also injected into muscles characterized with "repetitive use" disorders such as "tennis elbow" and "violinist wrist" and to treat chronic spasticity of skeletal muscle in cerebral palsy, and cervical dystonia, primary auxiliary hyperhidrosis (severe underarm sweating); it is also being investigated for the treatment of severe migraine and overactive bladder. In spastic disorders the objective is to permit the contralateral muscle to grow while the spastic muscle is relaxed.

When botulinum toxin is injected intramuscularly, it causes partial chemical denervation and diminishes involuntary contracture without causing complete paralysis. Some patients may develop tolerance to botulinum toxin by forming neutralizing antibodies.

Because botulinum toxin inhibits ACh release from all parasympathetic and cholinergic postganglionic sympathetic neurons, it may be useful for treating patients with conditions such as hyperhidrosis and detrusor sphincter dyssynergia.

**Pharmacovigilance: Side Effects, Clinical Problems, and Toxicity**

Problems associated with the use of compounds that relax skeletal muscle are summarized in the Clinical Problems Box.

**Neuromuscular Blocking Drugs**

The major side effects of the neuromuscular blocking agents are cardiovascular effects and histamine release. Their significance varies, with some older compounds exhibiting greater effects and the newer drugs having fewer effects. The long-acting nondepolarizing neuromuscular blocking drugs are generally selective for nicotinic cholinergic receptors in skeletal muscle, cholinergically innervated parasympathetic and sympathetic ganglia and cardiac parasympathetic neuroeffector junctions can all be affected if drug concentrations are sufficiently high. At normal doses most agents do not exhibit these effects except for tubocurarine, which produces a significant degree of ganglionic blockade. Because of the structural similarity of succinylcholine to ACh, succinylcholine binds to ganglionic nicotinic and cardiac muscarinic receptors and stimulates cholinergic transmission. Pancuronium exerts a direct blocking effect on muscarinic M2 receptors at doses used for neuromuscular blockade, but tubocurarine and atracurium produce muscarinic blockade only at much higher concentrations. Pancuronium and succinylcholine also produce direct muscarinic effects that result in cardiac dysrhythmias. Pancuronium also causes tachycardia and hypertension by blocking norepinephrine reuptake. The reduced cardiac effects of the newer agents greatly increase their safety margins.

Histamine release is a major problem with tubocurarine and a lesser problem with succinylcholine and mivacurium. Because of its marked histamine release and ganglionic blockade leading to hypotension and reflex tachycardia, tubocurarine is now seldom used, except as a pre-curarizing agent before the administration of succinylcholine.

The main disadvantage of atracurium is histamine release, which occurs in approximately 30% of patients. Pancuronium does not release histamine or block ganglia, but it does cause moderate increases in heart rate, blood pressure, and cardiac output as a consequence of sympathomimetic and anticholinergic effects. Histamine release may also occur with cisatracurium and mivacurium, but there are no cardiovascular effects at clinical doses.

Long-term use of several neuromuscular blockers in the intensive care unit to maintain controlled ventilation has resulted in prolonged periods of paralysis. Indications for reversal of neuromuscular block are postoperative residual curarization—that is, the inability of the patient to breathe adequately after discontinuation of anesthesia, or when it is impossible to artificially ventilate the patient after administration of a muscle relaxant. Although many criteria, such as the ability of the patient to sustain voluntary activities (adequate swallowing, coughing, eye opening, and head lifting), are used to evaluate the return of muscle function immediately after the use of muscle relaxants, monitoring the response to electrical stimulation is one of the most accurate methods to detect residual neuromuscular blockade. Other methods include electroencephalography, electromyography, mechanomyography, and accelerography.

The K+ efflux elicited by succinylcholine is dangerous in patients with neuromuscular disorders such as hemiplegia, paraplegia, intracranial lesion, peripheral neuropathy, and in patients with extensive soft-tissue damage such as burns. Plasma K+ concentrations ≥13 mM produce cardiac fibrillations and arrest. In these patients a marked resistance to nondepolarizing neuromuscular agents called extrajunctional chemosensitivity is present, probably because of an increased number of extrajunctional receptors. In addition, a combination of succinylcholine and halothane or other volatile anesthetics may result in a malignant hyperthermia syndrome in patients, which is a pharmacogenomic disorder of skeletal muscle that presents as a hypermetabolic response that can be fatal. This disorder involves an uncontrolled rise of muscle Ca++2, which is treated with dantrolene.

Neuromuscular blocking agents must be used with caution in patients with underlying neuromuscular, hepatic, or renal disease or electrolyte imbalance. Patients with neuromuscular disorders such as myasthenia gravis may be resistant to succinylcholine because of a decrease in the number of ACh receptors; the dose of muscle relaxants must be reduced by 50% to 75% in such patients. Patients with myasthenia gravis are also more likely than healthy patients to develop a phase II block in response to succinylcholine, particularly when repeated doses have been administered. Patients with myasthenia gravis exhibit much greater sensitivity to nondepolarizing agents, and the use of long-acting muscle relaxants such as pancuronium, pipercuronium, and doxacurium must be avoided in these patients. Intermediate- and short-acting nondepolarizing drugs can be administered carefully in lower doses with close monitoring of neuromuscular transmission. Lambert-Eaton Myasthenic syndrome, an autoimmune