Effective regional block is not possible without the use of local anesthetics. Even though local anesthetics have been used for more than 115 years, details about balancing risks of their toxic effects with the benefits of their therapeutic effects remain poorly focused for many clinicians. In this chapter, the most frequent toxic effect of local anesthetics – local anesthetic systemic toxicity – will be covered, as will the less-frequent clinical situations of allergy to local anesthetics and myelotoxicity.

History of Local Anesthetic Systemic Toxicity

Local anesthetic toxicity was recognized even before cocaine was introduced as a surgical anesthetic in humans. In 1868, the first report of cocaine-induced seizures in animals was cited by Moreno y Maiz. At the same time, Maiz also reported cutaneous anesthesia and asked whether cocaine might be used as a local anesthetic. Almost 20 years passed before Koller introduced regional anesthesia to the world by applying cocaine to the eye. Shortly after the introduction of cocaine as a topical anesthetic, physicians across the world began injecting cocaine near peripheral nerves, as well as into the spinal and epidural spaces. Within 10 years of the introduction of regional anesthesia, reviews of “cocaine poisoning” appeared in the literature. Mattison cited more than 125 cases of toxic reactions to cocaine, including seven deaths, with the initial report.

Despite this cocaine toxicity, the use of cocaine for peripheral nerve block was a real advantage during the later half of the 19th century, when general anesthetic techniques were still in their infancy. Nevertheless, although knowledge about the pharmacodynamics of cocaine accumulated, individuals paid a price in terms of toxicity and time. Rapid absorption limited the safe quantity of cocaine to 30 mg and the useful duration of anesthesia to 10–15 minutes. Reclus suggested that during infiltration anesthesia with cocaine, a weak solution be used to avoid toxic reactions and fatalities. It seems that Reclus clearly understood that the basic cause of accidental deaths during cocaine anesthesia was from the use of unnecessarily high concentrations and, thus, high total doses. It was this toxicity of cocaine, coupled with its tremendous advantages for surgery, which led to a search for less-toxic substitutes. In 1904, such a substitute – procaine (Novocain) – was introduced by Einhorn.

The introduction of a safer local anesthetic did not stop interest in local anesthetic toxicity. In 1919, Eggleston and Hatcher published a comprehensive summary of the prevention and treatment of local anesthetic reactions. At this early time, they were able to identify most issues of importance in the prevention and treatment of local
anesthetic systemic toxicity. They found that animals were a suitable experimental model, that different local anesthetics were additive in their toxicity, that the combination of artificial respiration and stimulation of the heart by intravenous epinephrine allowed twice the average fatal dose of local anesthetics to be administered to cats, and that the addition of epinephrine to subcutaneous injection of local anesthetics significantly reduced local anesthetic systemic toxicity. In 1925, Tatum, Atkinson, and Collins matured the concepts of Eggleston and Hatcher by identifying that artificial respiration alone was insufficient to increase the minimal fatal dose of cocaine in the rabbit, whereas the prophylactic administration of barbiturates to the dog produced a condition in which the tolerance to a toxic dose increased fourfold. Likewise, they identified that seizures related to local anesthetic systemic toxicity are completely, practically, and instantaneously controlled by barbiturate injection and that the likelihood of recovery from such a reaction to cocaine in the dog is roughly inversely proportional to the duration the seizures were permitted to continue.

In addition to the insights about local anesthetic systemic toxicity provided by these early researchers, Vandam identified two other major contributions to the understanding and treatment of local anesthetic reactions. He believed that Tanaka and Yamasaki report on the selective blocking of cortical inhibitory synapses by lidocaine (a surrogate for other local anesthetics) with the excitatory synapses being more resistant to the drug was a major contribution. He outlined a second major contribution by Englesson, who in 1974 reported the observance of seizure activity in the amygdala on cortical electroencephalography (EEG) after the intravenous infusion of several different local anesthetics in the cat. These two contributions helped mature physicians' understanding of the anatomic and neurophysiologic locus of local anesthetic-induced seizures and led to more complete knowledge of the basic science of a local anesthetic reaction.

**Basic Science**

As the researchers detailed, local anesthetic systemic toxic responses are related to blood levels of the local anesthetic and, more specifically, to the levels found in the central nervous system (CNS). There is an initial generalized excitatory phase of a local anesthetic systemic toxic reaction related to increasing levels of local anesthetic in the blood of the CNS, which again is a result of a blocking of inhibitory pathways in the amygdala. This inhibition allows facilitatory (excitatory) neurons to function unopposed. As levels of local anesthetic in the blood and brain increase further, both inhibitory and facilitatory pathways are inhibited, eventually resulting in CNS depression. Can this brief and simplified view of neurophysiologic anatomy and reaction to local anesthetic systemic toxicity be expanded to deepen our understanding?

The amygdala is indeed central to understanding a local anesthetic-induced seizure and is part of the limbic system. It is located anterior to and partly superior to the tips of the inferior horn of the lateral ventricle (Figure 4-1). The amygdala itself can be divided into basilateral and corticomedial nuclear groups, of which the former is highly developed in humans. Afferent pathways to the amygdala include dual olfactory sensory pathways, and efferent paths projecting to the hypothalamus, the thalamus, and the reticular formation. The function of the amygdala is complex. In humans, ablation of lesions in the amygdala results in a decrease in aggressive behavior and electrical stimulation of the amygdala in animals reveals changes in both visceral and autonomic function. With electrical stimulation, animals often turn their head and eyes to the contralateral side and demonstrate chewing, licking, and swallowing movements, as well as reactions of attention, rage, and fear. Amygdala stimulation in humans results in confusional states and amnesia.

Although most information suggests that the amygdala is the main and initial neurophysiologic focus for local anesthetic-induced seizures, some investigators have