ABSTRACT: Patients with paralysis due to damage to the central motor pathways often develop spasticity, defined as the velocity-dependent increase in the muscle response to phasic stretch. Such patients are usually also impaired by weakness and muscle shortening, and other forms of muscle overactivity such as spastic co-contractions and spastic dystonia. Pharmacologic treatment to reduce all types of muscle overactivity should be used only as an adjunct to programs of lengthening of overactive muscles and of training of their antagonists.

Local treatments allow selective weakening of those muscles where overactivity is most disabling, by injection into muscle (neuromuscular block) or close to the nerve supplying the muscle (perineural block). Before the emergence of botulinum toxin, two types of compounds have been used: local anesthetics (lidocaine and congeners) with a reversible action of short duration, and alcohol (ethanol and phenol) with a longer duration of action. Whichever blocking agent is under consideration, the technique of exploratory stimulation should be used for injection, whether a nerve or a muscle is targeted.

Local anesthetics (lidocaine, bupivacaine), which transiently block afferent and efferent impulses in muscle or nerve, may precede casting or intramuscular injection of other agents, or be used as a trial when there is consideration for long-term block. Chemical neurolysis using neurolytic agents (ethanol or phenol) acts by destruction (necrosis by non-selective protein denaturation) of peripheral nerve. Side effects are numerous and include pain during injection, chronic dysesthesia and chronic pain, and episodes of local or regional vascular complications by vessel toxicity. Whether the benzyl core of phenol carries a significant myelotoxic and genotoxic risk after repeat injection, especially in children, has not been evaluated. Studies of chemical neurolysis have rarely been controlled. Pharmacoeconomic considerations mandate that controlled comparative studies between neurolytic agents and botulinum toxin be carried out in specific patient populations to determine the appropriate indications for each.

CHAPTER 5

Traditional Pharmacologic Treatments for Spasticity Part I: Local Treatments

Jean-Michel Gracies, MD, PHD*
Elie Elovic, MD**
John R. McGuire, MD***
David M. Simpson, MD*

* Departments of Neurology and Clinical Neurophysiology, The Mount Sinai Medical Center, New York, NY

** Kessler Medical Rehabilitation Research Education Center, West Orange, NJ

*** Department of Physical Medicine and Rehabilitation, Medical College of Wisconsin, Milwaukee, WI

Address for Correspondence:
Jean-Michel Gracies, MD, PHD
Department of Neurology
The Mount Sinai Medical Center
One Gustave L Levy Place
Annenberg 2 / Box 1052
New York, New York 10029-6574
Fax 1 (212) 987-7363 / Tel 1 (212) 241 8569
e-mail: jean-michel.gracies@.mssm.edu

General Introduction – Indications for Local Treatment of Muscle Overactivity

Patients with paralysis due to damage to the central motor pathways often develop a common clinical feature, which is the increase in the muscle response to phasic stretch.[1,2] This increase in response to stretch invariably follows a rule, whereby the higher the velocity of stretch, the more increased the reflex.[3,4] This led to the definition of spasticity as a velocity-dependent increase in stretch reflex.[5] Patients with spasticity form a clinically and physiologically recognizable population, and are usually impaired by far more than their spasticity.

Mechanisms of Impairment in Patients with Spasticity

To appreciate the potential role of local treatments in patients with spasticity, it is important to recognize the pathophysiological mechanisms of impairment in these patients. Severe damage to central motor pathways provokes two series of events in the neural-muscular-skeletal chain contributing to movement (Figure 1).

Acute Events: Paralysis, Flaccidity, Muscle Shortening

This series of events occurs immediately or within hours of injury, while the patient is still at the site of the accident, in the emergency room or in the acute care unit. The injury to motor centers disrupts the function of several descending pathways, including the corticospinal pathway involved with the execution of voluntary command. The resulting paralysis — i.e., decreased maximal voluntary spatial motor unit recruitment — immediately leaves the paralyzed muscles immobilized. In the acute care setting, patients are typically placed supine in stretchers continuously, usually with the paralyzed lower limbs in full extension, and the paralyzed upper limbs positioned in shoulder internal rotation, elbow flexion and pronation, and often wrist and finger flexion. Thus, among the paralyzed muscles, some are commonly immobilized in short position. These often include extensors in the lower limbs, and internal rotators, pronators and flexors in the upper limbs. Immobilization in short position is the initial mechanism for muscle contracture, which includes loss of sarcomeres (shortening) and accumulation of connective tissue, as has been shown in animals and humans.[6,7] Injury to motor centers and descending pathways also disrupts the descending flow that normally influences spinal cord reflex circuitry. This commonly results in the immediate extinction of many spinal reflex responses including stretch reflexes, with its clinical translation of flaccidity.

Subacute Events: Muscle Overactivity, Changes in Passive and Active Muscle Properties, Aggravation of Muscle and Joint Retractions

This second cascade of events unfolds in the following weeks, and mostly consists of plastic neural rearrangements, which follow both the injury and the paralysis-related disuse. As interrupted descending fibers degenerate, extensive sprouting occurs at segmental spinal levels, whereby interneuronal endings branch out onto other interneurons or somatic motoneuronal membranes to occupy the spaces left empty by the missing descending fibers.[8] The physiological result is the gradual emergence of abnormal and often excessive reflex responses to peripheral inputs, such as cutaneous stimuli,[9] or muscle stretch.[1] All these abnormal muscle responses contribute to global muscle overactivity,[2] i.e., involuntary abnormally increased temporal motor unit recruitment. In addition to these spinal plastic rearrangements, higher centers select new strategies to elicit movement, involving either the remaining intact descending pathways (e.g. reticulospinal, rubrospinal, vestibulospinal), or the remaining intact corticospinal fibers that may branch and sprout abnormally at the motoneuron level.[10,11] Both mechanisms are a source of abnormal patterns of supraspinal descending drive, which contribute to muscle overactivity.

KEY POINTS

- Patients with spasticity are usually also impaired by weakness, muscle shortening, spastic co-contractions and spastic dystonia
- Function may be the most difficult parameter to assess, although function is what is most relevant to the patient
- Physical treatments aimed at lengthening overactive muscles are a fundamental part of the local treatment of muscle overactivity
- Local anesthetics act by transiently blocking the sodium channels of motor and sensory nerves, and at the neuromuscular junction

Muscle overactivity: We find it useful to group muscle overactivity into two categories, depending upon whether it involves high stretch sensitivity, i.e., excessive motor unit recruitment that is aggravated or ameliorated by the recruitment of stretch receptors in the overactive muscle. The first category comprises the stretch-sensitive forms of muscle overactivity and includes spasticity, spastic dystonia, and spastic co-contraction. These are distinguished by their primary triggering factor: phasic muscle stretch, tonic muscle stretch, or volitional command.

- ***Spasticity*** is a velocity-dependent increase in stretch reflex, i.e. an excessive muscle contraction in response to phasic stretch in the absence of volitional motor command.[5] Spasticity is thus measured with the muscles at rest.

- ***Spastic dystonia,*** as characterized by Denny-Brown,[12] is the phenomenon of tonic muscle contraction in the absence of phasic stretch or volitional command. Spastic dystonia is primarily due to an abnormal pattern of supraspinal descending drive, which is characterized by the inability to relax muscles despite efforts to do so. Spastic dystonia is sensitive to the degree of tonic stretch imposed on the dystonic muscle.[12]

- ***Spastic co-contraction*** is the inappropriate recruitment of an antagonist that is triggered by the volitional command on an agonist. It occurs in the absence of phasic stretch, and is sensitive to the degree of tonic stretch of the co-contracting antagonist.[13]

Like spastic dystonia, spastic co-contraction is primarily due to an abnormal pattern of supraspinal descending drive. Both can be aggravated by abnormal peripheral reflex reactions, in particular to the degree of tonic stretch imposed on the overactive muscle.

The second category of muscle overactivity comprises forms that are not prominently stretch-sensitive. They include pathologic extrasegmental co-contraction (i.e. synkinesis, overflow, chorea), excessive cutaneous or nociceptive responses, and inappropriate muscle recruitment during autonomic or reflex activities, such as breathing, coughing, and yawning. These forms of overactivity are

