6

General Pharmacological and Toxicological Aspects of Local Anesthetic Agents

Local anesthetic agents are usually applied to the specific area of the body where they exert their primary pharmacological action of conduction blockade. However, as discussed in Chapter 5, local anesthetic drugs are absorbed systemically and can affect organs other than peripheral nerves. Since these drugs may act on any excitable membranes, the cardiovascular and central nervous systems are particularly susceptible to the action of local anesthetic agents.

CENTRAL NERVOUS SYSTEM EFFECTS

Local anesthetic agents readily cross the blood-brain barrier to cause alterations in the central nervous system (CNS).

Behavioral and EEG Alterations

In general, a consistent sequence of events is observed following a progressive increase in the dose and subsequent blood level of a local anesthetic agent. At nontoxic levels, minimal CNS changes occur; the initial signs of CNS toxicity are usually excitatory in nature. Various symptoms have been described by human volunteers receiving intravenous local anesthetic drugs.[265,316–318] Numbness of the tongue and circumoral tissues is the earliest subjective symptom and probably does not reflect a CNS effect, but rather a high local tissue concentration of

drug in this highly vascular area. A generalized feeling of lightheadedness and dizziness is the first indication of CNS alterations, followed by visual and auditory disturbances, such as difficulty in focusing and tinnitus. Drowsiness, disorientation, and temporary unconsciousness have also been reported. Objective signs of early CNS toxicity consist of slurred speech, shivering, muscular twitching and tremors in muscles of the face and distal parts of the extremities. Electroencephalographic recordings do not correlate well with these early subjective and objective signs and symptoms. The appearance of slow waves and an increased amount of delta-theta activity and a decrease in alpha activity have been observed in the EEG of some subjects.[228,316]

Electroencephalographic studies in animals have revealed that the amygdala shows the most consistent changes in activity following administration of local anesthetic agents. Subconvulsive doses of lidocaine are usually associated with an electrical pattern described as rhythmic spindling.[319] Slow high-voltage cortical activity appears after the onset of changes in the amygdala. As the dose and subsequent blood level of a local anesthetic agent are increased, these initial CNS signs and symptoms progress into a generalized convulsive state of a tonic-clonic nature. This overt convulsive activity is correlated with amygdaloid spike-spindle complexes, spiking, and finally ictal episodes of a generalized nature.[319] Following this period of CNS excitation, a further increase in the amount of local anesthetic drug administered results in cessation of seizure activity and a flattening of the brain-wave pattern, consistent with generalized CNS depression. Respiratory depression and ultimately respiratory arrest are the overt manifestations of this CNS depressive state.

Since local anesthetic agents generally exert a depressant effect on excitable membranes, the cause of the initial central nervous system excitation has been a subject of considerable interest. The mechanism of the initial CNS excitation and subsequent depression is explained by the stabilizing effect of local anesthetic agents on cell membranes. Convulsive doses of lidocaine produce initially a blockade of inhibitory pathways in the cerebral cortex.[319–323] The specific site of action involves either inhibitory cortical synapses[320,321] or inhibitory cortical neurons.[323] This inhibition of inhibitory pathways allows facilitory neurons to function unopposed, leading to an increase in excitation of the CNS, ultimately manifested in convulsive activity. Further increases in dose produce a depression of both inhibitory and facilitory pathways, which results in a generalized state of CNS depression.[319]

Factors Influencing the CNS Effects of Local Anesthetic Agents

The convulsive action of local anesthetic agents is a function of the specific drug employed, the acid-base status of the patient, and the concomitant use of other CNS active agents.

LOCAL ANESTHETIC AGENT

Acute intravenous toxicity studies in animals[324–328] and human intravenous tolerance studies[23,316–318] have revealed that the dose of a local anesthetic agent required to produce preconvulsive signs and symptoms in man and frank convulsions in animals is directly related to the intrinsic anesthetic potency of the compound. For example, procaine which shows the lowest intrinsic anesthetic potency of the clinically useful local anesthetic agents, possesses the highest convulsive ED_{50} value, i.e., the dose which will produce convulsions in 50% of animals following a rapid IV injection. On the other hand, bupivacaine, which is intrinsically a very potent compound, exhibits a very low convulsive ED_{50} value (Fig. 6-1).[327] Lidocaine, mepivacaine, and prilocaine are intermediate both with respect to anesthetic potency and convulsive activity.[326]

The convulsive threshold of local anesthetic agents also has been defined in terms of the anesthetic blood level associated with the onset of seizure activity[325,326,328] and again is directly related to intrinsic anesthetic potency. For example, bupivacaine produces convulsions in

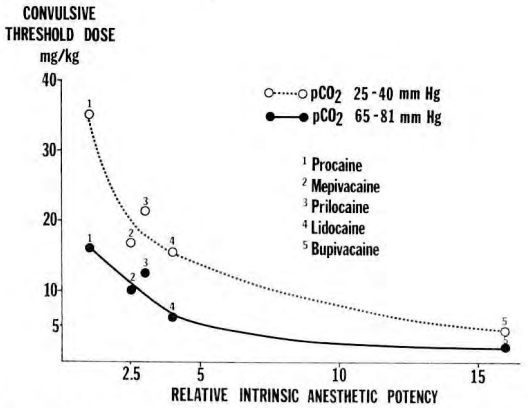


Fig. 6-1. The convulsive threshold of various local anesthetic agents as related to their intrinsic anesthetic potency and arterial pCO_2.

monkeys at a blood level of 5.5 μg/ml, whereas lidocaine-induced convulsions occur at a blood level of 26 μg/ml (Table 38).[326] A precise correlation has not been observed between venous blood levels of local anesthetic agents and CNS alterations in man.[316,318] Scott has demonstrated that the administration of etidocaine to the same subject resulted in symptoms of CNS toxicity at a venous plasma level of 2.6 μg/ml on one occasion and no signs of CNS toxicity at a venous plasma level of 3.7 μg/ml on a second occasion.[318] Possibly, arterial blood levels may serve as a more precise predictor of CNS toxicity than venous anesthetic levels. Moreover, the rate of IV administration is also an important determinant of the toxic threshold of a particular agent.[319]

Although all local anesthetic agents can induce convulsions, the preconvulsive alterations in CNS activity may vary depending on the specific local anesthetic drug administered. Subconvulsive doses of lidocaine and procaine are often associated with sedative-like symptoms of drowsiness and temporary loss of consciousness.[316,317] This type of behavioral change has not been described for other local anesthetic agents. EEG recordings in monkeys treated with lidocaine have also shown a characteristic preconvulsive pattern of diffuse slowing and irregular appearance of large spikes and slow waves leading directly into general seizure activity (Fig. 6-2).[325,328] Other local anesthetic agents such as mepivacaine, bupivacaine, and etidocaine do not consistently produce distinctive preconvulsive EEG changes. Usually a generalized seizure pattern, at the time of overt convulsions, is the only EEG alteration observed[325,326,328] (Fig. 6-2).

