4

Clinical Aspects of Local Anesthesia

GENERAL COMMENTS

Local anesthetic requirements and activity vary considerably, depending on such factors as anesthetic procedure, surgical procedure, and physiological status of the patient.[128] It is unlikely that any single chemical compound can provide sufficient versatility for all clinical conditions. Thus, selection of an appropriate agent in a specific situation requires knowledge of the clinical needs and the pharmacological properties of the various anesthetic drugs currently available. The regional anesthetic procedure itself probably exerts the greatest influence on the type of agent to be used, due mainly to the marked anatomical and physiological differences between various sites of administration. Primarily on the basis of anatomical considerations, regional anesthesia may be divided into four categories: infiltration, peripheral nerve blockade, central neural blockade, and topical anesthesia (Table 15). Infiltration anesthesia involves inhibition of excitation primarily at nerve endings. Peripheral nerve blockade impedes conduction in nerve fibers of the peripheral nervous system. Central neural blockade interferes with conduction in nerve fibers considered to be part of the central nervous system. Topical anesthesia requires diffusion through tissue barriers such as skin or mucous membranes to peripheral nerve endings where inhibition of excitation occurs.

Variations in anesthetic activity may occur as a function of many conditions, e.g., (1) the regional procedure employed, (2) the physical or clinical status of the patient, (3) factors associated with the surgical procedure or (4) the composition of the anesthetic solution.

Table 15

CLASSIFICATION OF REGIONAL ANESTHESIA

1. INFILTRATION
   a. EXTRAVASCULAR
   b. INTRAVASCULAR
2. PERIPHERAL NERVE BLOCKADE
   a. MINOR NERVE BLOCKADE, i.e. SINGLE NERVE BLOCK
   b. MAJOR NERVE BLOCKADE, i.e. MULTIPLE NERVE BLOCK OR PLEXUS BLOCKADE
3. CENTRAL NEURAL BLOCKADE
   a. EPIDURAL BLOCKADE
      1. THORACIC
      2. LUMBAR
      3. CAUDAL
   b. SUBARACHNOID BLOCK
4. TOPICAL ANESTHESIA

Differences in anesthetic activity as a function of the regional procedure are demonstrated in Table 16 in which the properties of lidocaine and bupivacaine are compared.[129–134] Onset of action occurs immediately in infiltration anesthesia, whereas the longest latency (14–23 minutes) is observed in peripheral nerve blockade of the multiple nerve type, e.g., brachial plexus block. The shortest duration of anesthesia for most agents occurs in central neural blocks of the subarachnoid type. The duration of action at other sites, however, depends upon the local anesthetic agent used. For example, duration of action persists for the longest period following percutaneous infiltration for an agent such as lidocaine, whereas the longest duration of bupivacaine is observed when it is administered for peripheral nerve

Table 16

ONSET AND DURATION OF ACTION OF LIDOCAINE AND BUPIVACAINE FOLLOWING VARIOUS FORMS OF REGIONAL ANESTHESIA

ANESTHETIC PROCEDURE	LIDOCAINE			BUPIVACAINE		
	SOLUTION	SENSORY ONSET (min)	SENSORY DURATION (min)	SOLUTION	SENSORY ONSET (min)	SENSORY DURATION (min)
1. INFILTRATION						
a. EXTRAVASCULAR	1% w/epi 1:200,000	—	416.2 ± 25.8	0.25% w/epi 1: 200,000	—	428.6 ± 39.9
b. INTRAVENOUS REGIONAL	0.5%	—	111.0 ± 26.6	0.25%	—	344.0 ± 27.7
2. PERIPHERAL NERVE BLOCKADE						
a. ULNAR NERVE BLOCK	1% w/epi 1:200,000	3.00±0.5	178.0 ± 17	0.25% w/epi 1: 200,000	16.00 ± 4.7	395.0 ± 22
b. BRACHIAL PLEXUS BLOCK	1% w/epi 1:200,000	14.04±3.83	195.0 ± 26.3	0.25% w/epi 1: 200,000	23.26 ± 7.93	613.0 ±126
3. CENTRAL NEURAL BLOCKADE						
a. EPIDURAL	2% w/epi 1:200,000	5.07±0.58	156.6 ± 15	0.5 % w/epi 1: 200, 000	6.27 ± 1.19	228.6 ± 23
b. SUBARACHNOID	5%	4.30±1.5	94.0 ± 28	1%	30 - 90 sec	128.0 ± 19

block, e.g., brachial plexus blockade. Bupivacaine demonstrates a fivefold difference in anesthetic duration depending on the type of regional anesthetic procedure, e.g., 128 minutes of spinal anesthesia as compared to 613 minutes of brachial plexus blockade.[131–134]