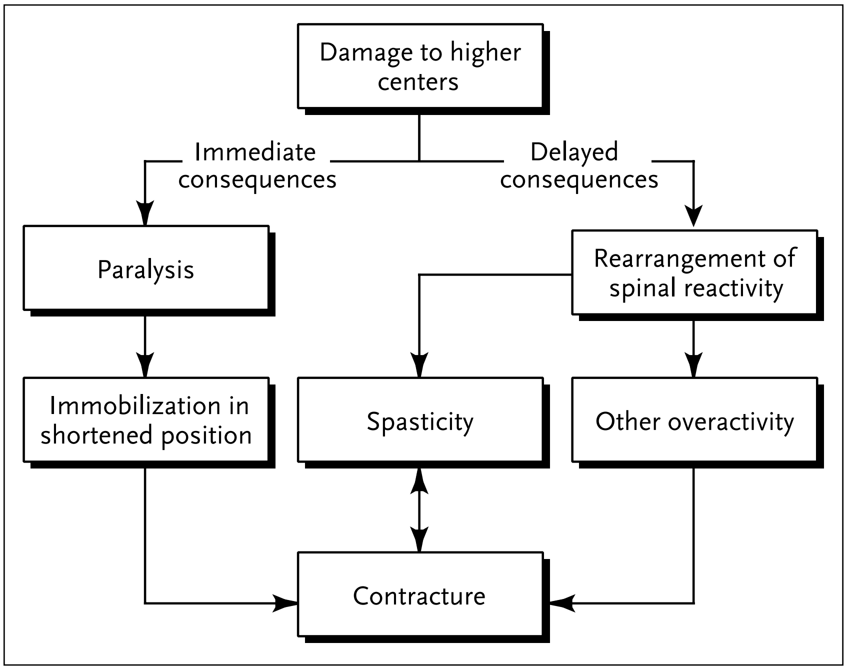

Figure 1. Pathophysiology of Impairment After a Central Nervous System Lesion

Damage to higher centers will affect the function of several descending pathways, among which is the corticospinal tract involved with voluntary movement. The resulting immediate paralysis will leave some of the muscles immobilized in a shortened position, which will be the first cause of muscle shortening. Muscle shortening by itself may then be the first generator of spasticity.[15-17] The damage to the descending pathways will also provoke an imbalance in spinal reactivity that will undergo rearrangements after a variable period of time. These rearrangements in spinal reactivity will result in abnormal muscle contractions and abnormal reflex responses, some of which will meet the classical definition of spasticity. Then, spasticity and other types of muscle overactivity will continue to aggravate contracture.[40] Note the vicious cycle set up between contracture and spasticity. This reciprocal potentiation has therapeutic implications: Spasticity cannot be addressed without treating contracture, and contracture cannot be addressed without treating all types of muscle overactivity.

also likely to involve some stretch sensitivity, but this has not been clearly established.

Other factors of spastic hypertonia; changes in passive and active muscle properties: Clinicians often note increased tone in patients with damage to the central motor pathways, i.e. increased resistance to passive movement, that is often measured regardless of the movement velocity.[14] In addition to the forms of overactivity discussed, hypertonia may result from other mechanisms. Resistance to stretch may result from prolonged changes in passive muscle properties that are caused by immobilization and overactivity.[7,15-17] In particular, these involve decreased passive extensibility of muscle. In patients with spasticity, resting muscle passively opposes its stretch with an abnormally increased torque for the same lengthening, as compared with normal muscle.[7] There are also immobilization- or overactivity-related changes in active muscle properties,[18-21] which involve increased torque development per motor unit recruited.

Clinical Assessment: Indications for Local Treatment and Evaluation of Outcome

Our assessment in patients with spasticity evaluates six parameters: five markers of the mechanisms of functional impairment, and functional impairment itself. The qualitative assessments of co-contractions and of spastic dystonia, and the measures of passive range of motion, help select muscles for local treatment. Measures of spasticity and active range of motion before and after local treatment are used to evaluate its effect on the treated spastic muscle and on the antagonist function.

1. Muscle shortening and joint retraction are evaluated by the passive range of motion. This is measured by the angle of arrest of the passive movement performed at extremely slow velocity (slow enough to minimize stretch reflex activity). Marked muscle shortening is an indication for an intensive program of muscle stretch, but this therapy is facilitated by prior local treatment by a neuromuscular blocking agent.

2. Spasticity is measured by the difference between the angle of arrest obtained at very slow stretch velocity (passive range of motion) and the angle of arrest obtained at a pre-specified high stretch velocity, that involves stretch reflex activity (method of Tardieu).[22] By definition, the presence of spasticity implies that the catch at fast speed is always followed by release when maintaining pressure, such that the angle difference is always greater than zero. Spasticity is the only type of muscle overactivity easily quantifiable in practice at the bedside.[22] We do not rely on spasticity rating to select muscles for local treatment by a blocking agent. However, we use spasticity ratings before and after treatment as a quantitative clinical marker of the weakening effect of local treatment of muscle overactivity.

3. Weakness (reduction of voluntary spatial recruitment) cannot be accurately quantified in the clinical assessment of patients with spasticity, because of the challenge inherent in simultaneously computing agonist recruitment, antagonistic shortening and antagonistic co-contraction in the isometric resistance perceived by the clinician. It is more realistic to evaluate active range of motion, although this parameter also depends on antagonist shortening and co-contraction. Active range of motion is often useful as an indicator of improvement of active function after injection of a neuromuscular blocking agent.

4. Spastic co-contraction. An inventory of the co-contracting muscles should be performed during the evaluation of active range of motion. We record all the muscles that clinically appear to co-contract inappropriately during attempts at voluntary movement. This qualitative assessment involves palpation and visual observation of the antagonists during agonist movements. This assessment guides muscle weakening by local treatment for improvement of active function.

5. Spastic Dystonia. Similarly, an inventory of the muscles affected by spastic dystonia is performed with the patient at rest. This assessment guides muscle weakening by local treatment for improvement of "passive" function and disfigurement.

6. Function itself may be the most difficult parameter to assess, although function is what is most relevant to the patient. Measurements of limb impairment in the clinic setting may not be transferable to functional disability in everyday life. We recommend combining an objective assessment of motor performance at the clinic,[23] which may be improved using blinded videotape review in clinical research, with a subjective self-assessment by the patient of everyday function, such as with the use of analog scales.

Principles of Treatment: Rationale for the Use of Local Treatment

Despite the emphasis of the chapter title on "spasticity," we address here the treatment of all types of disabling muscle overactivity in spastic patients, with the rating of spasticity providing a means to evaluate an effect of these treatments. After most central nervous system lesions, muscle overactivity is not equally distributed throughout all muscles in the body, but is particularly severe in some muscles. There is often imbalance between mildly hyperactive lengthened agonists and severely hyperactive shortened antagonists.[7,12] Thus, hyperactivity is often "relative:" the more hyperactive antagonist, even though less responsive to voluntary command than before the injury (motor weakness), is no longer opposed by a less hyperactive agonist. The paired agonist-antagonist produces torque oriented in the direction of the antagonist only. This imbalance of agonist and antagonist most often impairs purposeful functional movements. In such cases, the use of general (oral) or regional (intrathecal) therapies is not likely to improve function, since these administration routes lead to indiscriminately reduced motoneuron excitability and recruitment in both agonists and antagonists. In contrast, local treatments allow selective weakening of targeted hyperactive muscles. It is necessary to ensure that overactivity in a given muscle group is more disabling than helpful, before treating that muscle group.

KEY POINTS

- Use of local anesthetics requires resuscitation equipment and trained personnel available close by
- The primary question addressed by a short-term block is whether a long-term block of the same muscle or nerve might be functionally useful.
- Chemical neurolysis is a nerve block that impairs nerve conduction by means of destruction of a portion of the nerve
- Side effects are numerous and include pain during injection, chronic dysesthesia and chronic pain, and episodes of local or regional vascular complications by vessel toxicity

Local Pharmacologic Treatment Is Not To Be Used in Isolation

Treatment of aggravating factors: There are several other factors that aggravate muscle overactivity, and require treatment before consideration of pharmacological therapy. Enhancement of regional or diffuse muscle overactivity may be the consequence of stimulation of afferents other than stretch receptors, such as flexor reflex afferents.[24] Such stimulation may be provoked by various conditions, including urinary tract infection, urolithiasis, stool impaction, pressure sores, fracture, dislocation, in-grown toenail, restrictive clothing or condom drainage appliance. These conditions should be treated before or in combination with any pharmacologic management of muscle overactivity.

Stretch: Since muscle overactivity produces muscle shortening[25,26] and muscle shortening in turn increases spindle sensitivity,[15-17] muscle contracture and stretch-sensitive muscle overactivity are intertwined. Therefore, physical treatments aimed at lengthening overactive muscles are a fundamental part of the local treatment of muscle overactivity.[27] Thus, treatment regimens should address both shortening and overactivity. Chemical treatment aimed at relaxing a muscle should be combined with a physical treatment aimed at lengthening the muscle. As muscle shortening occurs acutely following immobilization (see above), muscle stretch should be implemented as early as possible.[27]

Physical therapy maneuvers commonly involve passive range-of-motion exercises or short posturing sessions, sometimes following the use of a heating modality to increase the elasticity of tissue. However, for long-term prevention of contracture, muscle stretch is probably most efficient when applied continuously for several hours each day.[28] Rigid or semi-rigid devices including rigid splints, serial casting, and dynamic splints are helpful for this purpose.[29,30,22] The efficacy of prolonged daily muscle stretch is optimal if applied to relaxed muscles.

Before the emergence of botulinum toxin, two types of compounds had been used to provide local muscle relaxation: local anesthetics (lidocaine and congeners) with a fully reversible action of short duration, and alcohols, chiefly ethyl alcohol (ethanol) and phenyl alcohol (phenol), with a longer duration of action. This chapter reviews these classical chemical local treatments, their physiological action, pharmacology, risks, and indications (see Tables 1 and 2). Controlled studies evaluating traditional neurolytic therapy vs. botulinum toxin are scarce. We propose a theoretical comparison of these treatments in the final section.