Table 38

THRESHOLD FOR PRODUCTION OF CNS TOXICITY BY VARIOUS LOCAL ANESTHETIC AGENTS

Agent	Convulsive threshold Monkey*		Convulsive threshold Cat**	Threshold-CNS symptoms Man		
	Dose-mg/Kg	Arterial blood level-μg/ml	Dose mg/Kg	Dose mg/Kg 1	2	3
PROCAINE	–	–	50	18–55	19.2	–
CHLOROPROCAINE	–	–	–	–	22.8	–
LIDOCAINE	14–22	18–26	22	6–9	6.4	>4
MEPIVACAINE	18	22	21	–	9.8	–
PRILOCAINE	18	20	35	–	–	>6
BUPIVACAINE	4.3	4.5–5.5	5.8	–	–	1.6
ETIDOCAINE	5.4	4.3	–	–	–	3.4
TETRACAINE	–	–	–	–	2.5	–

* data from Munson (326,328) ** data from Englesson (334)
1 " " Usubiaga (317)
2 " " Foldes (23)
3 " " Scott (318)

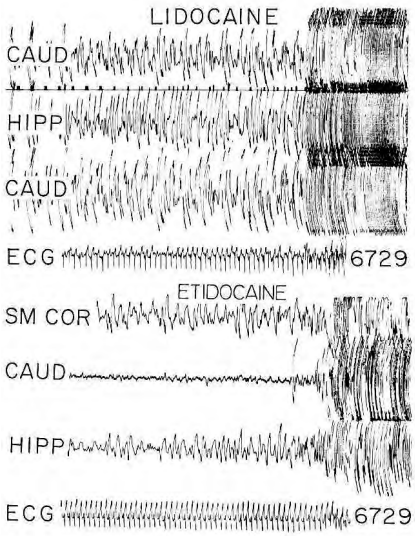


Fig. 6-2. EEG changes in one monkey (6729) following the IV administration of a convulsive dose of lidocaine and of etidocaine. Preconvulsive EEG changes are noted during the lidocaine infusion, but not during etidocaine administration. (Courtesy of Dr. E. Munson.)

ACID-BASE STATUS

The relationship of pH and pCO_2 to the convulsive threshold of various local anesthetic agents has been studied by several investigators.[319,327,329] In general, the convulsive threshold is inversely related to the arterial pCO_2 level. An increase in pCO_2 is associated with a reduction in the dosage and blood level of local anesthetic agent required to induce seizures, whereas a decrease in pCO_2 requires that a greater amount of local analgesic drug be administered in order to produce convulsive activity. For example, Englesson has reported that the convulsive threshold dose of procaine in cats was decreased from approximately 35 mg/kg to 15 mg/kg when the pCO_2 was elevated from 25–40 torr to 65–81 torr (Fig. 6-1).[327] Similar changes in convulsive threshold were observed with mepivacaine, prilocaine, lidocaine, and bupivacaine.

A decrease in arterial pH also will decrease the convulsive threshold of local anesthetic agents.[327] A study of the interrelationship between pCO_2, pH, and local anesthetic activity has shown that respiratory acidosis always decreases the convulsive threshold of local

anesthetic agents, but the degree of threshold alteration is dependent on the underlying metabolic condition.[327] A high pCO_2, associated with a decrease in arterial pH due to metabolic acidosis, will cause a greater decrease in convulsive threshold than the same pCO_2 level which is achieved in the presence of a normal or elevated arterial pH, i.e., metabolic alkalosis.

Several mechanisms have been postulated to explain the inverse relation between arterial CO_2 tension and local anesthetic convulsive threshold.[329] An elevated pCO_2 may enhance cerebral blood flow so that more anesthetic agent is delivered to the brain or may exert an excitatory CNS effect which is additive to or potentiates the convulsive action of local anesthetic drugs. A high pCO_2 also may produce a fall in intracellular pH which, in turn, will cause an increase in the intraneuronal level of the active cationic form of the local anesthetic agent.

The seizures induced by local anesthetic drugs may be prolonged by certain feedback mechanisms related to changes produced by the convulsive activity. A progressive metabolic acidosis occurs during the period of generalized seizures, which tends to prolong the hyperexcitable CNS state as the local anesthetic blood level declines.[330] In addition, an increase in cerebral metabolism and cerebral blood flow has been reported during local anesthetic-induced convulsions. Such increases would deliver more drug to the brain, which would prolong the period of seizure activity.[331]

CONCOMITANT USE OF OTHER CNS ACTIVE AGENTS

The convulsive threshold of local anesthetic agents can be increased by the prior or concomitant administration of CNS depressant drugs such as diazepam, barbiturates, and general anesthesia.[332-335] Premedication with 0.25 mg/kg of diazepam intramuscularly produced a 100% increase in the convulsive ED_{50} of lidocaine in cats,[332] whereas ventilation with 70% nitrous oxide caused a 50% increase in the convulsive ED_{50} of lidocaine. No additive protective effect was observed when 70% inspired N_2O and diazepam were employed together prior to the administration of a convulsive dose of lidocaine.[334] An increase in the convulsive threshold of lidocaine persisted for at least 5 hours following pretreatment of cats with diazepam.[335]

Studies involving the prophylactive use of barbiturates to alter the convulsive threshold of local anesthetic agents have yielded conflicting results. No difference in seizure activity has been reported

by some workers following the administration of local analgesic agents to rats and man pretreated with thiopental.[317,336] Other investigators have demonstrated a prophylactic anticonvulsant action of pentobarbital.[337,338] A comparison of 0.25 mg/kg diazepam and 10 mg/kg pentobarbital by de Jong and Heavner revealed a similar protection against lidocaine-induced seizures in cats. However, the pentobarbital-lidocaine-treated animals exhibited a greater degree of CNS and cardiorespiratory depression than did the diazepam-lidocaine-treated group.[338]

Although some discrepancies may exist concerning the relative merits of diazepam and barbiturates in the prevention of local anesthetic-induced convulsions, both types of agents are effective in terminating seizure activity produced by local anesthetic drugs. Intravenous thiopental (4 mg/kg) and diazepam (0.1 mg/kg) have been demonstrated to rapidly stop both EEG and muscle seizures in man and monkeys.[317,339]

Neuromuscular blocking agents also have been employed to prevent or reverse local anesthetic-induced convulsions. Munson and Wagman have demonstrated that gallamine can increase the lidocaine threshold for electrical seizure activity in monkeys from 26 μg/ml to 36 μg/ml.[340] Usubiaga and co-workers reported that succinylcholine terminated muscle seizure activity in man, but did not affect the duration or pattern of EEG seizure activity.[317]

Anticonvulsive Actions

Although the CNS effects of local anesthetic agents are usually considered to be undesirable, the depressant action on the CNS has proven to be of therapeutic value in certain clinical conditions.[341] Studies in animals have demonstrated that procaine, lidocaine, and prilocaine are capable of preventing various forms of experimentally induced convulsions. Infiltration of exposed scalp wound margins with 30 mg of lidocaine or 60 mg of procaine significantly increased the threshold for electrically induced cortical after-discharges in cats.[342,343] Lidocaine also exhibited anticonvulsant activity in cats with penicillin-induced epileptogenic foci[344] and in mice with audiogenic seizures and electrically induced convulsions,[345,346] while procaine was shown to protect mice against electroshock-induced convulsions.[347] Most of the clinically useful local anesthetic agents demonstrate anticonvulsant activity, and a correlation has been observed between the anticonvulsive and intrinsic anesthetic potency of the various compounds (Fig. 6-3).[341]