The physical and clinical status of a patient can markedly affect local anesthetic activity. The dose requirements of local anesthetic agents may be altered by patient characteristics, e.g., the dose per segment requirement of local analgesic drugs administered epidurally has been reported to be inversely proportional to age, stage of pregnancy, and degree of arteriosclerosis and directly proportional to the height of the patient (Table 17).[135] Duration of infiltration anesthesia and peripheral nerve blockade also may be influenced by the clinical status of the patient. The expected duration of lidocaine for brachial plexus blockade was significantly shorter in subjects with chronic renal failure,[136] whereas the duration of infiltration anesthesia and digital nerve block with lidocaine was prolonged markedly in patients with scleroderma.[137, 138] In general, the activity of amide-type agents may be prolonged in the presence of severe liver dysfunction and the action of ester-type drugs may be enhanced if a deficiency of the enzyme, pseudocholinesterase, exists. In either situation, a decreased rate of degradation and elimination of the local anesthetic agent would occur.

Factors associated with the surgical procedure also may affect local anesthetic activity. A significantly longer duration of pain relief has been observed in patients treated with lidocaine when two or more units of blood were lost during surgery.[139] Blood loss may result in hypotension and a reflex state of generalized vasoconstriction, which decreases the absorption of local anesthetic agents from their injection site and prolongs the duration of anesthesia.

Table 17

INFLUENCE OF PATIENT STATUS ON LOCAL ANESTHETIC ACTIVITY

PATIENT STATUS	INFILTRATION ANESTHESIA	PERIPHERAL NERVE BLOCKADE	EPIDURAL ANESTHESIA
PREGNANCY	—	—	↑ ANESTHETIC SPREAD
ARTERIOSCLEROSIS	—	—	↑ ANESTHETIC SPREAD
RENAL FAILURE	—	↓ DURATION	—
SCLERODERMA	↑ DURATION	↑ DURATION	—
LIVER DISEASE	↑ DURATION OF AMIDE-TYPE AGENTS	↑ DURATION OF AMIDE-TYPE AGENTS	↑ DURATION OF AMIDE-TYPE AGENTS
PSEUDOCHOLINESTERASE DEFICIENCY	↑ DURATION OF ESTER AGENTS	↑ DURATION OF ESTER AGENTS	↑ DURATION OF ESTER AGENTS

Table 18

EFFECT OF SOLUTION COMPOSITION ON ANESTHETIC ACTIVITY

	ONSET OF ANESTHESIA	DURATION OF ANESTHESIA	FREQUENCY OF ANESTHESIA
↕ DOSAGE (vol. or conc.)	↓	↑	↑
VASOCONSTRICTOR AGENT	↓ —	↑	↑
METHYLPARABEN	—	—	—
SODIUM METABISULFITE	—	—	—
CO_2	↓	—	—
EXCESS K^+	↓	↑	—

The composition of the solution employed can influence the primary pharmacological activity of the anesthetic agent (Table 18). An increase in anesthetic dosage will decrease the onset time and increase both duration and frequency of satisfactory analgesia[140] (Fig. 4-1). This dose-related effect may be achieved by alterations in either

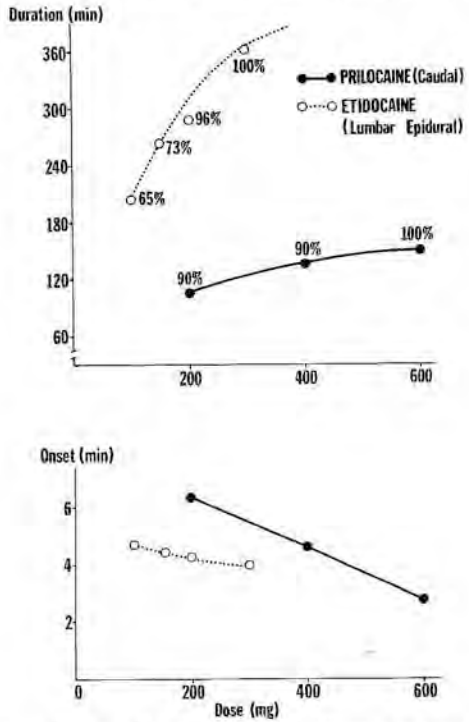

Fig. 4-1. Effect of local anesthetic dosage on onset, duration, and frequency of analgesia.