Reversible Ion Channel Blocks: Local Anesthetic Agents

Lidocaine, etidocaine and bupivacaine are currently the preferred local anesthetics for relaxation of overactive muscles or in physiological research.[31-34] They have replaced procaine, the first to be synthesized in 1905, which was commonly used up to the 1970s.[35-38]

In 1919, Liljestrand and Magnus[39] reported that intramuscular injection of procaine reduced the triceps rigidity of a decerebrate cat. However, this fundamental observation was reported at a time when most of the scientific community still accepted the response of a muscle to its own stretch as an intrinsic muscle property and not as a reflex mediated through neurons in the central nervous system. That demonstration came only five years later with Liddell and Sherrington.[40] Interest in the observations of Liljestrand and Magnus and their implications for therapy emerged over 40 years later, following another major step in the understanding of stretch reflexes: the elucidation of the role of the gamma motoneurons.[41]

Definition and Physiology

Local anesthetics are drugs that block nerve conduction when applied locally to nerve tissue, and whose action is reversible, without causing structural damage to nerve fibers or cells when used in appropriate concentrations.[34] Local anesthetics act on peripheral and central neurons.[42-44] The conduction block involves decreasing or preventing the large transient increase in the membrane permeability to sodium ions that is produced by a slight depolarization of the membrane, especially at the nodal regions.[45] Increases in potassium conductance, and blocks of abnormal impulses arising from non-inactivating sodium channels have also been reported.[46,47] These channel effects seem to be mediated by changes in the lipid phase of the membrane.[46] Therefore, a local anesthetic in contact with a nerve trunk causes both sensory and motor paralysis in the innervated area.[48] Since ionic mechanisms of excitability are similar in nerve and muscle, these agents also act on all types of muscular tissue. However, several physiological principles determine differences in the rate and magnitude of the clinical effects on different tissue types.

Differences in Sensitivity According to Fiber Type

It was thought that local anesthetics block impulses more readily in small than in large nerve fibers, since Gasser and Erlanger published their first studies, based on changes in compound action potentials.[49] In 1957, Matthews and Rushworth reported that muscle proprioceptive afferent and muscle efferent fibers, which are of the same diameter, were equally sensitive to procaine.[35] However, the smaller gamma fibers supplying the muscle spindles were more rapidly blocked by the local anesthetic. Franz and Perry suggested that this could be due to the shorter internodal distance in smaller axons, since more nodes were immediately accessible to the local anesthetic, whereas larger axons require more time for the anesthetic to diffuse to an equivalent number of nodes.[36] The same might account for the slower recovery of small axons at reversal of the process.[34,50] This faster block of the gamma fibers resulted in confusion in the neurological[37,51,52] and physiological[38] literature of the sixties, with several studies relying on the belief of exclusive gamma block with local anesthetics. Similar confusion appeared regarding the properties of alcohol and phenol[37,51,52] (see below). However, more recent clinical studies clearly established that all fiber types are sensitive to local anesthetics,[53] and some physiological studies of lidocaine effects show even higher sensitivity of large fibers.[54,55]

Differences in Sensitivity According to Pattern of Impulse Transmission

Frequency and pattern of nerve impulse transmission also determine the types of nerve that are primarily affected, probably by varying the duration of the open states of sodium channels. For instance, etidocaine appears to block somatic motor nerves more than somatic sensory fibers,[56] while the opposite is true for tonicaine, a derivate of lidocaine.[57] Indeed, the firing frequency of motoneurons rarely surpasses 10 Hz, in both normal subjects and hemiplegic patients. In contrast, the frequency of muscle spindle afferents is about 15 to 20 Hz within intermediate ranges of static muscle stretch, and can increase to more than 40 Hz during dynamic stretch or contraction, as measured in microneurographic experiments in normal,[58] and in hemiplegic patients.[59] In the central nervous system (CNS), lidocaine has been reported to preferentially block neurons that discharge at high frequencies.[60]

Differences in Sensitivity According to Recent Firing History

The degree of block produced by a given concentration of local anesthetic depends on how much and how recently the nerve has been stimulated.[34] Thus, a resting

Table 1. Local Treatments: Theoretical Data

	Mechanism	Site of Injection	Structure Blocked	Onset	Duration*
Local Anesthetics	Ion channel block	Perineural or intramuscular	Sensory and motor nerve Muscle Neuromuscular junction	Minutes	Hours
Ethyl Alcohol (>10%)	Tissue destruction Circulatory damage	Perineural or intramuscular	Sensory and motor nerve Muscle Neuromuscular junction	< 1 hour	2 to 36 months
Phenol (>3%)	Tissue destruction Circulatory damage	Perineural or intramuscular	Sensory and motor nerve Muscle Neuromuscular junction	< 1 hour	2 to 36 months
Botulinum Toxin	Presynaptic block of ACh release	Intramuscular	Neuromuscular junction	Days	3 to 6 months

* We indicate conservative limits, in agreement with what most authors observed for neurolytic agents and botulinum toxin. Anecdotal cases of duration outside these limits have also been reported.

or normoactive nerve is less sensitive to a local anesthetic than one that has been recently and repetitively stimulated.[61] Therefore, a local anesthetic can be expected to have greater efficacy on the overactive muscles that are the target of therapy, and a smaller paralyzing effect on normally active muscles that the anesthetic may have reached by diffusion. A similar phenomenon has been suggested for botulinum toxin.[62]

Effect at the Neuromuscular Junction

Local anesthetics also affect transmission at the neuromuscular junction[63,64] by unclear mechanisms.[65] To our knowledge, the question of whether this effect is greater or weaker than the conduction block on muscle afferent and efferents has not been examined. If greater, one may speculate that the intramuscular injection of a threshold dose of local anesthetic into endplate areas (see below) might be used as a short-term mimic of botulinum toxin, and might allow the clinician to preview the effects of botulinum toxin injections.

Pharmacology and Risks

Onset of Action

When a local anesthetic is injected close to a peripheral nerve, its effect begins within minutes (3 minutes for lidocaine, 15 minutes for bupivacaine). The delay of onset is greater when there is a need for diffusion of the agent from its site of injection to its site of action, for example, when a nerve plexus is blocked (the delay of onset of the effect of lidocaine injected about the brachial plexus reaches 10 min).[34,66]

Duration of Action

The duration of action of a local anesthetic depends primarily on the lipid solubility and the protein binding affinity of the compound. It is also proportional to the time during which the anesthetic is in actual contact with nervous tissues and inversely related to the regional blood flow at the injection site.[67] Consequently, procedures that keep the drug at the nerve by reducing local blood flow prolong the period of anesthesia. They also help reduce its systemic toxicity by slowing its absorption into the circulation. Therefore in clinical practice, solutions of local anesthetics often contain vasoconstrictors: epinephrine or a suitable synthetic congener, norepinephrine or phenylephrine.[34] However, because of the possibly intense vasoconstriction, epinephrine-containing solutions should not be injected into tissues supplied by end arteries, such as fingers and toes. Clonidine is another compound that prolongs the duration of block and permits a reduction of the lidocaine dose needed for a given duration of block, whether it is administered locally with the lidocaine, or orally before the lidocaine block administration.[68]

Risks

The risks described below require that resuscitation equipment and personnel trained in the management of acute cardiopulmonary emergencies are immediately available when local anesthetic is infiltrated into a tissue.

Toxic systemic effects: If local anesthetics inadvertently enter the systemic circulation, they will interfere with the function of all organs where impulse conduction or transmission occurs.

Central nervous system effects may begin with central stimulation, including restlessness, tremor and convulsions, which may respond to benzodiazepines. The

Table 2. Local Treatments: Practical Considerations

	Maximum Dose or Concentration	Main Risks	Indications*	Technique*
Local Anesthetics	Lidocaine (0.5 to 2%): <4.5 mg/kg Bupivacaine (0.25 to 0.75%): <3 mg/kg Etidocaine (1 to 1.5%): <6 mg/kg	CNS and cardiovascular toxicity Hypersensitivity	Efficacy test before long-term block Muscle relaxation before casting Analgesic before IM injection	Stimulation Motor point Resuscitation equipment available
Ethyl Alcohol (>10%)	10% to 98%	Pain at injection (intramuscular++) Chronic dysesthesia and pain (perineural++) Vascular complications Permanent peripheral nerve palsy	Proximal and large muscles Sensory integrity not a primary concern Hygiene and comfort purposes? Combination with botulinum toxin	Stimulation Motor point? Intramuscular "wash"?
Phenol (>3%)	<1gr (10 ml of 5% phenol)	Pain at injection (intramuscular++) Chronic dysesthesia and pain (perineural++) Vascular complications Permanent peripheral nerve palsy	Proximal and large muscles Sensory integrity not a primary concern Hygiene and comfort purposes? Combination with botulinum toxin	Stimulation Motor point?
Botulinum Toxin	≤600 U within 3 months (for BOTOX)	No major risk	Muscles accessible for IM injection Sensory integrity indispensable Purposes of active function Combination with neurolytic agents	Stimulation Endplate targeting? Dilution 100, 50, or 20 U/mL?

* Since there are no controlled data regarding indications and techniques, the entries reflect what is generally accepted in the community from experience.
? Question marks have been added to points that may be critical but need to be evaluated with controlled studies.
++ indicates a serious risk

mechanism responsible for these stimulation effects is not clear; both reduced gamma-aminobutyric acid (GABA)-mediated inhibition and direct stimulation of cortical cells have been reported.[69,70] However, in cases of severe overdose, stimulation effects are followed by CNS depression, and death can occur due to respiratory failure.[34] In cases of slight overdose and mild diffusion into systemic circulation, patients may experience temporary symptoms such as dizziness, fuzziness, blurred vision and auditory impairment.[71] These mild systemic symptoms may last about one hour following lidocaine overdose.