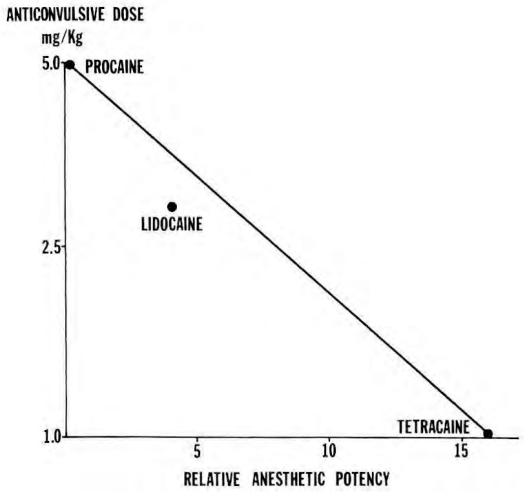


Fig. 6-3. Relationship of anticonvulsant activity of various local anesthetic agents to their relative anesthetic potency.

In general, the anticonvulsant activity of local anesthetic agents occurs at doses and blood levels considerably lower than the dose and blood level associated with seizure activity. Julien has correlated the arterial blood levels of lidocaine with the antiepileptic and seizure-inducing properties of this agent in cats in whom epileptiform activity was produced by intracortical injections of penicillin. A marked antiepileptic effect was observed at lidocaine blood levels of 0.5–4.0 μg/ml. When the blood level of lidocaine reached 4.5–7.0 μg/ml, signs of increased cortical irritability again were observed. At blood levels in excess of 7.5 μg/ml, seizure activity reoccurred.

Clinically, procaine and lidocaine have been employed to prevent and/or reduce the duration of electrically induced seizures in patients.[348,355] The anticonvulsant dose of both agents was found to be lower than the dose which caused seizure activity, e.g., 5–11 mg/kg was the anticonvulsant dose of lidocaine, whereas 16 mg/kg produced a seizure state.[348] Procaine and, particularly, lidocaine also have been utilized to terminate or decrease the duration of grand mal or petit mal seizures.[341] Presumably, the mechanism of the anticonvulsant action of local anesthetic agents in epileptic patients involves a depression of hyperexcitable cortical neurons.

CARDIOVASCULAR EFFECTS

Regional anesthesia can produce profound changes in the cardiovascular system due to the direct effect of local anesthetic agents on cardiac tissue and peripheral vasculature and also indirectly by conduction blockade of autonomic nerve fibers that regulate cardiac and peripheral vascular functions.

Direct Action of Local Anesthetic Agents

CARDIAC EFFECTS

Much information has been obtained concerning the cardiac effects of local anesthetic agents, particularly, lidocaine, because of the clinical use of this drug for the treatment of ventricular arrhythmias. Detailed studies concerning the effect of lidocaine on the electrophysiological properties of isolated cardiac tissue have revealed a consistent sequence of events as the dose and subsequent blood level of local anesthetic agent are increased[349-351] (Table 39). At doses and blood levels of lidocaine that are nontoxic, but sufficient for antiarrhythmic activity, the only discernable electrophysiological effects observed were a prolongation or abolition of the phase of slow depolarization during diastole (phase 4 depolarization) in Purkinje fibers and a shortening of the action potential duration (APD) and of the effective refractory period (ERP). However, the ratio of effective refractory period to action potential duration (ERP/APD) increased both in Purkinje fibers and in ventricu-

Table 39

CARDIOVASCULAR ALTERATIONS WITH PROGRESSIVE INCREASES IN LOCAL ANESTHETIC DOSE (LIDOCAINE)

Dose	Blood levels	Electrophysiological effects		Hemodynamic effects	
µg/kg/min	µg/ml	Cellular change	Surface changes	Cardiac	Peripheral Vascular
20-50	2-5	↓ Phase IV Depolarization ↓ APD ↓ ERP ↓ ERP/APD ↓ Conduction velocity PF-VM	–	–	–
50-75	5-10	↓ Phase 0 Depolarization ↓ AP amplitude ↓ Conduction velocity	↓ PR interval ↓ QRS duration Sinus bradycardia	↓ End-diastolic volume ↓ Intraventricular pressure ↓ Myocardial contraction ↓ Cardiac output	Vasodilation ↓ Blood pressure
>75	>10	↓↓ Phase 0 Depolarization ↓↓ AP amplitude ↓↓ Conduction velocity	↓↓ PR interval ↓↓ QRS duration Sinus bradycardia AV block Aystole	↓↓ End-diastolic volume ↓↓ Intraventricular pressure ↓↓ Myocardial contraction ↓↓ Cardiac output	↓↓ Blood pressure Circulatory collapse

lar muscle. No change was evident in resting potential, rate of rise of the action potential, or action potential amplitude. The conduction velocity in Purkinje fibers was minimally altered, whereas conduction at the junction between Purkinje fibers and ventricular muscle was enhanced. Toxic concentrations of lidocaine resulted in a decrease in maximum rate of depolarization of Purkinje fibers and ventricular muscle, a decrease in amplitude of the action potential, and a marked reduction in conduction velocity. However, even at a lidocaine concentration of 50 μg/ml, the resting potential remained unchanged. In general, local anesthetic agents appear to modify in a similar fashion the electrophysiological events in cardiac tissue and in peripheral nerve, i.e., the rate of rise of the various phases of depolarization is reduced as the concentration of local anesthetic agents is increased with no appreciable alteration in resting membrane potential and no marked prolongation of the repolarization phase. Electrophysiological studies of the heart in intact dogs and man essentially reflect the findings observed in isolated cardiac tissue.[352-355] Doses of lidocaine that are considered nontoxic produce minimal changes in intraatrial, intraventricular, and atrioventricular conduction, absolute refractory period, and diastolic threshold. As the dose of lidocaine is increased, a prolongation of conduction time through various portions of the heart as well as an increase in diastolic threshold occurs. These changes are reflected in the electrocardiogram as an increased PR interval and QRS duration and decreased automaticity, as shown by sinus bradycardia and, finally, cardiac arrest, i.e., asystole, when extremely high local anesthetic blood levels are obtained.