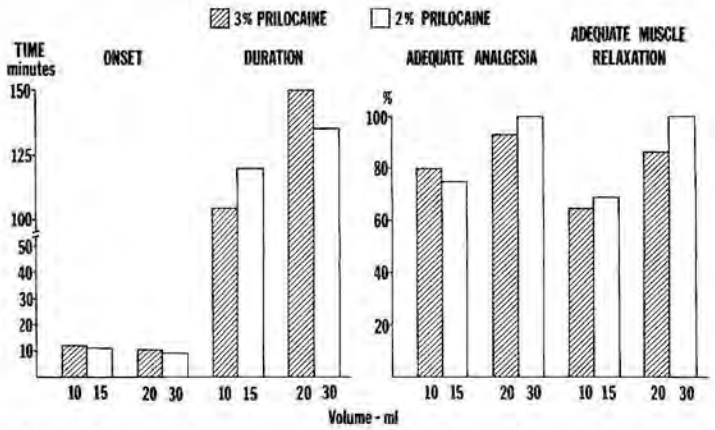

Fig. 4-2. Influence of concentration and volume of anesthetic solution on various anesthetic parameters.

volume or concentration[141] (Fig. 4-2). Vasoconstrictor agents, usually epinephrine, frequently are added to local anesthetic solutions to decrease the rate of drug absorption from the site of injection and prolong the duration of anesthesia. Such prolongation of anesthesia by epinephrine is dependent on the local analgesic agent and the type

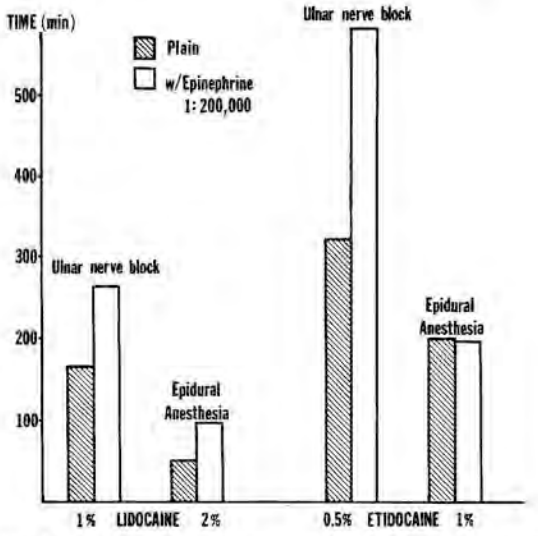

Fig. 4-3. Influence of epinephrine on the anesthetic duration of lidocaine and etidocaine in ulnar nerve blockade and epidural anesthesia.

of regional procedure. Epinephrine will extend significantly the action of agents such as procaine and lidocaine for infiltration, peripheral, and central neural blockade.[129, 135, 142, 143] A prolongation of local anesthetic activity may occur when prilocaine, bupivacaine, and etidocaine are combined with epinephrine for peripheral nerve blockade,[142] whereas the duration of epidural anesthesia with these agents is not altered by the addition of a vasoconstrictor drug[135, 143–145] (Fig. 4-3).

Local anesthetic solutions may contain other ingredients such as methylparaben, which serves as an antibacterial preservative in multiple dose vials, and sodium metabisulfite, which is employed as an antioxidant in epinephrine-containing solutions. The amount of these substances commonly found in commercial local anesthetic solutions does not exert any influence on the basic analgesic properties of the drug.

INFILTRATION ANESTHESIA

This anesthetic procedure involves administration of a local anesthetic agent into an extravascular or intravascular site and subsequent diffusion to nerve endings where excitation is inhibited.[146] The extravascular form also has been termed percutaneous infiltration. The intravascular form consists of the injection of anesthetic drug into the vasculature of a tourniquet-occluded limb such that the drug cannot enter the central circulatory compartment, but instead diffuses from the peripheral vascular bed to nonvascular tissue such as nerve endings.

Extravascular Infiltration

Intradermal wheals have been utilized to evaluate the infiltrative anesthetic properties of various agents.[129, 147, 148] The infiltration anesthetic potency of the clinically useful drugs is similar to their relative intrinsic anesthetic potencies, i.e., 2% procaine, 1% lidocaine, mepivacaine, and prilocaine, and 0.25% bupivacaine are equivalent in terms of frequency of adequate analgesia. Onset of action is almost immediate for all agents following intradermal or subcutaneous administration. However, the various agents can be differentiated according to duration of infiltration anesthesia (Table 19). Procaine has a short duration, whereas lidocaine, mepivacaine, and prilocaine are agents of moderate duration and bupivacaine

Table 19

COMPARATIVE DURATION OF INFILTRATION ANESTHESIA OF VARIOUS AGENTS FOLLOWING INTRADERMAL ADMINISTRATION

AGENT	CONC. (%)	DURATION (min ± S.E. or range) Plain	Epinephrine 1:200,000
PROCAINE	0.5	20 (15-30)	56 (15-120)
LIDOCAINE	0.5	75 (30-340)	228 (60-435)
LIDOCAINE	1.0	127.6 ± 17.4	416.2 ± 25.8
MEPIVACAINE	0.5	108 (15-240)	240 (135-315)
PRILOCAINE	1.0	99.1 ± 19.1	288.7 ± 10.2
BUPIVACAINE	0.25	199.5 ± 33.4	428.6 ± 39.9

demonstrates long anesthetic activity. Epinephrine will markedly prolong the duration of infiltration anesthesia of all local anesthetic agents. However, the duration of anesthesia appears to be prolonged most dramatically when epinephrine is added to solutions of lidocaine. For example, plain bupivacaine produces a duration of analgesia 65% longer than that of plain lidocaine. Addition of epinephrine 1:200,000 significantly extends the duration of both agents, but no difference in analgesic duration exists between lidocaine and bupivacaine solutions that contain epinephrine.