The cardiovascular system may be affected at higher systemic concentrations than those affecting the CNS. Local anesthetics injected systemically have a spasmolytic action on smooth muscles, and most cause arteriolar dilatation (though cocaine does not), likely due to decrease in sympathetic nerve efferent activity.[34] Therefore, a decrease in arterial pressure and an inhibition of cardiovascular reflexes are possible, as was shown with lidocaine in animal experiments.[67,72] Lidocaine has been associated with sudden cardiac collapse after injection at high doses in humans (100 mg intravenously plus 300 mg intramuscularly).[73] In the heart, local anesthetics act primarily in the myocardium, in decreasing excitability, conduction rate and force of contraction, similarly to quinidine. For these reasons, lidocaine is commonly used to prevent ventricular fibrillation at the initial phase of an acute myocardial infarction.[73]

Hypersensitivity: This rare but potentially major adverse reaction may result in a mild allergic rash to a fatal anaphylactic reaction.[34,64] It is especially encountered with local anesthetics of the ester type (cocaine, procaine, tetracaine).

Precaution in liver insufficiency: Since the metabolism of local anesthetics occurs mainly in the liver (especially for lidocaine), the extensive use of a local anesthetic in patients with severe hepatic dysfunction should be avoided.[34]

Neural toxicity: Animal experiments suggest that local anesthetics also carry a low risk of neural toxicity (myelin and axon destruction) after perineural injection, which is proportional to the concentration used and to the conduction blocking potency of the compound.[74,75]

Hematoma at injection site: this risk exists for any injection of blocking agent when the patient is anticoagulated.[76]

Fall or Joint Injury (lower limb injections): Following a local anesthetic block in the lower limb there can be very significant change in ambulation and transfers. Patients may have become used to the joint position and tension from their overactive muscles. When overactivity is suddenly removed the risk of immediate joint sprain or fall is real and mandates careful monitoring by the clinician.

Choice of the Local Anesthetic

There are a large number of synthetic local anesthetics. They differ by their delay and duration of action, anesthetic potency and associated risks.[34] Local anesthetics may be divided into three categories by their duration of action: short (20 to 45 minutes) such as procaine, intermediate (1 to 3 hours) such as lidocaine and prilocaine, and long (several hours) such as tetracaine, etidocaine and bupivacaine. Duration increases with the amount of drug injected, and so does the risk of systemic toxic reactions. Therefore, duration of action is more safely prolonged by the addition of epinephrine[34] (see above). As noted above, lidocaine, etidocaine, and bupivacaine are now generally preferred over procaine.

Lidocaine produces more prompt, intense, long-lasting and extensive anesthesia than does an equal amount of procaine.[77,34] Unlike procaine, which is an ester, lidocaine is an aminoethylamide and, therefore, is less likely to provoke hypersensitivity reactions.[34] Systemic side effects characteristic of lidocaine include sedation and dizziness. Lidocaine is available as lidocaine hydrochloride (Lignocaine, Xylocaine, others) in dilutions from 0.5% to 4%, with or without epinephrine (1:200000; 5µ/ml), which can double the duration of effect.[34] Dilutions of lidocaine used for infiltrations and blocks are usually between 0.5% and 2%.[32,33] When used without epinephrine, up to 7 mg/kg of 0.5–2% lidocaine solution (0.7 ml/kg for a 1% solution) can be used for nerve block or infiltration anesthesia.[34] The difference between the 1% and 2% concentrations has been studied in ulnar nerve motor blocks: lidocaine 2% demonstrated a faster onset (5 minutes at 2% vs 7 minutes at 1%; maximal blockade achieved after 15 minutes and 11 minutes, respectively) and longer duration of action (4 hours for 2% vs 3 hours for 1%) than lidocaine 1%.[78]

Etidocaine (Duranest®) and bupivacaine hydrochloride (Marcaine®) are now preferred by many rehabilitation teams for tests of muscle relaxation, because their duration of action is greater than that of lidocaine. Bupivacaine is also more potent than lidocaine, and can be used in amounts up to 3 mg/kg of 0.25 to 0.75% solution (0.6 ml/kg for a 0.5% solution).[34] Bupivacaine may be preferred to lidocaine, especially to determine whether functional improvement may result from long-term chemodenervation, since its longer duration of action may allow more thorough assessment during the anesthetic period. Etidocaine is a long-acting derivative of lidocaine that is favored by some clinicians for its propensity to block motor fibers more than sensory fibers.[56] Its effects last 2–3 times as long as lidocaine, with about the same induction time.

Etidocaine is available in 0.5% and 1.0% solution with or without epinephrine, and in 1.5% solution with epinephrine (1:200,000; 5 mg/ml). The maximal dose is 6 mg/kg without epinephrine and 8 mg/kg with epinephrine.

Technical Issues for Use in Patients with Muscle Overactivity

Site of Local Anesthesia

In patients with spasticity, the preferred sites for local anesthetic block are intramuscular and perineural. Both can be useful and for both we recommend the use of the technique of exploratory stimulation (see below).

Intramuscular Local Anesthesia

The maximum effect of an intramuscular block may be obtained when the drug is injected within the target muscle in the vicinity of the neuromuscular junctions,[79] which is consistent with the known sensitivity of neuromuscular junctions to local anesthetics.[63-65] Intramuscular blocks may be more painful than nerve blocks at proximal branches or sensorimotor trunks.[80] Larger volumes of anesthetic increase the likelihood of spread of the solution to nearby muscles or other structures (nerve trunks) that one may not wish to affect.[34]

Nerve Block Anesthesia

A mixed peripheral nerve consists of individual nerve fascicles surrounded by an epineurium. The vascular supply is usually centrally located. When a local anesthetic is injected near a peripheral nerve, it diffuses from the outer surface toward the core down its concentration gradient, blocking first the nerve fibers located in the outer mantle of the trunk. These fibers usually innervate more proximal structures than those situated near the core. The duration of their blockade is also longer than for central fibers, because the vascular uptake of the anesthetic usually occurs primarily in the core of the mixed nerve.

Stimulation Technique

For both intramuscular and nerve block techniques, we recommend the exploratory stimulation technique, as for botulinum toxin injections,[81-83] which is the technique traditionally used for nerve blocks in anesthesiology.[84] The same needle that will inject the drug is used to transmit repetitive monopolar stimulation of the targeted nerve or muscle, in order to adjust its position. The tip of the needle is directed as close as possible to the nerve trunk by searching for the minimal stimulation able to elicit the appropriate paresthesia or muscle twitch. Similarly, the needle will lie selectively in the targeted muscle when the largest bulk of twitch, as assessed clinically, is obtained in isolation with the minimal possible stimulation. For the most precise localization among muscles, the stimulation area must be as small as possible. Therefore, pulse widths should be as short as possible (0.1 to 0.5 ms) and needles of small caliber (27G) should be used. These needles are commonly used for botulinum toxin injections, as opposed to the 22G needles often used for nerve blocks in anesthesia, and are rigid enough to penetrate even deep limb muscles.

Indications: Diagnostic Procedures and Therapeutic Tests

Intramuscular local anesthesia (lidocaine, etidocaine, bupivacaine) has long been used as a diagnostic tool.[85] The short duration of effect of local anesthetic blocks makes them useful as temporary tests, before providing a long-lasting treatment.[86] A local anesthetic block can help answer a number of questions, not only about therapeutic indications, but also about the mechanisms involved in the functional impairment.

Prediction of Functional Changes with Long-term Therapy

The primary question addressed by a short-term block is whether a long-term block of the same muscle or nerve might be functionally useful. In order to answer this question, objective means of functional assessment must be designed before the block.

Understanding of Impairment Mechanisms

To accurately evaluate the mechanisms of impairment using short-term block, we recommend that the block be powerful enough to significantly weaken the muscle injected (as opposed as to merely reduce reflex reactions to stretch). The experience with alcohol and phenol injections (see below) as well as with botulinum toxin[87] suggest that, regardless of the blocking agent, significant weakening of the injected muscle may be required to allow function of antagonists in spastic patients. The issues that a local anesthetic block may then help address include:

I. *What are the relative roles of muscle overactivity and of contracture in the pathologic resistance to movement and the impairment of function?* By temporarily paralyzing a muscle without lengthening it, the block may provide an answer to this question.

II. *Which muscles contribute to the pathologic posturing?* Glenn has provided a remarkable illustration of this question with the example of foot inversion during gait.[80] In some cases of foot inversion during swing phase of gait, the deformity may result from the inability of the tibialis anterior to overcome overactive or contractured plantarflexors, so that all of its contractile force attracts the foot towards inversion rather than dorsiflexion.[80] In such cases, blocking the pure plantarflexors (soleus and gastrocnemii) may confirm this hypothesis by reducing the varus deformity if the resistance opposed by the pure plantarflexors is due to overactivity and not shortening. In other cases, inversion during swing phase is primarily due to overactivity of the tibialis posterior, which may be confirmed by blocking this muscle.

III. *What is the level of active performance of the antagonistic muscles, once free of opposing co-contraction?* One may answer this question only if the shortening of the injected muscle is not severe enough to block the range of movement of the antagonists (see preceding question).

IV. *What are the contributions of spasticity and contracture in the resistance to passive stretch?* This is a more technical issue relating to the interpretation of the clinical examination. It is overlooked by any rating scale that assesses both active and passive tissue reaction by examining only its subjective severity (mild, more marked, considerable)[14] instead of assessing its type (existence of a catch-and-release or of a clonus, fatigable or not, which are specifically produced by muscle contraction in reaction to stretch, and not by soft tissue resistance).[22]

Other Uses of Local Anesthetics in Overactive Muscles

Local anesthetic blocks have also been used as preparation for casting (plaster or fiberglass) treatment of contractures.[80] Placing the extremity in a cast soon after the block stretches the relaxed muscle, which may inhibit the return of overactivity and help improve the efficacy and tolerability of the cast. However, forceful overactivity may return within the cast so that the angle of the cast may be adjusted at only 50% of the gain in passive range of motion obtained from the block.