The electrophysiological changes produced by lidocaine are related to effects on ion flux across the membrane of the cardiac cell. Slow depolarization during diastole, i.e., phase 4 depolarization, is a function of the gradual decrease in potassium permeability across the cardiac cell membrane. Studies on isolated cardiac tissue in which ion flux measurements have been made prior to and during treatment with lidocaine have revealed an increase in potassium efflux.[356] This efflux of potassium ions may be responsible for the prolongation or abolition of the slow phase of depolarization. The increase in potassium efflux occurred in ventricular muscle, but not in atrial muscle treated with lidocaine. This observation correlates well with the antiarrhythmic efficacy of lidocaine in clinical practice, i.e., lidocaine is effective in the treatment of cardiac arrhythmias of ventricular origin, but is considerably less efficacious in controlling atrial arrhythmias. Higher doses of lidocaine were associated with a decrease in the rate of phase 0 depolarization, which presumably reflects an inhibition of sodium conductance similar

to the situation in peripheral nerve leading to conduction blockade. Detailed cardiac electrophysiological studies have not been conducted with other local anesthetic agents. However, mepivacaine, prilocaine, and bupivacaine also demonstrate antiarrhythmic activity in various animal models.[357,358]

The effect of local anesthetic agents on the mechanical activity of cardiac muscle has also been extensively studied. The results in animals are somewhat contradictory, since at relatively low doses a decrease, an increase, and no change in myocardial contractility or cardiac output have been reported.[359,360] As the dosage of local anesthetic agent is increased to toxic levels, these drugs do exert a direct negative inotropic action on cardiac muscle.[361,362] The relative myocardial depressant action of various local anesthetic agents is correlated with their intrinsic anesthetic potency.[361] For example, the anesthetic potency and myocardial toxicity of lidocaine in relation to procaine have both been reported to be approximately four to one (Fig. 6-4). In general, the hemodynamic effects of local anesthetic agents in man correlate quite well with the results obtained from animal studies.[352,363-368] At lidocaine doses and blood levels considered nontoxic, but still sufficient for antiarrhythmic activity, no alterations in myocardial contractility, diastolic volume, intraventricular pressure, and cardiac output are usually observed. A progressive increase in dose and blood levels results in decreased myocardial contractility, increased diastolic volume, decreased intraventricular

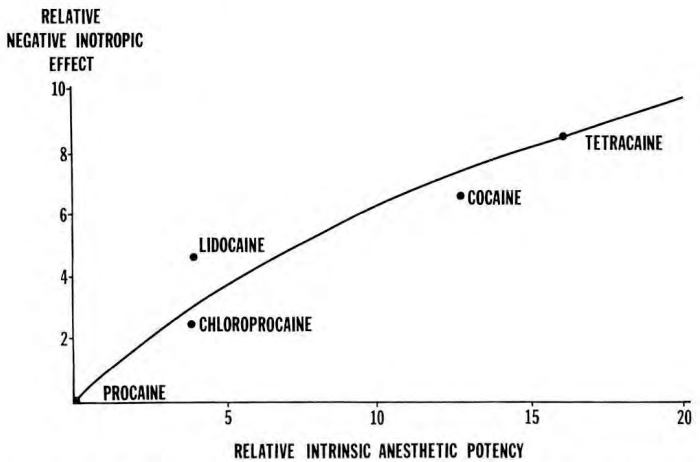


Fig. 6-4. Relative negative inotropic effect and intrinsic anesthetic potency of various local anesthetic agents.

pressure, and decreased cardiac output (Table 39). The usual doses of the various local anesthetic agents employed for regional anesthesia result in peak blood levels which generally are not associated with a cardiodepressant effect. However, the inadvertent rapid intravenous administration of a local anesthetic agent or the administration of excessive doses may cause a significant decrease in myocardial contractility and cardiac output, contributing to circulatory collapse.

PERIPHERAL VASCULAR EFFECTS

Local anesthetic agents tend to produce a biphasic effect on vascular smooth muscle (Table 40). In vitro studies have demonstrated that, at low concentration, all agents studied stimulated spontaneous myogenic contractions in preparations such as the isolated rat portal vein and, in some cases, augmented the basal tone of the vascular smooth muscle preparation.[263,369-371] The increase in the height of spontaneous smooth muscle contractility did not appear to be correlated with the anesthetic potency of the various compounds. For example, prilocaine produced the greatest enhancement of myogenic activity while etidocaine was least effective. Prilocaine, mepivacaine, and procaine also produced the greatest increase in basal tone, whereas minimal changes were seen with lidocaine, tetracaine, bupivacaine, and etidocaine[263] (Table 40).

In vivo studies have confirmed this initial stimulatory effect of local anesthetic agents on vascular smooth muscle. Intra-arterial administration of mepivacaine in human volunteers produced a decrease in forearm blood flow without altering arterial pressure, which is indicative of an increase in peripheral vascular resistance. Similar studies with lidocaine also showed an increased tone of capacitance vessels with less consistent effects on resistance vessels.[372] Moreover, in animal preparations in which vascular tone had been

Table 40

BIPHASIC PERIPHERAL VASCULAR EFFECT OF VARIOUS LOCAL ANESTHETIC AGENTS

AGENT	ISOLATED RAT PORTAL VEIN % Increase (constriction)		CANINE FEMORAL BLOOD FLOW % Increase (dilation)
	Spontaneous contractions	Basal tone	
LIDOCAINE	173	68	25
MEPIVACAINE	228	162	36
PRILOCAINE	293	163	42
TETRACAINE	237	82	38
BUPIVACAINE	184	37	45
ETIDOCAINE	147	—	44

reduced by alpha-adrenergic blockade or spinal section, mepivacaine and procaine were found to produce an increase in hind-limb vascular resistance.[373,374]

An increase in the dose of local anesthetic agent administered was associated with an inhibition of myogenic activity in vitro and vasodilation in vivo.[263,266] Lidocaine, mepivacaine, prilocaine, and tetracaine were all found to produce an increased blood flow in the hind limb of dogs and cats following intraarterial administration.[110,266] Similar studies in man have also shown that lidocaine, mepivacaine, and bupivacaine caused vasodilation and an increase in forearm blood flow.[264] A comparison of the peripheral vascular effects of various local anesthetic agents revealed a 25% to 45% increase in canine femoral blood flow following the intraarterial administration of 1 ml of 1% lidocaine, mepivacaine, tetracaine, prilocaine, etidocaine, and bupivacaine (Table 40).[263] Although no correlation was observed between peripheral vascular effects and anesthetic potency, a relationship existed between duration of anesthesia and vasodilation produced by these various agents. At 5 minutes following the intraarterial administration of lidocaine, mepivacaine, and prilocaine, femoral blood flow had returned to normal, whereas those agents that possess a longer duration of local anesthetic activity, i.e., bupivacaine, etidocaine, and tetracaine continued to show a 14% to 30% increase in femoral arterial flow.[263]

Cocaine is the only local anesthetic agent that produces systemic vasoconstriction at doses commonly employed for regional anesthetic procedures.[266] Direct blood flow studies in dogs have revealed that the initial effect of cocaine is one of vasodilation, followed by a prolonged period of vasoconstriction. As indicated previously, this vasoconstrictor action appeared related to an inhibition of the uptake of norepinephrine into tissue-binding sites.[267] This property has not been demonstrated with other drugs, such as lidocaine and mepivacaine.[375]

The biphasic peripheral vascular effect of local anesthetic agents may be related to changes in smooth muscle concentrations of calcium. A competitive antagonism exists between local anesthetic drugs and calcium ions in smooth muscle.[376,377] Local anesthetic compounds may displace Ca^{++} from membrane-binding sites, which results in diffusion of this ion into the smooth muscle cytoplasm. Such an increase in cytoplasmic calcium concentration will stimulate the interaction between contractile proteins leading to an increase in myogenic contractility, i.e., vasoconstriction. Ultimately, the displacement of calcium by increasing doses of local anesthetic agents will decrease both the cytoplasmic Ca^{++} concentration and the interaction between the

contractile protein elements of smooth muscle, which results in a state of muscle relaxation, i.e., vasodilation.