The most extensive studies of infiltration anesthesia have been conducted in the dental field, since infiltration of the gingival mucosa is frequently performed for many routine dental procedures. Agents commonly used in dentistry are shown in Table 20.[149,150] In an attempt to objectively evaluate the factors that influence pulpal anesthesia, a technique of electrical stimulation of teeth has been

Table 20

LOCAL ANESTHETIC AGENTS COMMONLY EMPLOYED FOR INFILTRATION ANESTHESIA IN DENTISTRY

AGENT	CONC. (%)	EPINEPHRINE CONC.	FREQUENCY OF SATISFACTORY ANALGESIA (%)	DURATION OF SOFT TISSUE ANALGESIA (min ± S.E.)
LIDOCAINE	2	1:100,000	93.9	147±7.4
MEPIVACAINE	2	1:20,000 (Neo-cobefrin)	92.0	140±8.0
MEPIVACAINE	3	NONE	90.2	134.5±16.3
PRILOCAINE	4	NONE	93.0	62± 7.0
PRILOCAINE	4	1:200,000	92.6	124.7± 4.8

employed to determine pain threshold and its modification by local anesthetic agents.[151, 152] There are distinct differences in anesthetic potency between various agents. For example, 3% procaine is required to provide an analgesic frequency comparable to that achieved with 1% lidocaine. When the various agents are employed in equipotent concentrations, the concomitant use of a vasoconstrictor agent (epinephrine) exerts the greatest influence on infiltration anesthetic properties.[151] Although plain procaine was ineffective at a concentration of 2%, the addition of epinephrine (25 μg/ml) resulted in an 80% frequency of satisfactory pulpal anesthesia. The addition of epinephrine to solutions of lidocaine was more efficacious than an increase in the concentration of the anesthetic solution (Fig. 4-4). Use of a 4% concentration of plain lidocaine produced approximately an 80% frequency of satisfactory analgesia. On the other hand, 1% lidocaine which was ineffective as a plain solution provided 100% analgesic frequency when used in combination with 25 μg/ml of epinephrine. In general, epinephrine tends to increase the frequency and duration and shorten the onset time for satisfactory analgesia.

Cowan has compared most of the local anesthetic agents commonly used for infiltration anesthesia in dentistry by means of a standardized minimum dosage technique.[153] Two percent procaine with epinephrine (25 μg/ml, 1:40,000) showed the lowest incidence of satisfactory analgesia (70%). All of the other agents, i.e., lidocaine, mepivacaine, and prilocaine produce satisfactory analgesia for dentistry in 90% to 100% of the cases when administered with a vaso-

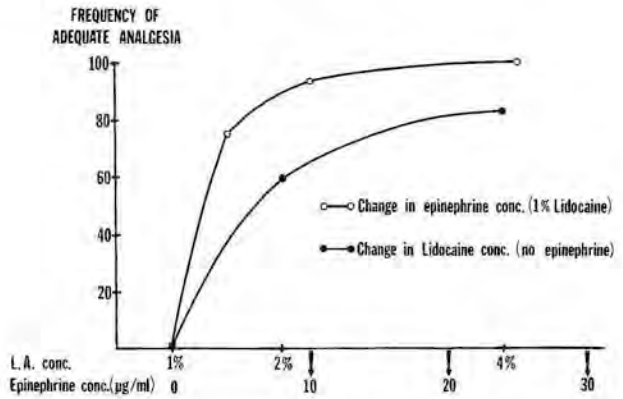

Fig. 4-4. Relative influence of anesthetic concentration and epinephrine on frequency of adequate infiltration anesthesia.

constrictor drug. The importance of a vasoconstrictor agent is also demonstrated by the decrease in frequency of satisfactory analgesia from 90 to 95% to 82% when solutions of 2% mepivacaine with and without epinephrine were compared. As in intradermal wheals, the duration of lidocaine following gingival infiltration is prolonged to a greater extent by the addition of epinephrine than is either mepivacaine or prilocaine. The longest duration of gingival anesthesia was produced by a 2% lidocaine solution containing epinephrine 1:80,000.[153]