Finally, lidocaine has been used as analgesic for intramuscular injection procedures when mixed with the medication to be injected. It has been demonstrated to reduce the pain associated with intramuscular injection of antibiotics,[88] at the time after the injection, and at 10-minute, 20-minute and 6-hour intervals. A similar effect has been demonstrated with prilocaine for intramuscular injections of the anesthetic propofol.[89] Authors have used lidocaine in this indication when injecting alcohol into muscles,[32,90,91] and for steroid injection around nerves or epidurally.[92-94] However, propofol was required in greater amounts when mixed with prilocaine than when mixed with saline. A binding between the algesic part of the propofol molecule and the local anesthetic agent may explain this finding.[89] The possibility of similar interference should be considered when using lidocaine mixed with alcohol.[32]

Local Anesthetics: Summary
Local anesthetics block both afferent and efferent impulses in muscle. Their use requires available resuscitation equipment. When long lasting blocking treatment is being considered, a temporary block with a local anesthetic may be useful to assess the mechanisms of functional impairment and to help predict what improvement may be expected. In order to answer these questions, we recommend that the block produce measurable weakening in voluntary power of the targeted muscles, since spastic co-contraction, a phenomenon of primarily descending origin, is likely to play a major role in pathologic resistance to movement in patients with spasticity.[13,87]

Blocks By Structural Damage: Alcohol and Phenol

Chemical Neurolysis in Spasticity
Glenn[80] has defined a nerve block as "the application of chemical agents to a nerve to impair, either temporarily or permanently, the conduction along the nerve," while chemical neurolysis "is a nerve block that impairs nerve conduction by means of destruction of a portion of the nerve."

Initial reports of chemical neurolysis used as local or regional treatment of muscle overactivity involved injections of 2–5% carbolic acid (phenol) intrathecally,[95,96,51] perineurally[97] and intramuscularly,[98] and of 35–45% ethyl alcohol (alcohol), epidurally,[99] intramuscularly[90] and perineurally,[100,52] and intrathecally.[101] As with local anesthetic blocks, this early experience was encouraged by the speculation that phenol and alcohol would selectively affect small-diameter fibers.[37,51,52] However, this was later disproven.[102] While Tardieu performed controlled studies of chemical neurolysis,[103,104] the literature contains mostly anecdotal reports. These have indicated that spasticity is relieved following these treatments, with effects lasting from months to years.[79,80] Intrathecal neurolysis is now rarely used, and the main types of injections currently used are perineural,[105] i.e. close to a nerve trunk, also called "mixed sensorimotor nerve blocks", and intramuscular at the motor point, called "motor nerve blocks"[80] or "neuromuscular blocks."[79] Perineural injections are considered easier and more effective than intramuscular, and are usually preferred for proximal muscles or when several muscles are to be injected in the same nerve territory. For example, perineural injections can be used for treating muscle overactivity in muscle groups that are less accessible to direct injection, such as iliopsoas, quadratus lumborum, or paraspinals[100] (see below).

KEY POINTS

- Alcohol appears to be safe and efficient in relieving muscle overactivity when injected in intramuscular injections close to the motor point

Alcohol Injections

Ethyl alcohol ("alcohol" hereafter) was the first alcohol compound to be studied experimentally on nerve cells[106,107] and used for neuromuscular block,[99,103] and the only one assessed in controlled protocols for this indication.[103,104] Despite a better safety record than phenol (see below), alcohol has not been used as extensively for the treatment of spasticity.[80] Neurologists used local injections of alcohol for sympathectomy (lumbar paravertebral injections) and for the treatment of pain (trigeminal neuralgia, intractable carcinoma with paraganglionic and plexic injections)[108] prior to its use in spasticity. We review its mechanisms of action based on animal research, and its risks, results and clinical indications.

Histological and Physiological Effects
Perineural injections: At low concentrations (5 to 10%), alcohol acts as a local anesthetic by decreasing sodium and potassium conductance; at higher concentrations, alcohol is a hypobaric compound that non-selectively denatures proteins and injures cells by precipitating and dehydrating protoplasm.[108] In 1912, May showed in animals that absolute alcohol causes degeneration of neurons, with extensive fibrosis and partial regeneration.[106] At lower concentrations, axonal destruction was inconstant. Functionally, there was always full recovery of paralysis, and with 50% alcohol, no weakness was detected. Gordon studied 80% alcohol, producing various degrees of neuronal degeneration and surrounding fibrosis.[107] Functionally these injections caused some degree of weakness without complete paralysis. Labat, using 48% and 95% alcohol in dogs, also provoked temporary paralysis with both concentrations, lasting usually less than 2 months.[109] The degree of weakness was not correlated with the concentration used.

Tardieu and colleagues applied 35% alcohol into the posterior tibial nerve on one side in healthy cats, with the other side left untreated.[103,104] The cats were first observed for several weeks: they walked, ran, and jumped normally despite the block. A midcollicular section was then performed for decerebration. Despite the preservation of strength in the "blocked" leg before decerebration, there was diminution of spasticity after decerebration resulting from the nerve block. Furthermore, tension produced by the stretch reflex was reduced, while tension produced by stimulation of the tibial nerve was not.

Histological analyses were performed three weeks after application of alcohol. On the injected side, there were lesions in the myelin, mostly in small fibers, with no axonal damage.[103] Endplate cholinesterase activity was measured on both sides, and was reduced in the endplates of the muscle spindles on the treated side only. The authors did not find any abnormality in the cholinesterase activity of the extrafusal fibers. Clinically, voluntary movement was normal. Tardieu suggested that these findings supported a selective effect of alcohol at 35% on small diameter gamma motoneurons. However, Fisher and colleagues studied the evoked response of fibers injected with 35 to 47% alcohol soon after exposure, and found that the injection had a non-selective effect on the responses of fibers of various diameters.[110] The absence of selectivity of the effect of perineural alcohol injections was later corroborated by further histological studies with alcohol 10 to 50%, which showed that all fiber types and sizes were affected equally.[111]

Intramuscular injections: Absolute alcohol injected at doses up to 10 ml/kg into muscle in the hind leg of rats produces local dose-dependent coagulation necrosis, followed by granulation tissue formation and subsequent fibrosis.[112] Biopsies of sites previously injected with 45% alcohol have demonstrated muscle necrosis and inflammatory cells within the damaged areas.[113] At lower concentrations, from 20 to 40%, alcohol is still myotoxic in animals[112,114] with creatine kinase release inhibited by adjunction of dibucaine, a potent local anesthetic.[114] The destructive effect of alcohol on tissue has led some authors to propose absolute alcohol as a local antitumoral treatment by topical injection for cancer,[115] in thyroid or parathyroid nodules,[116,117] or as sclerotherapy for venous malformations.[118]

Adverse Effects

There have been relatively few reports of adverse effects of intramuscular and perineural alcohol injections as compared to phenol. This may correspond to greater safety of alcohol or to the fact that phenol has been used more extensively in the last three decades, with more reports of adverse events using this compound. The adverse effects of alcohol injection include:

Pain at injection: Ethyl alcohol injected intramuscularly causes burning pain, such that some have suggested conscious sedation or general anesthesia, particularly in children.[79] Application of lidocaine spray or cream over the skin insertion site (Emla®), or injection of lidocaine or other local anesthetic into the injection site prior to alcohol injection, also decreases the pain experienced during the procedure.[100,32]

Vascular complications: Carpenter has reported the possibility of local hyperhemia (redness) usually lasting less than 36 hours after alcohol injection.[85,113] O'Hanlan and colleagues reported several cases of phlebitis, which they ascribed to poor preparation of the alcohol ("state store" alcohol). They observed no cases of phlebitis when alcohol was prepared in a pharmacy.[119] A case of transient spinal ischemia following a deep plexus alcohol injection has also been reported.[120]

Permanent peripheral nerve palsy has been reported in the obturator and peroneal nerves.[79,80]

Skin irritation may be secondary to superficial injection. Torpid ulcerations have also been reported after alcohol injection of superficial nerve fibers.[121]

Systemic effects. Ninety to 98% of ethyl alcohol that enters the body is completely oxidized, and patients may exhibit signs and symptoms of acute intoxication in the immediate post injection period.[79]

Painful muscle necrosis has been a rare problem in children when using alcohol concentrated beyond 75%.[122]

Motor Nerve Blocks in Spasticity: Clinical Results and Current Indications

In the early 1960s, Tardieu and colleagues proposed injection of a local chemical neurolytic compound directly into muscle.[100,90,103] They injected 45% alcohol into muscles at the motor point in children with cerebral palsy and reported that spasticity was reduced in most cases without affecting voluntary strength. They reported a duration of effect from 6 to 12 months and occasionally as long as 2 or 3 years.[100,90,103,104] The treatment was then evaluated by other authors[119,123,85,113,124] and modifications in the technique were proposed.[119,85,113] O'Hanlan used the same dilution of alcohol, but did not try to target the motor nerves specifically.[119] He injected large quantities of 45% alcohol (between 10 and 40 ml according to the muscle) into multiple locations within the target muscles of spastic patients. Like Tardieu, O'Hanlan observed significant reduction of spasticity in the 10 cases reported without loss of voluntary motor power. Sensation was also reported to remain intact.[119] Carpenter and Seitz, using 45 to 50% alcohol, popularized this technique under the name "intramuscular alcohol wash."[85,113] The procedure was performed under general anesthesia because of the local pain during injection. These authors obtained their best results with gastrocnemius muscle injections. The muscle was divided into quadrants, and 2 to 6 ml of alcohol were injected into each quadrant. The authors reported that the treatment eliminated the equinus gait in 128 of 130 children injected. Results from injections into other muscles were not as consistently good. However, the duration of effect was shorter than that reported by Tardieu et al., with a return of equinus posture 7 to 20 days after the gastrocnemius injections. Overall, the effects lasted only from 1 to 6 weeks. Muscle biopsies performed in 6 patients 4 to 6 weeks after the injection revealed a round cell infiltrate without fibrosis.