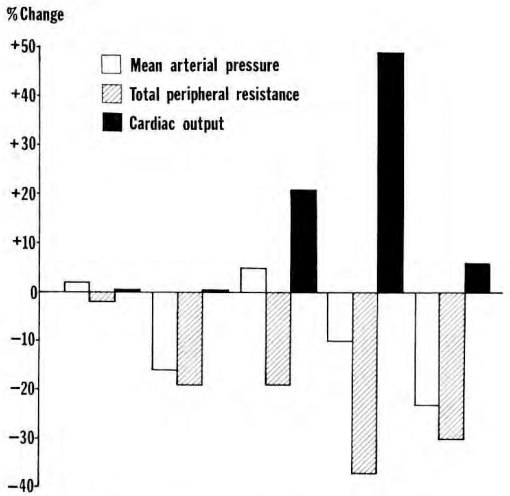
In general, the sequence of cardiovascular events observed following a progressive increase in local anesthetic dosage can be summarized as follows: at doses of local anesthetic agents that produce nontoxic blood levels, either a slight increase or no change in blood pressure occurs. The slight increase in blood pressure is probably related to (a) an increase in cardiac output and heart rate which is believed due to an enhancement of sympathetic activity and (b) a direct vasoconstriction of certain peripheral vascular beds. Blood levels of local anesthetic agents approaching toxic concentrations cause hypotension as a result of peripheral vasodilation resulting from a direct relaxant effect on peripheral vascular smooth muscle. A further elevation of local anesthetic blood levels produces a decreased myocardial contractility, which results in a fall in cardiac output. This combination of reduced peripheral vascular resistance and cardiac output leads to profound hypotension. Finally, at lethal blood levels of local anesthetic agents, cardiovascular collapse ensues due to massive peripheral vasodilation, marked reduction in myocardial contractility, and slowed heart rate, which ultimately results in cardiac arrest.

The direct circulatory actions of local anesthetic agents may be altered by the concomitant administration of other drugs. As indicated previously, nontoxic doses of local anesthetic agents may produce either minimal changes in blood pressure or may have a stimulatory effect on the myocardium and peripheral vasculature. The use of CNS depressant drugs such as general anesthetic agents and ganglionic blocking agents will block the positive inotropic action of lidocaine that is mediated via the sympathetic nervous system.[378, 379] Therefore, nondepressant doses of a local anesthetic agent may result in cardiovascular depression when administered in the presence of barbiturates or other drugs that inhibit CNS activity. Diazepam, which can effectively prevent the CNS toxicity of local anesthetic agents, does not modify the circulatory depression of these drugs.[380]

Indirect Effect of Local Anesthetic Agents

The cardiovascular changes due to the direct effect of the local anesthetic agent itself should be distinguished from alterations secondary to the regional anesthetic procedure performed. Central neural blocks of the lumbar epidural or subarachnoid type are frequently associated with a fall in systemic blood pressure.[222, 381–383] For example,

Moore and his co-workers reported hypotension in 38% to 45% of patients following spinal or epidural anesthesia.[222] Subarachnoid anesthesia to the T_5 level caused a decrease in stroke volume, cardiac output, and peripheral vascular resistance, which undoubtedly accounts for the rather high rate of hypotension.[384] Since the doses used for spinal anesthesia are quite small, such cardiovascular changes during subarachnoid anesthesia appear related solely to the sympathetic blockade produced by this procedure, rather than a direct effect of the local anesthetic agent. Hypotension may also occur following epidural anesthesia, but the mechanism appears to be more complex. The degree of hypotension following peridural blockade is related, in part, to the level of anesthesia, the local anesthetic agent, the concomitant use of vasoconstrictor drugs, and the status of the patient[385] (Fig. 6-5). For example, Bonica and associates reported that epidural anesthesia extending to the first thoracic segment or higher was associated with a fall in mean arterial blood pressure of 16%, a decrease in total peripheral



Anesthetic level	T_5	T_1	$T_{2\text{-}3}$	T_5	T_5
Lidocaine blood level (μg/ml)	<4.0	<4.0	>4.0	<4.0	<4.0
Epinephrine	0	0	0	+	+
Hypovolemia	0	0	0	0	+

Fig. 6-5. Cardiovascular effects of epidural anesthesia as influenced by analgesic dermatomal level, anesthetic blood level, epinephrine, and presence of hyporvolemia.

resistance (TPR) of 18%, and little change in cardiac output.[386] However, analgesia to T_4 or below failed to produce a significant change in blood pressure, peripheral resistance, or cardiac output.[386] These differences were related to the extent of the sympathetic blockade. T_1 blocks resulted in a significant increase in both upper- and lower-limb blood flow and a fall in TPR, which indicates widespread sympathetic blockade and peripheral vasodilation. T_4 blockade produced an increase in lower-limb blood flow, but a fall in upper-limb flow and little change in TPR, which suggests a compensatory vasoconstriction in the upper half of the body.

Relatively large doses of local anesthetic agents are employed for epidural anesthesia. As indicated in Chapter 5, local analgesic drugs are well absorbed from the epidural space. For example, lidocaine blood levels of 4–7 μg/ml occurred in some of the subjects involved in the epidural study conducted by Bonica, Berges, and Morikawa.[386] In these subjects, a fall in TPR was offset by an increase in cardiac output such that little change in mean arterial blood pressure occurred. The increased cardiac output was believed due to a direct effect of lidocaine on the vasomotor center in the CNS. The use of excessive amounts of local anesthetic drug for regional anesthesia will result in blood levels that may produce direct cardiac and peripheral vascular depression, exaggerating the hypotensive state caused by sympathetic blockade.

Central neural blockade may also cause a decrease in renal plasma flow and hepatic blood flow.[387,388] Since amide-type local anesthetic drugs are metabolized in the liver and excreted via the kidney, decreases in renal and hepatic blood flow will retard the clearance of these agents and possibly augment their direct cardiovascular effects.

The specific local anesthetic agent employed can influence the changes in cardiovascular function produced by the regional anesthetic procedure. A comparison of drugs of different inherent anesthetic duration, i.e., lidocaine and etidocaine, in epidural analgesia revealed that the magnitude of cardiovascular changes was similar for the two agents, but the duration of hypotension following etidocaine blockade was significantly prolonged.[211] This prolonged hypotensive action was directly related to the longer duration of epidural anesthesia and sympathetic blockade produced by etidocaine.