Intravascular Infiltration

This form of infiltration anesthesia is commonly referred to as intravenous regional anesthesia or the Bier block in honor of August Bier who initially described this technique in 1908.[154, 155] Numerous articles and several reviews and symposia have been devoted to this topic.[156, 157] The essential features of this procedure are its simplicity and relatively rapid disappearance of analgesia following tourniquet release. The procedure involves the intravascular administration of a local anesthetic agent into a tourniquet-occluded limb. It is imperative that the venous flow from the involved limb be completely obstructed in order to prevent the rapid entrance of local anesthetic drug into the central vascular compartment, which could result in serious toxicity. The type of equipment and the methodology necessary for the safe use of this technique are described in many articles and the requisite precautions should be observed prior to attempting this procedure.

The technique as reported by Bier consisted of exsanguination of the involved extremity by an Esmarch bandage, placement of two elastic bandages, one proximal and one distal to the operative site, and administration of 0.5% procaine into a vein between the two elastic bandages. The method was repopularized in 1963 by Holmes utilizing 0.5% lidocaine as the anesthetic drug.[158]

TECHNICAL CONSIDERATIONS

Although intravenous regional anesthesia is a relatively simple technique, there are a number of factors that may influence both the safety and effectiveness of this procedure.

Tourniquet. Both the safety and efficacy of this regional anesthetic procedure depends on the interruption of blood flow to the involved limb. Calibration of the occlusive cuff is of vital importance

since a malfunctioning cuff can lead to inadequate occlusion and potential side effects due to the rapid introduction of local anesthetic agents into the central circulatory compartment.[159] Diffusion of the local anesthetic agent from the intravascular injection site to nonvascular tissue compartments apparently occurs extremely rapidly, since no difference in venous blood levels of the local anesthetic agent could be observed in the occluded limb, following tourniquet release, when the total time of circulatory occlusion was varied between 5 and 100 minutes.[160, 161] A technique of intermittent tourniquet release has been advocated as a means of increasing the safety of this procedure, although there is considerable difference of opinion on the value of this form of tourniquet release. Since peak blood levels of local anesthetic agents occur within 30 sec following cuff deflation, the cyclic deflation/inflation procedure should take place at 10–15 sec intervals in order to decrease the peak levels of local anesthetic drug in the central circulatory compartment. Use of a double pneumatic cuff has also been advocated as an additional safety precaution and as a means of decreasing ischemic pain associated with the tourniquet.

Preinjection Exsanguination. Exsanguination of the involved limb appears to be of value from a safety and efficacy point of view since less drug is required to achieve adequate anesthesia if the limb has been exsanguinated prior to injection. Most commonly, the extremity is elevated to ensure gravity drainage and then tightly wrapped in an Esmarch bandage.

Preinjection Ischemia. Bell, Slater, and Harris have advocated the use of a 20-minute period of ischemia between the time of tourniquet inflation and injection of the local anesthetic solution.[162] This period of preinjection ischemia significantly decreased the dosage of lidocaine required to produce satisfactory surgical analgesia from 3.0 mg/kg to 1.5 mg/kg. Therefore, preinjection ischemia has been advocated as a means of increasing the safety of IV regional anesthesia without sacrificing the quality of analgesia. An increase in tissue pCO_2 and decrease in tissue pH are probably responsible for the increased effectiveness of low doses of local anesthetic agents employed when an adequate period of preinjection ischemia is utilized. The disadvantage of this specific procedure is the increase in patient discomfort during the period of ischemia.[163]

Injection Site. The majority of studies of intravenous regional anesthesia have involved surgical procedures on the upper

limbs.[156, 157, 163] It is considerably more difficult to obtain a satisfactory degree of surgical analgesia with this technique in the lower limbs due to the greater mass of tissue involved. In addition, considerably more drug may be required for lower limb procedures, which is a consideration in terms of the safety aspects of this technique.[164] The particular blood vessel in the occluded area chosen for injection does not appear to influence the adequacy of analgesia.[165]

DRUG-RELATED CONSIDERATIONS

Any of the clinically available local anesthetic agents may be utilized for intravascular infiltration anesthesia (Table 21).[163, 166–168] Approximately 18,000 cases of IV regional anesthesia have been reported in the published literature. Lidocaine was the agent utilized in approximately 15,000 patients described in these various studies. Prilocaine, mepivacaine, chloroprocaine, procaine, bupivacaine, and etidocaine also have been used successfully for the production of intravascular regional anesthesia. However, thrombophlebitis has been reported in several patients in whom chloroprocaine was utilized. This phenomenon was not observed with lidocaine or prilocaine in the same study.[166] A relationship does exist between the basic anesthetic properties of the various agents and the duration of analgesia persisting after tourniquet release (Table 21). Residual analgesia following cuff deflation persists for approximately 1–2 hours with agents such as prilocaine and lidocaine, whereas durations of residual analgesia of 3–5 hours have been observed with the use of the more potent, longer-acting agents such as etidocaine and bupivacaine.[130]