Chua and Kong recently reported their open experience with alcohol injection into the musculocutaneous nerve, the sciatic nerve, and the obturator nerve in hip adductor spasticity.[125-127] After neurolysis of the musculocutaneous nerve with 50% alcohol, effects on elbow flexor tone and passive range of elbow extension lasted at least 6 months.[125] Similar outcome was observed in knee flexor spasticity after injection of 50% to 100% alcohol into the sciatic nerve (6 of the 8 patients treated were non-ambulatory before the injection).[127] Only qualitative information on functional changes is available from these open reports.[125-127]

Other Indications in Intramuscular Injections

The expanding indications for intramuscular alcohol injections should encourage clinicians to consider alcohol more often for muscle overactivity in spastic conditions. Alcohol has recently been used in association with 0.5% to 1% lidocaine, in repeated injections as local treatment of upper limb dystonia (10% dilution)[32] or spasmodic torticollis (99% dilution).[91] Its lesional effects on muscular tissue have also been exploited to lesion the "re-entry circuits" characteristic of Wolff-Parkinson-White Syndrome; intracardiac injections of absolute alcohol for this indication have been studied in animals[128] and used in patients.[129,130]

Other sites of Injections

There are few reports of intrathecal alcohol injections for spasticity.[101,131,132] In a recent case report concerning a bedridden patient with severe spastic paraparesis, no adverse effects occurred and tone relief was marked in the lower limbs.[132] However, the authors consider this site of injection a last-resort solution, when other treatments are impossible or not suitable.[132]

Dilutions Used

The dilution range most commonly reported in treatment of spastic overactivity with alcohol injections has been 35% to 60%.[99,119,124] In our experience in adults, these dilutions have proved insufficient to achieve long duration of effect and we routinely use absolute (98%) dehydrated alcohol (Faulding Pharmaceuticals Co, or Taylor Pharmaceuticals) for motor point injections.

Conclusion: Alcohol for Chemoneurolysis

Alcohol appears to be safe and efficient in relieving muscle overactivity when injected in intramuscular injections close to the motor point, although it acts by destruction of muscle and nerve tissue. Perineural injections carry the risk of temporary sensory deficit or pain.[52,101,127] Controlled clinical studies are required to assess the value of alcohol compared to phenol and to botulinum toxin in spastic muscle overactivity.

KEY POINTS

- Whichever blocking agent is under consideration, the technique of exploratory stimulation should be used for injection, whether a nerve or a muscle is targeted.
- Many clinicians combine alcohol or phenol blockade of large muscles with botulinum toxin injection into smaller and more distal muscles that can be targeted selectively

Phenol Injections

Phenol (benzyl alcohol, or carbolic acid) is the major oxidized metabolite of benzene, a known human leukemogen and ubiquitous environmental pollutant, which has widespread use as a disinfectant and antiseptic. Cell damaging properties of phenol were first exploited in antispasticity treatment with intrathecal administration.[95,96] Khalili and collaborators[97] then performed perineural injections and Halpern and Meelhuysen,[98] Delateur[133] and Awad[134,135] pioneered intramuscular injections. Since then, phenol has been used mainly in adult stroke or brain trauma patients.[79,136-139] Successful use of phenol in children with cerebral palsy has also been reported.[140,105]

Metabolism and Risks

Following oral or intravenous administration in mice, phenol is metabolized into phenol sulfate, phenol glucuronide, and hydroquinone glucuronide.[141] Both phenol and hydroquinone have synergistic effects in myelotoxicity and genotoxicity in the bone marrow of mice.[142] Benzene causes leukemia and aplastic anemia in humans, and its oxidative metabolites phenol and hydroquinone have been implicated in producing leukemia associated with benzene exposure, because they reproduce the hematotoxicity of benzene, cause DNA and chromosomal damage found in leukemia, and alter hematopoiesis and clonal selection.[143] To our knowledge, no retrospective or prospective studies have been reported in patients, in particular in children, about the genotoxic and myelotoxic risk of repeat phenol injections. However, methods for detection and quantification of phenol in plasma have been developed to increase safety in environmental and industrial use, and for children given injections of dilute phenol.[144,145]

Histological Effects

Perineural injections: Like alcohol, phenol denatures protein, causing tissue necrosis. As with local anesthetics and alcohol, the destructive effects of phenol are non-selective across fiber types, and correlate with the concentration of phenol applied.[102] At 5% in saline, coagulation of peripheral nerves at the site of injection occurs one hour following injection, with the axons in the center of the nerve less affected when phenol is dripped onto the nerve. Wallerian degeneration occurs in the weeks following injection and eventually, there is regrowth of most axons,[146] including gamma efferent axons.[147] However, after administration of only 2% aqueous phenol, the main effect around the nerve is damage to the microcirculation, including slugging, oscillation, plasma skimming and inverted flow.[148] This may lead to occlusion of small blood vessels and fibrosis in the injected area, and might account for long-term effects.[146,148,149]

The tissue-destructive effect of phenol is potent. A case of focal necrosis of the ureter was reported following CT-guided phenol sympathectomy,[150] and intramural injections of phenol are commonly used in experimental cardiology in to produce localized heart infarction.[151] However, Koman reported that neutralization with alcohol limits damage to surrounding soft tissue when phenol is applied directly to an exposed peripheral nerve.[79] This technique has been used in some of the "open" techniques that have become more frequent in recent years.[105,136,137,152]

Intramuscular injections: Intramuscular injection of aqueous phenol in rats and dogs produces neurogenic atrophy of the muscle by 2 months, and collateral reinnervation and regeneration of muscle fibers.[153] Halpern[153] observed local necrosis of muscle and an associated inflammatory reaction of the fascia and subfascial tissues. The reaction began within days of the procedure in dogs and rats, was intensified by the end of two weeks, and then began to resolve. Return to normal of the muscle at three months only occurred if the concentration of aqueous phenol used was lower than 3%.[153]

Other sites of injections: The risks associated with other injection sites, in particular intrathecal and epidural, are now well documented.

Following the first reported intrathecal injection of phenol[154] and the early work of Nathan, and Kelly and collaborators[95,96] in spasticity, subarachnoid administration of phenol was often used in the 1960s and 70s.[155-158] This technique is now rarely used in antispastic indications, and is generally reserved for severe tetra- and paraplegic patients,[159,160] because of the spinal risks.[161-166] However, it continues to be used in analgesic indications for pain related to intractable cancer or multiple sclerosis.[167]

Epidural phenol injections have been used to target otherwise inaccessible proximal muscles (i.e. iliopsoas, quadratus lumborum), or lumbar or sacral paraspinal muscles.[168] Histopathologic changes in spinal cord after epidural 3% and 6% phenol administration have been studied.[169,170] With both dilutions, damage affected predominantly posterior nerve roots, and there was also direct spinal cord injury.[170] Katz and colleagues report the greater difficulty controlling the spread of epidural versus subarachnoid phenol, and they suggest that the risks of epidural phenol might outweigh the benefits.[170] Finally, the intrinsic complications of any epidural intervention must be considered, especially the possibility of spinal subdural hematoma.[171]

Lumbosacral paravertebral blocks with phenol carry the risk of accidental intrathecal injection via the root sleeves,[172] and this could also cause cauda equina or spinal cord injury (see below).

Physiological Effects

Concentration lower than 3%: With perineural injections of concentrations up to 2% in water, phenol has only local anesthetic properties. It may be faster acting than with 2% lidocaine,[173] and has been used as a topical local anesthetic agent.[174] This rapid effect probably accounts for the transient anesthesia and weakness that are commonly seen after nerve blocks, and can be a confounding effect if the assessment is made too early after the injection. Studies of the action potentials obtained by electrical stimulation after injection of 2% phenol around a nerve show a depression with a biphasic time course.[148] A first depression occurs soon after injection, followed by transient recovery, and then a second depression appears after 30 minutes. The first depression corresponds to the local anesthetic property, while the second depression is considered to be due to circulatory damage of the nerve fibers[148] (see above). At very low concentration (0.5%), the local anesthetic effect of phenol is synergistic with that of a local anesthetic of long duration (bupivacaine),[175] in contrast with the propofol/prilocaine combination discussed above.[89] Clinically, phenol concentrations lower than 3% generally give poor results and require frequent repetition of blocks.[176] Hence, the dilution used most usually in clinical indications is 3 to 6%.