Anesthetic solutions employed for epidural analgesia frequently contain a vasoconstrictor drug, usually epinephrine, which influences the circulatory changes associated with the anesthetic procedure. Epidural blockade to the T_5 level with plain lidocaine produced a 5% to 10% change in cardiac output, peripheral resistance, and arterial pres-

sure. In contrast, lidocaine with epinephrine resulted in a 49% increase in cardiac output, 37% decrease in total peripheral resistance, and a 10% decrease in mean arterial pressure. The marked increase in cardiac output and decrease in TPR were ascribed to the beta-adrenergic receptor-stimulating effect of absorbed epinephrine.[389]

The physiological status of the patient also influences the circulatory changes following regional anesthesia. The use of lidocaine-epinephrine solutions to induce epidural analgesia in hypovolemic subjects caused a 23% decrease in arterial pressure compared to a 10% fall in normovolemic volunteers. This difference was due to the absence of a compensatory increase in cardiac output in the hypovolemic subjects. Epidural administration of plain lidocaine in the presence of hypovolemia produced signs of severe cardiovascular depression which were believed related to a greater myocardial uptake of lidocaine, leading to a significant decrease in cardiac contractility.[390]

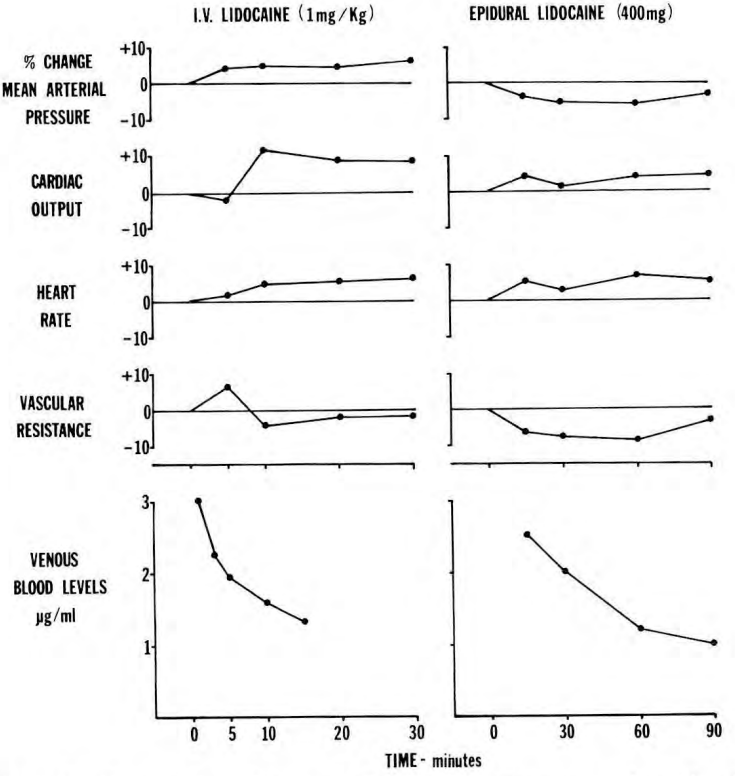


Fig. 6-6. Cardiovascular changes following intravenous and epidural administration of lidocaine.

The circulatory effect of other forms of regional anesthesia has also been studied.[391] Sciatic-femoral blocks utilizing either 125 mg of bupivacaine or 500 mg of lidocaine with epinephrine 1: 200,000 caused a decrease in peripheral resistance, an increase in cardiac output and heart rate, and no change in blood pressure. The increase in cardiac output may be reflex in origin or may be related to absorbed epinephrine and the CNS-stimulating effect of the local anesthetic agent, since lidocaine exerted a significantly greater positive inotropic action than bupivacaine.

The direct cardiovascular effect of local anesthetic agents and the circulatory alterations due to the regional anesthetic procedure can be compared in the following manner (Fig. 6-6): the blood level of lidocaine following the administration of 400 mg of this agent into the lumbar epidural space is similar to that produced by the IV injection of 1 mg/kg of lidocaine. However, the cardiovascular effects are quite different. Little or no change in blood pressure, peripheral vascular resistance, cardiac output, and heart rate occurs following the IV administration of 1 mg/kg lidocaine. On the other hand, epidural anesthesia results in a significant fall in arterial blood pressure, due primarily to a decrease in peripheral vascular resistance, with little or no change in cardiac output, and a slight rise in heart rate. These cardiovascular effects are obviously due to sympathetic blockade and a subsequent reduction in peripheral vascular tone rather than a direct vasodilator effect of the local anesthetic agent.

RESPIRATORY EFFECTS

Local anesthetic agents exert a biphasic effect on respiration. At subtoxic doses, a direct relaxant effect on bronchial smooth muscle may offset any depressant action on CNS respiratory centers.[392] Intravenously administered mepivacaine and bupivacaine in man did not produce a significant alteration on pCO_2, pO_2, pH, or oxygen saturation.[393] Excessive amounts of local anesthetic agents can cause respiratory arrest due to their generalized CNS depressant action.

Certain regional anesthetic procedures may be associated with alterations in pulmonary function. Thoracic epidural anesthesia extending from T_2–T_{12} produced a significant decrease in various pulmonary function tests such as FVC and $FEV_{1.0}$, whereas minimal changes occurred following thoracolumbar epidural anesthesia from T_4–L_4.[394,395] Subarachnoid or epidural blockade to the T_5 level did not result in any deleterious change in blood gas tensions.[384]

Postoperative respiratory function is frequently abnormal in patients undergoing upper-abdominal procedures. Comparisons of the pulmonary status of patients treated with either parenteral opiates or epidural analgesia for postoperative pain relief have demonstrated that epidural nerve blocks may be superior to narcotic analgesia in reducing the degree of postoperative pulmonary dysfunction which can lead to hypoxemia.[396,397]

Numerous studies have been conducted to evaluate fetal acid-base status following epidural or paracervical blocks for obstetrical anesthesia. Minimal alterations in the acid-base status of the fetus have been associated with the use of a variety of local anesthetic drugs for obstetrical analgesic procedures.[281,284,286,398] However, other factors, such as maternal hypotension associated with the anesthetic technique or addition of epinephrine 1:200,000 to the local anesthetic solution, may cause changes in the acid-base status of the fetus.[284,399]

MISCELLANEOUS EFFECTS

Other pharmacological actions ascribed to local anesthetic drugs include ganglionic blockade,[400] neuromuscular blockade,[401] anticholinergic,[402] antihistaminic,[403] and antibacterial activity.[404]

The effect of local anesthetic agents on neuromuscular transmission has been studied extensively. Procaine, lidocaine, mepivacaine, prilocaine, and bupivacaine have been demonstrated to inhibit in vitro myoneural junction preparations and to block neuromuscular transmission in man.[401,405–408] Although localized neuromuscular paralysis occurs following the intra-arterial injection of local anesthetic drugs in man, minimal alterations in neuromuscular activity have been observed when these agents were administered intravenously.[401,408]