Table 21

LOCAL ANESTHETIC AGENTS EMPLOYED FOR INTRAVENOUS REGIONAL ANESTHESIA

Agent	Usual Conc.(%)	Usual Volume(ml) (Upper extremity)	Usual Dosage (mg/Kg)	Duration of Residual Anesthesia (min)
A. Short Duration				
PROCAINE CHLOROPROCAINE	0.5	20-40	1.5-3.0	30-60
B. Moderate Duration				
LIDOCAINE MEPIVACAINE PRILOCAINE	0.5	20-40	1.5-3.0	60-120
C. Long Duration				
BUPIVACAINE ETIDOCAINE	0.25	20-40	0.75-1.0	200-350

The concentration and volume of local anesthetic solution influences analgesic adequacy and potential safety of intravascular regional anesthesia.[168, 169, 170] In general, the use of large volumes of more dilute solutions offers the optimal conditions for satisfactory anesthesia and enhanced safety. Tucker and Boas demonstrated that the peak systemic arterial blood concentration of lidocaine following the use of a 0.5% solution was approximately 40% lower than the level observed when a 1% solution was utilized with the total dosage being equal.[170] Studies with prilocaine have shown that the peak systemic arterial blood concentration varies directly with the concentration of the anesthetic agent.[168] In general, concentrations of 0.5% lidocaine, prilocaine, or mepivacaine and 0.25% of etidocaine and bupivacaine have been utilized to produce satisfactory analgesia.[130, 163, 166] The volume of solution required depends upon the mass of tissue to be anesthetized. Thus, as stated previously, a greater volume of solution is required for procedures involving the lower limbs.

Varying dosages have been employed in intravenous regional anesthesia. Agents such as lidocaine have been administered in doses varying between 1.5 and 5 mg/kg for procedures involving the upper arm. Most commonly, 40 ml of an 0.5% solution of lidocaine (200 mg) have been found to produce satisfactory analgesia for the upper arm which would correspond to a dosage of approximately 3 mg/kg. As indicated previously, Bell, Slater, and Harris have suggested that the use of a preinjection ischemia period permits the use of a 1.5 mg/kg dosage of lidocaine with adequate analgesic effects.[162] Since larger volumes of local anesthetic solution are required for procedures involving lower limbs, the use of 75–100 ml of a dilute anesthetic solution, e.g., 0.25% lidocaine, has been advocated in order to preclude the use of excessive amounts of drug that might lead to potential adverse effects.[156, 157]

PHARMACODYNAMIC CONSIDERATIONS

Studies involving the intravascular administration of local anesthetic agents to tourniquet-occluded limbs in animals and man have shown that the drugs diffuse rapidly from the vascular compartment to the extracellular space where they are taken up by muscle and nerve.[171–173] de Jong demonstrated in cats that conduction in the small delta and C fibers was markedly reduced following intravenous regional analgesia, whereas the large alpha fibers were unaffected.[174] Studies in man have also revealed that the action potential amplitude of major nerve trunks is not significantly altered by the intravascular

administration of local anesthetic drugs in a tourniquet-occluded limb.[175, 176] These studies indicate that initially the primary site of analgesic activity following intravenous regional anesthesia is at the peripheral nerve endings. However, if the dosage of anesthetic drug is increased or the period of circulatory occlusion is prolonged, conduction in major nerve trunks may be reduced.[173, 176, 177] It has also been suggested that the muscle relaxation and motor paralysis which occurs following intravenous regional analgesia may be related in part to an inhibitory effect of the local anesthetic agent on the neuromuscular junction.[175]

PERIPHERAL NERVE BLOCKADE

Regional anesthetic procedures that involve the inhibition of conduction in nerve fibers of the peripheral nervous system can be classified together under the general category of peripheral nerve blockade. This form of regional anesthesia has been subdivided arbitrarily into minor and major nerve blocks. Minor nerve blocks are defined as procedures involving single nerve entities, e.g., ulnar or radial nerve, while major nerve blocks comprise those procedures in which two or more distinct nerves or a nerve plexus are blocked, e.g., sciatic-femoral block and brachial plexus blockade.

