of peripheral nerve (both nondiabetic and diabetic animals), both as monotherapy and in combination therapy, before any additional use in humans is considered safe for large-sample study involving patient consent. Although the anti-inflammatory properties seem intuitively to be desirable, the effects of perineural dexamethasone on supporting cells (eg, Schwann cells) require proper evaluation before healthy patients would consent to appropriate prospective clinical study. It seems that dexamethasone-induced perineural protection in healthy patients (after animal safety is validated) would need to be profound before subjecting diabetic patients to such study would be considered ethical.

PERINEURAL INSULIN AND MAINTAINED CONDUCTION VELOCITY IN RAT

A potentially fruitful bench research initiative for the subspecialty of regional anesthesia may involve the coadministration of regular insulin (injected simultaneously with local anesthetic or perineural analgesic) to determine whether the injected perineural insulin is protective against peripheral nerve toxicity. This concept is based on the work of Singhal et al[107] in which repeated perineural injections of insulin (3 times a week) led to the prevention of sciatic neuropathy in STZ-diabetic rat. The insulin was combined with normal saline (not local anesthetics). Insulin seems to act as a trophic molecule either via insulin receptors or insulin growth factor receptors[107–111] to help maintain nerve function including conduction velocity. Local insulin has a trophic influence on myelinated fibers that is prominent in diabetic nerves and is independent of hyperglycemia. In this context, efforts to promote research in diabetic nerve regeneration have gained increasing importance,[112] but such research has not yet been promising with respect to the development of neurotrophic factors. Disturbed nerve regeneration in diabetes has been ascribed at least in part to all or some of decreased levels of neurotrophic factors, decreased expression of their receptors, altered cellular signal pathways, and/or abnormal expression of cell adhesion molecules.[112] In addition to the steady-state changes of peripheral nerves in diabetic neuropathy, additional nerve injury induces specific changes in individual neurotrophic factors, their receptors, and their intracellular signal pathways, which are closely linked with altered neuronal function, varying from neuronal survival and neurite extension/nerve regeneration to apoptosis. Data regarding specific mechanisms seem to be either preliminary or pending.[112] Rationally accepted replacement therapy with neurotrophic factors has not provided any success in treating diabetic neuropathy,[112] but this does not rule out potential value of bench science study of neurotrophins coadministered with perineural anesthetics or analgesics. Coadministration of perineural insulin for neuroprotection from local anesthetic effects may represent a novel treatment strategy (and as only 1 injection as opposed to repeated injections over days). Little is known about potential doses and/or risks of perineural insulin (or any other relevant perineural trophic factors) in the clinical setting, and safety studies will be necessary before carrying out clinical trials combining insulin with perineural anesthetics and/or analgesics.

SUMMARY AND CONCLUSION

Given these gaps in scientific knowledge, an ambitious agenda for research and clinical care is needed. The critical objectives include (i) determining the peripheral perineural toxicity of bupivacaine and ropivacaine in STZ-diabetic rats; (ii) determining if another diabetic-hyperglycemic neuropathy model (eg, the Zucker type 2 diabetic fatty rat[9]) may be more valid than those models involving STZ induction; (iii) determining (ie, ruling out) peripheral perineural toxicity of clonidine, buprenorphine, midazolam, and tramadol (alone, in combination with each other, and/or in combination with bupivacaine and/or ropivacaine) in nondiabetic and diabetic animals; (iv) avoiding the use of dexamethasone in the peripheral nerve blocks in diabetic patients; (v) considering the risks of adding epinephrine to perineural blocks for diabetic patients, based on theoretical concerns and animal studies that admittedly have no confirmatory human data; and (vi) determining in an animal model the extent to which coadministered regular insulin with perineural anesthetics and/or analgesics confers protection of the peripheral nerve. The outcomes of these studies will have relevance to clinical care and may reveal that (i) bupivacaine and ropivacaine in clinical concentrations may be neurotoxic to the diabetic rat peripheral nerve, similar to procaine and lidocaine,[14] and (ii) clonidine[49] and dexmedetomidine[51] seem likely to be neuroprotective in perineural injections of local anesthetics. This latter point may be relevant in diabetic animal models and patients, because the antileukocyte effect of clonidine (and perhaps with dexmedetomidine in future research) has been shown when coadministered with local anesthetics in other animal models of chronic pain. It should be interesting to determine if coadministered clonidine/dexmedetomidine, buprenorphine, midazolam, and/or tramadol prove to reduce the perineural toxicity of local anesthetics in the diabetic animal model. It is premature to draw the needed clinical inferences about dexamethasone in healthy clinical patients, let alone in diabetic patients, in the absence of any meaningful animal model toxicology studies. Finally, additional research is needed to determine whether (i) electrical thresholds need to be raised for diabetic patients receiving stimulator-based peripheral nerve blocks or (ii) electrical stimulation will be of any use in diabetic patients given recent findings by Rigaud et al.[6] Ultrasound-guided imaging may prove to be useful in this clinical context, as previously demonstrated in the case report by Sites et al.[31] In time though, the drug or drugs injected may prove to be as important as how the peripheral nerve is located in such patients.

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