Local anesthetic neuromuscular blockade may involve either pre- or postjunctional structures. Galindo ascribed the depressant action of procaine at the myoneural junction to an inhibition of the prejunctional motor-nerve terminal.[407] Other investigators have reported that local anesthetic agents either decrease the sensitivity of the postjunctional motor end plate to acetylcholine or block the depolarizing action of acetylcholine on the motor end plate.[401,405,406] Measurements of ionic conductances across the end-plate membrane have demonstrated that procaine exerts a profound inhibitory effect on sodium flux, which suggests that the basic action of local anesthetic agents is similar for all excitable membranes, i.e., a block of sodium channels in the cell membrane.[409]

Drug Interaction

The miscellaneous actions of local anesthetic drugs do not appear to be clinically relevant when the agents are employed alone. However, the interaction of local anesthetic agents with other types of drugs may be clinically significant. This is a particular problem in anesthesiology, since patients frequently receive multiple medications.[410] For example, the neuromuscular blocking action of local anesthetic agents alone is clinically irrelevant, but such agents can significantly enhance the action of both depolarizing and nondepolarizing myoneural blockers.[401,408] It has been demonstrated in dogs and man that the duration of apnea produced by succinylcholine or curare can be considerably prolonged by lidocaine.[411,412] As shown previously, premedication with CNS depressant drugs such as barbiturates can decrease the CNS toxicity, but may potentiate the cardiodepressant effect of local anesthetic agents. Other agents such as iproniazid, isoniazid, chloramphenicol, promethazine, and meperidine have been reported to enhance or prolong the convulsive action of local anesthetic drugs in animals.[413,414]

The concomitant use of local anesthetic agents and other drugs that share common metabolic pathways may cause adverse effects in patients. Prolonged apnea may occur if succinylcholine and the procaine-like ester drugs are employed together, since plasma pseudocholinesterase is required for the hydrolysis of both types of drugs.[292] Inducers of hepatic microsomal enzyme systems may alter the rate of metabolism of the lidocaine-like amide agents,[415] as indicated by an increase in the rate at which metabolites of lidocaine are formed in phenobarbital-treated dogs.[416]

TOXICOLOGICAL EFFECTS

Allergy

Most investigators believe that true allergic reactions to local anesthetic agents are extremely rare.[182,417,418] However, reports of suspected allergic, hypersensitivity, or anaphylactic responses to local anesthetic compounds appear periodically in the literature.[419–421] Usually, the diagnosis of such reactions is made when no obvious explanation is available for an adverse effect in a patient exposed to a local anesthetic drug. The ester derivatives of para-aminobenzoic acid, such as procaine, were responsible for most of the dermal allergic phenomena which were usually experienced by members of the dental profession. Such reports have been infrequent with the amide-type local analgesic

compounds. True allergy requires the formation of an antibody to an antigenic substance. To date, no evidence is available that antibodies are formed in response to a challenge by an amide-type local anesthetic drug. Aldrete and Johnson used the technique of intracutaneous testing to study patients with and without a presumptive history of local anesthetic allergy.[422] Positive skin reactions were observed in 25 of 60 patients in the nonallergic group. In all cases, the cutaneous reaction followed injection of an ester-type local anesthetic agent such as procaine, tetracaine, and chloroprocaine. No reactions were observed after treatment with the amide-type agents, lidocaine, mepivacaine, or prilocaine. Eleven patients had a history of alleged local anesthetic allergy. In eight of these cases, a positive skin reaction to procaine, tetracaine, or chloroprocaine was produced, but no positive skin response was seen with lidocaine, mepivacaine, or prilocaine. In none of these subjects were signs of systemic anaphylaxis observed. Solutions of the amide-type local anesthetic agents may contain as a preservative, methylparaben, whose structure is similar to para-aminobenzoic acid. Some patients presumed to be allergic to lidocaine have shown a positive skin response to methylparaben, but not to lidocaine itself.[423]

It is obviously difficult to study in a controlled fashion anaphylactic-type reactions. The low rate of adverse events reported in epidemiological studies involving local or regional anesthesia suggests that systemic anaphylaxis to local anesthetic agents must be quite rare.[424] Undoubtedly, anaphylactic-type reactions may occur with any drug. However, any unusual adverse response should be thoroughly investigated before a presumptive diagnosis of anaphylaxis is made. This may be particularly difficult with local anesthetic agents, since the circulatory crisis of true systemic anaphylaxis may be indistinguishable from the state of cardiovascular collapse that can follow an excessive dose, rapid absorption from a highly vascular site, or an inadvertent IV injection of a local anesthetic agent. Moreover, the addition of vasoconstrictor agents, particularly epinephrine, to local anesthetic solutions makes it difficult to differentiate the pharmacological effects of an excess level of catecholamines from the symptoms of anaphylaxis. Finally, the potential interaction of concomitant medications in anesthesia can obscure the differential diagnosis of adverse systemic reactions.

Local Tissue Toxicity

The effect of local anesthetic agents on various tissue cells has been investigated to determine their potential local irritation. Local anesthetic agents cause hemolysis of red blood cells in direct relationship to

the intrinsic anesthetic potency of the specific compound.[425] However, the concentrations of local anesthetic agents that produce red-blood-cell hemolysis in vitro are considerably higher than in vivo concentrations achieved clinically. The inhibition of leukocytic aggregation and the adherence of leukocytes to the intima of blood vessels at anesthetic blood concentrations which are achieved during regional anesthesia has been reported.[426] The clinical significance of these findings are, as yet, unclear.

The use of local anesthetic agents in the concentrations that are clinically available has not been shown to produce localized nerve damage.[427, 428] Studies on the isolated frog sciatic nerve have revealed that concentrations of procaine, cocaine, tetracaine, and dibucaine required to produce irreversible conduction blockade are far in excess of those used clinically.[425] A comparison of lidocaine, tetracaine, or etidocaine administered subdurally in rabbits revealed histopathological spinal cord changes following the use of 4% tetracaine, which is considerably greater than the concentrations (0.25–1%) employed for spinal anesthesia in man.[429] Fink and co-workers have described an inhibitory effect of local anesthetic agents on rapid axonal transport in the rat vagus nerve.[430] This change in rapid axonal transport is not associated with changes in the ultrastructure of peripheral nerve, and the clinical significance of these findings is not apparent at present.

It has also been suggested that preservatives in local anesthetic solutions may cause neurotoxicity. MacDonald and Watkins reported that the concentration of chemical preservatives in spinal anesthetic solutions was insufficient to cause paralysis.[431] Studies have been conducted to evaluate the neurotoxic effects of methylparaben, a common antibacterial preservative in multiple-dose local anesthetic containers. Methylparaben with and without lidocaine was administered into the subarachnoid space of rabbits and failed to produce any histopathological evidence of neurotoxicity.[432]

Several studies have been performed which indicate that local anesthetic agents can cause histological changes in skeletal muscle.[427,428,433] Skeletal muscle changes have been observed with most of the clinically used local anesthetic compounds such as lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine. In general, the more potent, longer-acting compounds appear to cause a greater degree of localized skeletal muscle damage than the less potent, shorter-acting agents. This effect on skeletal muscle is reversible and muscle regeneration occurs rapidly and is complete within 2 weeks following the injection of local anesthetic agents.[427,428] These changes in skeletal muscle have not been correlated with any overt clinical signs of local irritation.