Minor Nerve Blocks

A standardized ulnar nerve-blocking technique has been employed by Albért and Löfström to evaluate the anesthetic properties of different agents.[142, 178–181] The results obtained in these controlled human investigations agree quite well with data obtained from in vivo and in vitro animal studies. For example, a classification of the various agents according to their duration of action reveals that procaine possesses a short duration of anesthetic activity; lidocaine, mepivacaine, and prilocaine are agents of moderate duration; and tetracaine, bupivacaine, and etidocaine represent long-acting local anesthetic agents (Table 22). The duration of analgesia produced by tetracaine in these studies, however, was shorter than anticipated from clinical experience. Reappearance of pain sensation occurred in 135 minutes following the use of 0.25% tetracaine, which was significantly longer than the durations observed with the moderate acting agents, but considerably shorter than the values obtained with bupivacaine and etidocaine. Differences in anesthetic technique can

Table 22

COMPARATIVE ANESTHETIC DURATION OF LOCAL ANESTHETIC AGENTS AS DETERMINED BY A STANDARDIZED ULNAR-BLOCK TECHNIQUE

DURATION	AGENTS	CONCENTRATION
SHORT (15-45 min)	PROCAINE	1.0%
MODERATE (60-120 min)	LIDOCAINE	1.0%
	MEPIVACAINE	1.0%
	PRILOCAINE	1.0%
LONG (400-450 min)	BUPIVACAINE	0.25%
	ETIDOCAINE	0.5%

markedly affect anesthetic activity. Albért and Löfström observed the reappearance of pain sensation in 40 minutes following the intraneural injections of 1 ml of 1% lidocaine, whereas Poppers and co-workers reported a duration of sensory analgesia of 165 minutes when 5 ml of this agent were administered extraneurally.[44, 179]

Dosage and concomitant use of epinephrine also can influence the activity of local anesthetic agents employed for minor nerve blocks. A significant increase in the duration of sensory analgesia and motor blockade was observed when the dose of etidocaine for ulnar nerve blocks was increased from 12.5 to 25 mg.[44] In addition, the duration of both sensory analgesia and motor blockade was prolonged significantly when epinephrine was added to various local anesthetic solutions (Fig. 4-3).[44, 80, 181] As observed in infiltration anesthesia, lidocaine appears to benefit most by the addition of epinephrine. A 200% increase in duration of sensory analgesia was produced by the addition of epinephrine to lidocaine solutions, whereas a 20% to 50% prolongation of anesthetic action occurred when a vasoconstrictor was added to agents such as mepivacaine, bupivacaine, and etidocaine.[181]

Major Nerve Blocks

It is difficult to describe in general terms the effects of local anesthetic agents on major nerve trunks or plexi, due to the marked anatomical differences involved in the blockade of major nerves. These differences are illustrated best by comparing intercostal nerve blockade with brachial plexus block. Intercostal nerve blockade usu-

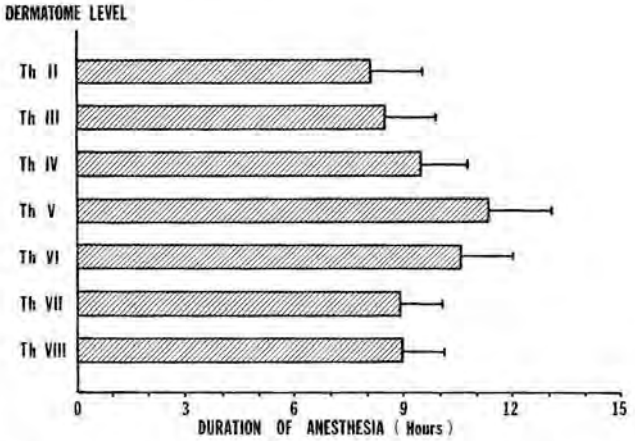

Fig. 4-5. Relative anesthetic duration at various thoracic dermatomal levels following intercostal nerve blockade with etidocaine.

ally is performed by injecting 2–4 ml of anesthetic solution around individual intercostal nerves.[182] The number of nerves to be blocked depends on the desired extent of anesthesia. In essence, this procedure consists of a series of multiple minor nerve blocks, i.e., each intercostal nerve being blocked individually. The only barriers to the neural uptake of anesthetic drug are the connective tissue and myelin sheaths of the individual intercostal nerves. An additive anesthetic effect does exist between contiguous nerves, such that the duration of anesthesia observed at the center of the area of block is significantly longer than at the peripheral dermatomal levels of the block (Fig.