Concentration above 3%: At phenol concentrations above 3%, there is almost immediate and then monophasic, constant denervation in EMG studies in humans.[173,174,177] A recent volume and concentration ranging study in animals shows that, in the range of 3% to 5% concentration, the conduction block is concentration- and volume-dependent.[148] This 3% limit is consistent with the pattern of histological results presented above.[153] A recent study examined the effect of a 5% aqueous solution of phenol when applied to a rat nerve.[179] Axonal degeneration was evident within the injected nerve two days following phenol application. By two weeks, the innervated muscles had atrophied to almost 50% of control. Reinnervation occurred between two and four weeks following the nerve block, but at five months, maximal tension of the innervated muscle was only 74% of control and the muscle consisted of more fast fibers on average. The authors concluded that the injury to the nerve caused by 5% phenol was chronic and more severe than a crush injury.

Differential Effect on Descending and Reflex Contractions?

With phenol treatment, as with local anesthetics and alcohol blocks, it appears that strength is more often preserved than stretch reflexes.[103,104,119] Animal studies show that phenol block results in complete denervation of muscle spindles, followed by a rapid sensory reinnervation, and that reinnervation by gamma motoneurons is either incomplete or significantly delayed.[147] As noted by Fisher,[110,180] the relative preservation of voluntary strength in the face of dramatic reduction in spasticity does not have to be the result of a putative immunity of motoneurons to neurolytic agents (a hypothesis which was ruled out histologically,[102] see above). Interrupting both efferents (alpha and gamma motoneurons) and afferents (from the muscle spindle) may be sufficient to cause synergistic effect upon reflex contractions, greater than the effect on contractions of descending origin, which bypass the segmental afferent pathway. This may be true even when only interrupting the alpha and gamma efferents, since gamma efferents act functionally as afferents, as they enhance the messages coming from spindles. Hence partial curarization, which affects only the neuromuscular junction and not afferents, has also been shown to reduce spasticity to a greater degree than voluntary strength.[181] We observed the same phenomenon with injections of botulinum toxin in the upper limb of hemiplegic patients.[182]

The differential effect on voluntary and reflex contractions may therefore depend largely on the number of paralyzed peripheral neurons, with reflex functions such as spasticity being affected by a relative small reduction in number, and voluntary strength, or other forms of "non-afferent" command of movements (including spastic co-contractions), requiring a quantitatively larger reduction. However, this differential effect may not be clinically useful, since only a mild weakening after nerve block has not been associated with functional benefit from the injection.[80,87,182]

When correlating histological and physiological effects of phenol injections, it appears that significant effect depends on the use of a concentration higher than 3%, with histological destruction of nerve, as with alcohol. Many side effects observed with phenol injections are the direct consequence of this histological damage.

Adverse Effects

Apart from pain at phenol injection sites, other tolerance issues are long-term side effects and have been an important problem with phenol injections.

Pain during injection: The patient usually feels a burning sensation during the injection.[80] To our knowledge, this has not been directly compared to the pain experienced during alcohol injections.

Chronic dysesthesia and pain: The incidence of dysesthesia reported after peripheral blocks with phenol has varied from 2 to 32%.[80,183,184] The risk appears to be higher with sensorimotor blocks (perineural injection) than with motor blocks (intramuscular injection)[80] but the number of patients treated has been smaller with the latter technique. Dysesthesias are usually reported from a few days to about two weeks after the procedure, and are generally experienced as burning paresthesiae, exacerbated by light tactile stimulation, often only in a small portion of the sensory distribution of the nerve that was blocked.[183] The typical duration is several weeks[80,183] but chronic dysesthesia has been reported.[134] The mechanism is not clear, although it may involve abnormal regrowth of sensory axons.

A uniformly applied compressive garment such as a sock, glove, elastic wrap, or Lycra sleeve,[22,30] may minimize the effects of other superficial stimulation and decrease edema if present. Some authors have attempted to reblock the nerve with phenol.[183] Braun and colleagues employed surgical neurolysis to resolve persistent dysesthesia caused by median nerve blocks in two patients.[185] Occasionally systemic analgesic treatment may be required.[133]

There have been only a few published reports of severe, lancinating pain after phenol sensorimotor blocks, including one in the forearm, following median nerve block with phenol at the elbow level.[184] However, the frequency of this side effect may be underestimated, since most cases are probably not reported. The same is true for alcohol blocks.[122]

Vascular complications: Peripheral edema, particularly in the lower extremity, may follow chemical neurolysis and is said to usually resolve within a week or two.[80] Accidental intravascular injection has not been reported in association with phenol neurolysis, but injections of phenol into the stellate ganglion and into the cervical subarachnoid space for analgesic indications have been associated with infarction in the cervical spinal cord and cerebellum.[164] Deep venous thrombosis has also been reported after phenol neurolysis.[186] Mechanisms may involve necrosis of the intima of arteries and veins and thrombotic occlusion of small vessels. This makes the routine precaution of aspirating before injecting even more important with this compound. Other mechanisms that could contribute to deep venous thrombosis in an injected limb include trauma to the vein or loss of muscle pumping action, leaving the extremity more susceptible to stagnation of venous blood. However, these mechanisms exist with injection of any blocking agent.

Cutaneous side-effects: Skin slough has been reported after phenol injections.[80]

Excessive motor weakness: Although aggravation of disability by excessive paralyzing effects may be a risk with both perineural and intramuscular blocks, strength has usually been reported to be preserved following phenol injections,[97,183] as with alcohol blocks. As discussed above, the use of diagnostic blocks with local anesthetic agents may help anticipate functional consequences of longer lasting procedure, even though local anesthetic block may not be equivalent to a block with phenol.

Sensory loss: Permanent functional loss of sensation is a rare occurrence following mixed sensorimotor nerve blocks with phenol.[80] Sensory loss is common in the first hours or days following the procedure but this usually resolves.[183,80]

Wound infection: Phenol is bacteriocidal at the concentrations used for neurolysis (as is alcohol), and local infection at the site of injection has been rarely reported.[79,187]

Systemic side effects: Overdose with phenol causes tremor,[188] convulsions, central nervous system depression, and cardiovascular collapse.[80] The amount of phenol routinely used for nerve blocks however, is usually well below the lethal range, which starts at 8.5 gr.[174] A 10 ml injection of 5% phenol contains 0.5 g of phenol. To remain within safe limits, no more than 1 g should be injected on any given day.[80] Overdosage has not been reported in association with phenol neurolysis. However, the possibility of general side effects warrants caution in avoiding accidental intravascular injection. The potential of myelotoxic and genotoxic complications[141-143] has been addressed above.

Particular tolerance issues with intramuscular injections: The additional side effects associated with motor nerve blocks are local pain and swelling that may be present for a few days or occasionally longer.[98,189] This local reaction can mimic deep venous thrombosis, especially when it occurs in the calf. Induration with tender nodules may appear one to three weeks after the injection.[190] A recent investigation of 9,845 children receiving repeated intramuscular injections of penicillin diluted by only 1.5–2 % phenol reported 122 cases of "gluteal muscle contracture", which corresponds to a morbidity of 1.36% for this side effect.[191]

Clinical Efficacy of Phenol Blocks in Spasticity

Intensity of Effect: The literature on the clinical efficacy of phenol in spasticity consists chiefly of anecdotal reports.[97,98,192-205] Khalili[192] used 2% to 3% phenol for tibial nerve blocks in a patient with dystonia, who developed superimposed spastic right hemiplegia following a neurosurgical procedure. While this resulted in reduced ankle clonus, dystonic and voluntary contractions of the plantar flexors were not affected, similar to the physiological observations reported above with this dilution of phenol. Halpern and Meelhuysen, however, reported good efficacy from 3% to 5% phenol injections on "extrapyramidal" rigidity of sternomastoid and leg adductors in two patients with Parkinson's Disease.[98] A possible explanation is the higher concentrations used. by the Danish authors[98,193] (3 to 5% used in paravertebral blocks[193]) than those used by Khalili (only 2 to 3% phenol[97,192]), which may have been sufficient to block descending outputs to the muscle rather than just the reflexes from afferents within the muscle.

To our knowledge the only double-blind evaluation of the effects of phenol in spasticity is the study published in 1998 by Kirazli et al.[138] These authors have reported a randomized study comparing 3 ml of 5% phenol injected perineurally about the tibial nerve in the popliteal fossa and 400 units botulinum toxin type A (BOTOX) injected intramuscularly to treat overactive calf muscles in chronic stroke patients.[138] Three months post-treatment, there was no difference in efficacy between the two techniques. Complications such as common peroneal nerve palsy occurred with perineural phenol only, such that intramuscular BTX-A was deemed safer than perineural phenol. There has not been a comparison of these two agents using intramuscular injection for both.

Modifications of afferent input to the spinal cord by the block may account for some clinical effects, whether these afferent modifications are due to direct afferent block by the compound or simply to a massive reduction of afferent impulses from a muscle that now does not contract as much. For example, Mooney and colleagues[149] found that two of eight patients with upper extremity synergy patterns had global weakening of these patterns following phenol neurolysis of only motor branches of the median nerve.

Duration of effect: The reported duration of clinical effect of phenol injections has been variable, in contrast to some precise physiological data.[179] The recurrence of overactivity in injected muscles is believed to be due to subsequent regeneration of injured motor nerves taking place after the Wallerian degeneration.[79,179] As discussed above, long-term effects may be secondary to muscle necrosis and fibrosis, endoneural fibrosis, or local vascular injury caused by non-specific protein denaturing within the injection zone.[79] Khalili[192] reported a duration of efficacy from 10 to 850 days in a series of 94 peripheral nerve blocks using 2% to 3 % phenol (average 317 days = 10 to 11 months). Petrillo and colleagues[183,202] reported an even longer duration of effect of tibial nerve blocks with 5% phenol (29 months in their long-term follow up report). Katz et al[203] found that of 31 effective peripheral nerve blocks out of a total of 56 using 3% phenol, only 9 lasted for longer than one month. After intramuscular neurolysis with 5% phenol, Easton and colleagues[190] reported similar variability in the duration of effect, ranging from 1 to 36 months. These are some examples of an abundant and divergent literature. There are no controlled comparisons of the effect of the treatment site on outcome.