However, an increase in blood levels of creatine phosphokinase (CPK) have been reported following the intramuscular administration of lidocaine, which is indicative of skeletal muscle damage.[434]

Systemic Toxicity

As described previously, local anesthetic toxicity involves essentially the central nervous system and the cardiovascular system. Adverse reactions are usually due to a rapid inadvertent intravenous injection, administration into a highly vascular anatomical site, or administration of an excessive amount of local anesthetic drug. In each instance, a high blood level of local anesthetic agent is achieved. Adverse reactions to a local anesthetic agent usually proceed in the following manner: (a) premonitory CNS symptoms such as dizziness, ringing in the ears, vague sensation of light headedness, nystagmus, fine skeletal muscle twitching of face and digits; (b) overt convulsions of a clonic and tonic nature; (c) CNS depression in which seizure activity terminates and respiratory efforts become shallow and, ultimately, cease; (d) fall in systemic blood pressure; and (e) a progressive bradycardia leading ultimately to cardiac arrest. Rapid achievement of an extremely high anesthetic blood level may produce respiratory depression and cardiovascular collapse without the usual signs and symptoms of CNS excitation.

Treatment of systemic local anesthetic reactions requires a recognition of the warning symptoms described above and knowledge of the organ systems affected by overdosage of local anesthetic agents. Initial treatment should be directed toward ensuring the presence of a patent airway and providing a source of oxygen. Maintenance of an adequate respiratory exchange will often suffice in the treatment of the early stages of acute systemic reactions. The occurrence of convulsive activity requires the use of CNS depressant agents to control the generalized seizures. Intravenous diazepam and short-acting barbiturates have been shown to be effective in aborting local anesthetic-induced seizures. Short-acting neuromuscular blocking agents, such as succinylcholine, have also been utilized to inhibit overt convulsions and to permit a more adequate control of respiration. However, neuromuscular blocking agents do not affect the increased electrical activity of the brain, so that CNS depressant drugs are still required to control the state of CNS excitation, and ventilation should be assisted until such time as the patient is capable of spontaneous respiration. Respiratory depression is usually indicative of an extremely high anesthetic blood level. As the anesthetic blood level

declines, the patient may reenter a phase of CNS excitation and convulsive activity may reoccur.

Signs and symptoms of cardiovascular collapse require treatment with vasopressor or positive inotropic agents in order to support the circulation. Since vasodilation is usually responsible for the initial fall in blood pressure, vasopressor agents such as phenylephrine and methoxamine, which act predominantly on the peripheral vasculature may be preferable. Later stages of circulatory collapse involve a decrease in myocardial contractility and cardiac output, and the use of vasopressor agents such as ephedrine or norepinephrine, which possess a positive inotropic action, may be desirable to constrict the peripheral vasculature and to increase cardiac contractility.

Knowledge of therapeutic methods to control the systemic toxicity of local anesthetic agents is essential. However, most adverse reactions can be avoided by observing certain precautions that involve a knowledge of the local anesthetic agent employed, the regional anesthetic procedure to be performed, and the clinical status of the patient. The selection of a proper anesthetic dose requires an awareness of the inherent anesthetic potency of a specific agent and the selective rate of systemic absorption from the injection site in order to avert the accidental administration of an overdose. Care and skill in performance of the anesthetic procedure are necessary to prevent an inadvertent intravascular injection. The clinical status of the patient will dictate the choice and dose of local anesthetic agent. For example, the clearance of local anesthetic agents is decreased in patients with cardiac failure and poor hepatic perfusion, which necessitates the use of lower dosages. Patients with advanced hepatic or renal disease are more vulnerable to the toxic effects of amide-type agents, whereas the presence of atypical pseudocholinesterase may enhance the potential for systemic reactions to ester-type drugs.

In general, local anesthetic agents possess a lower therapeutic ratio than normally would be considered clinically desirable. However, these agents are usually administered into a circumscribed area of the body by trained clinicians, so that the frequency of adverse reactions associated with local anesthetic drugs is remarkably low. Retrospective and prospective studies of epidural and spinal anesthesia involving more than 10,000 patients per study with a variety of anesthetic agents demonstrated a 0.3% to 1.5% frequency of complications associated with the anesthetic procedure.[218,435] A review of the world literature on epidural anesthesia by Dawkins in 1969 revealed a 0.2% frequency of toxic reactions in more than 60,000 cases.[424] Since some of the adverse events reported in these surveys are attributable to the anesthetic

technique itself or factors unrelated to the anesthetic agent, the incidence of true local anesthetic-induced reactions must be extremely low. Therefore, local anesthesia provides a safe and efficacious method of preventing or alleviating pain in circumscribed anatomical areas. However, the judicious use of regional anesthesia requires knowledge of the pharmacological properties of the specific agents employed, technical skill in the performance of the various nerve-blocking procedures, and a thorough evaluation of the patient's clinical status.

SUMMARY

1. Local anesthetic agents may exert pharmacological actions other than peripheral nerve blockade. The central nervous system and cardiovascular system are particularly susceptible to the effect of local anesthetic drugs.
2. As the dosage and blood level of local anesthetic agents are progressively increased, an initial excitatory CNS effect occurs followed by a state of generalized CNS depression. The convulsive action of local anesthetic agents is related to an inhibition of inhibitory cortical neurons such that facilitory pathways act in an unopposed fashion leading to seizure activity. At higher anesthetic dose levels an inhibition of both inhibitory and facilitory neurons causes generalized CNS depression.
3. Local anesthetic-induced changes in the cardiovascular system are characterized initially by an increase in peripheral vascular resistance due to a direct effect on peripheral vascular smooth muscle and an increase in cardiac output due indirectly to an action on the CNS. The predominant cardiovascular effects of high doses of local anesthetic agents include systemic hypotension due to a generalized vasodilation and a decrease in myocardial contractility, leading to a fall in cardiac output. Sinus bradycardia and, ultimately, cardiac arrest can occur due to the use of lethal doses of local anesthetic agents.
4. Respiration is unaffected by local anesthetic agents until doses causing overt CNS toxicity are achieved. The miscellaneous actions of local anesthetic drugs are usually not clinically relevant unless they are employed in combination with other agents such as neuromuscular blockers.
5. True allergic reactions to local anesthetic agents are extremely rare and are mainly referable to the use of the procaine-like ester compounds. Certain preservatives in local anesthetic solutions such as methylparaben may also cause allergic reactions.

6. The local tissue toxicity of regional anesthetic agents is limited primarily to skeletal muscle and is spontaneously reversible. No cytotoxic effects have been observed in nerves exposed to the normal concentrations of clinically available agents.
7. Systemic toxicity is usually due to an inadvertent intravascular injection, administration into highly vascular sites, or use of an excessive dose. Treatment consists of maintenance of a patent airway, adequate ventilation, use of anticonvulsant agents, such as diazepam or barbiturates, to control seizures, and vasopressor drugs to support circulation if hypotension should occur.