Overall, several different factors may influence the duration of effect, but none has been studied in a controlled fashion:

- Concentration and volume used for injection;[149,178]
- Site of the block: intramuscular, peripheral nerve, paravertebral, "intramuscular targeting endplates."[133]
- Treatment variables after the block; for example, if the muscle is effectively stretched after nerve block, spasticity may be further controlled and a longer-term benefit could ensue.[22]
- The presence of selective motor control in the muscles supplied by the nerve treated prior to the block may be associated with a longer duration of effect.[185]
- The outcome selected: global resistance to passive movement,[14] or specifically the component of this resistance due to spasticity.[22]
- Number of prior injections: Awad[134] and others have suggested that the effect of phenol injections may become definitive after 3 or 4 injections. Others have not reported a different duration of effect from first injections.[184]

Technical Issues

Dilution and dose: Selected peripheral nerves can be injected with 4% to 6% aqueous phenol percutaneously or at higher concentrations under direct vision.[152,105] Glycerin may be added to render the phenol more soluble in aqueous solutions.[79] Quantities of 5% aqueous phenol injected onto peripheral nerves usually vary from 1 to 10 ml.[183]

Injection procedure: Unlike lidocaine and other relatively short-acting agents, the effects of aqueous phenol have a long duration. Therefore, clinicians must be particularly careful with the injection technique as an adverse event may last for a long period of time. Adjustment of the appropriate position of the needle tip should be done using the same technique of exploratory stimulation as described above for local anesthetics.[81,82,86] The requirement of exploratory stimulation is particularly evident with "difficult" targets such as the nerves to the subscapularis muscle,[204,200] the obturator nerve,[135,86] or the nerves to the hip flexors.[135,205] For even more difficult locations, such as the motor branch of the ulnar nerve to release tone in the intrinsic muscles of the hand, surgical access may be helpful.[152,197] In children with cerebral palsy, general anesthesia has been recommended for perineural injections,[79,190,206] in particular when exposing the target peripheral nerve surgically, and at least deep conscious sedation for percutaneous injections in a safe manner.[79]

Sites of blocks

Perineural: In comparison with motor block, perineural block carries the additional risk of chronic dysesthesia, but may have a longer duration of effect. One must exercise caution in the use of a perineural procedure in a patient for whom mild pain might generate significant disability (i.e., secondary gain), or become the focal point for the displacement of other anxieties.[80]

Perineural in lumbosacral paravertebral regions: Taking the risk of chronic dysesthesia may be the only solution for muscles that are difficult to access directly, such as the psoas major, because of its size, the quadratus lumborum because of its proximity to the peritoneal cavity and the kidney, and the paraspinal lumbar or sacral muscles.[99] To target these muscles, injection can be made at the paravertebral level,[192,193] because the peritoneal cavity is protected by the combined depth of the paraspinal and psoas muscles.[80] Either mixed sensorimotor or motor nerves can be isolated in this area.[80] However, this site of injection also carries the risk of accidental intrathecal penetration of phenol[172] as discussed above. In addition, a muscle like iliopsoas is technically difficult to identify and fluoroscopy, ultrasound or CT guidance may be required.[205]

Intramuscular injections—endplate targeting technique: An intramuscular block, by destroying distal nerve branches, may allow easier titration of the effect than a more proximal block of the whole trunk, although the intramuscular procedure may be more painful.[206] The identification of small motor nerve branches can be facilitated by the use of atlases or charts that depict the usual location of motor points within a given muscle.[207,208] To optimize the efficacy, De Lateur[133] proposed injection as close as possible to endplate areas. Motor endplates do not occur at random in animal or human muscles.[209] They cluster at characteristic areas within most muscles (the "innervation band"), since the endplate generally lies near the midpoint of any given muscle fiber.[210] However, there are exceptions to this rule; for example, there are numerous innervation bands scattered throughout human sartorius, gracilis and gastrocnemius muscles.[210-212]

Since there is no noninvasive way to determine where the endplate-rich areas are in a muscle, DeLateur used a hollow Teflon®-coated injection needle as an electromyographic exploring electrode to find characteristic electrical potentials in the muscle at rest, signifying the immediate proximity of endplates.[133] These include the characteristic "endplate ripple" or "endplate noise,"[213-215] a low voltage increase in irregularity of the baseline of about 10 to 40 mV;[213] and monophasic spike discharges, or diphasic with negative onset, entirely or almost entirely negative in sign, with a random pattern of discharge (as opposed to fibrillation potentials). Buchtal and Rosenfalk showed that when the concentric needle was displaced slightly from the area of endplate ripple, the discrete monophasic negative spikes were reached.[213] Accordingly, when the monophasic negative spikes are found, the exploring electrode is close to the endplate zone.[133] However, the contact of the needle with endplate zones can be painful for the patient, even with slow movements of the exploring electrode. Ethyl chloride in spray, or skin wheals of Xylocaine can be used over each of the approximate cutaneous sites corresponding to endplate areas. Several areas can be explored through a single skin wheal over the predetermined cutaneous area. In addition, it is possible that the deafferentation of the skin also helps reduce clonic motor unit firing.[133] While DeLateur's technique seems attractive, it has not been replicated by other investigators and its practicality remains to be confirmed.

Open nerve blocks: These may be performed to ensure that only motor branches are being blocked, but this involves anesthesia, and an incision that might temporarily restrict the use of the extremity.[80,152] Sedation may be used if the adult patient is likely to have difficulty tolerating the procedure. In young children or aggressive, brain-injured patients, general anesthesia may be the only way to ensure a proper completion of the block.[184,190,206] Anatomic guides may help the practitioner in nerve localization.[172,216,217]

Topical Phenol and Alcohol in Other Indications

Apart from intramuscular use of phenol in spasmodic torticollis,[218-220] exploitation of the tissue-destructive effects of phenol and alcohol have included sclerotherapy in hemorrhoids[221] or esophageal varices,[222] chemonucleolysis in intradiscal injections as an alternative to surgical treatment for lumbar disc herniation,[223] retrobulbar injection for pain relief in cases of blind painful eyes,[224] subtrigonal injections in hyperactive bladder,[225] sympathectomy in limb ischemia,[226] proximal gastric vagotomy in refractory ulcers,[227] and caudal epidural injection in hyperhidrosis in patients with cervical cord injury.[228]

Conclusion

Patients with paralysis caused by CNS lesions are often affected by disabling muscle overactivity that may be treated by chemical neurolysis with alcohol or phenol into the overactive muscles or their supplying nerves. Whichever blocking agent is under consideration, we strongly encourage clinicians to use the technique of exploratory stimulation, whether a nerve or a muscle is targeted. Functional benefit from the block may depend on significant weakening in the targeted muscle. Local anesthetic blocks may be very useful to help predict whether long duration blocks are warranted, with the same caveat—without a significant weakening effect, a test with local anesthetic may not provide useful information on the potential for improvement or the mechanisms responsible for focal motor impairment.

In the last three decades, alcohol and phenol blocks have only rarely been evaluated in a controlled fashion. For each compound, there is a need for placebo-controlled studies to reach firm conclusions on their safety and efficacy. The experience with alcohol mainly concerns intramuscular injections in children, while phenol has chiefly been used with perineural injections in adults. The number of adverse effects reported with phenol is larger than with alcohol, as is the total number of publications reporting phenol use. Whether the benzyl core of phenol carries a significant myelotoxic and genotoxic risk after repeat injection, especially in children, remains to be evaluated. Physicians who regularly administer blocks emphasize that safety increases with the experience of the clinician and that nerve blocks should not in general be performed by physicians who use them only occasionally, since proper performance of the technique requires training and experience.

Comparison with Botulinum Toxin

In comparison with botulinum toxin, alcohol and phenol have advantages in their early onset of action and perhaps longer duration of effect, low cost, absence of antigenicity, and better stability. However, their lack of selectivity on motor function, tissue destructive effect, propensity to cause pain during injection, adverse effects such as chronic painful dysesthesia, local muscle transformations, and vascular reactions may favor the use of botulinum toxin.

In current practice, many clinicians use both types of treatment in combination. Alcohol and phenol are often injected perineurally to block large muscles, for which the effective botulinum toxin dose would approach or exceed the recommended ceiling dose. Botulinum toxin is usually reserved for injection into smaller and more distal muscles that can be targeted selectively.

In the future, indications for neurolytic agents and for botulinum toxin may also be based on the severity and prognosis of the disorder, and the goals of treatment. The absence of histological destruction after repeated botulinum toxin injections and the specific action on efferent fibers might make this the preferable agent where there is hope of recovery of active function in the injected limb. Because of their chronic histological effects and the destruction of sensory fibers, alcohol or phenol may prove more appropriate than botulinum toxin in cases where treating muscle overactivity is performed primarily for hygiene and comfort, i.e. in patients with severe deficits and poor functional prognosis, where preservation of intact sensory perception is not critical. Finally, pharmacoeconomic considerations mandate that controlled comparative studies between neurolytic agents and botulinum toxin be carried out in specific patient populations to determine the appropriate indications for each. ■

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