Table 23

COMPARATIVE ANESTHETIC PROPERTIES OF VARIOUS AGENTS EMPLOYED FOR MINOR AND MAJOR NERVE BLOCKS

ANESTHETIC TECHNIQUE	AGENT	CONC. (%)	VOLUME (ml)	AVERAGE ONSET TIME (min)	AVERAGE DURATION OF SENSORY ANALGESIA (min)
ULNAR NERVE BLOCK	A	1.0	1	4-5	60-120
	B	0.25-0.5	1	7-8	135-430
INTERCOSTAL NERVE BLOCK	A	1.0	4/nerve	3-5	157-196
	B	0.25-0.5	4/nerve	5-6	429-780
BRACHIAL PLEXUS BLOCK	A	1.0	40-50	14-17	195-245
	B	0.25-0.5	40-50	8-25	572-613

A - includes lidocaine, mepivacaine, prilocaine
B - includes bupivacaine, tetracaine, etidocaine

4-5).[183] A comparison of the anesthetic profile of intercostal nerve blockade, i.e., initial onset and total duration of analgesia, with ulnar nerve blocks and brachial plexus blockade reveals that intercostal blocks show the rapid onset of action which is characteristic of the minor nerve-blocking procedure and the long duration of analgesia which occurs following major nerve blockade (Table 23).[184, 185]

In contrast to the relative ease of depositing anesthetic drug next to intercostal nerves, it is quite difficult to inject local anesthetic agents close to the brachial plexus due to the peculiar anatomy of this region (Fig. 4-6). A "flooding" technique is frequently employed to achieve satisfactory brachial plexus blockade. This involves the use of large volumes of local anesthetic solution in order to maximize diffusion to the nerve plexus. If the solution is placed outside the connective tissue sleeve enveloping the brachial plexus, the anesthetic molecules must diffuse through several connective tissue layers surrounding the plexus. In addition, non-nervous tissue such as fat and muscle compete with the nerve trunks as depot sites for the anesthetic drug. In order to overcome such anatomical problems, various approaches to the brachial plexus have been employed such as the axillary, supraclavicular, and interscalene.[182, 186] Such technical differences can influence the analgesic results. Hollmén and Mononen reported a duration of sensory analgesia of 453 minutes when 30 ml of 0.5% etidocaine with epinephrine 1:200,000 were administered by an axillary approach,[187] whereas a duration of 572 minutes was obtained by Bromage and associates following the supraclavicular administration of the same dose of etidocaine.[188] Thus, a difference of approximately 2 hours of analgesia exists with the same

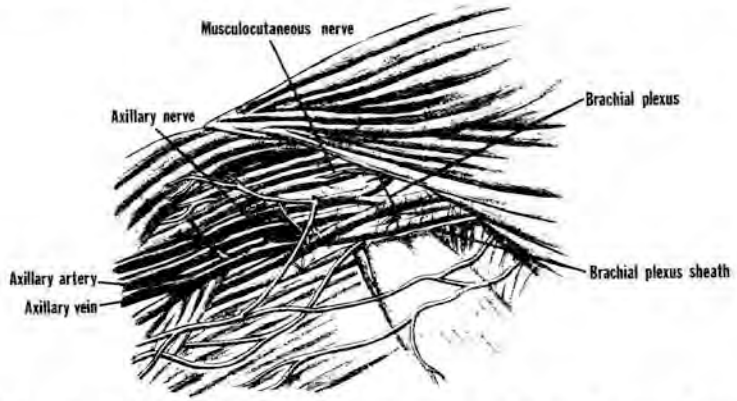

Fig. 4-6. Artist's concept of the anatomy of the axilla, with particular reference to the brachial plexus.

agent when different techniques are employed for brachial plexus blockade.

ONSET TIME

The greatest disparity between major nerve blocks, such as intercostal and brachial plexus blockade, involves the onset of anesthesia. All of the agents employed for intercostal blocks show a relatively rapid onset time, 3–6 minutes, which corresponds to the values obtained for minor nerve blocks (Table 23).[184, 185] The latency of anesthesia is considerably longer when these same drugs are used for brachial plexus or sciatic-femoral blockade (Table 23).[131, 184] In addition, a significant difference exists between the onset of various agents when brachial plexus or sciatic-femoral blocks are performed. In general, the agents of moderate duration, e.g., lidocaine and mepivacaine, exhibit a more rapid onset than the longer-acting compounds, e.g., bupivacaine and tetracaine (Table 23).[131] Bromage and Gertel have reported onset times of approximately 14 minutes for lidocaine and mepivacaine as compared to mean latency values of approximately 23 minutes for bupivacaine.[131] Etidocaine may be an exception, since the onset time of etidocaine (9 minutes) actually was shorter than that of lidocaine (14 minutes), although the duration of brachial plexus blockade with this agent (572 minutes) was similar to that of bupivacaine (575 minutes).[188]

The slow analgesic onset that characterizes major nerve-blocking procedures such as brachial plexus and sciatic-femoral blockade has been a deterrent to the use of peripheral nerve blockade for surgical procedures involving the upper and lower limbs. The onset time of agents such as lidocaine and bupivacaine can be shortened by the use of carbon dioxide salts rather than hydrochloride salts of these agents.[81, 131] Bromage and Gertel reported a reduction in the onset of brachial plexus blockade from a mean value of 14 minutes with lidocaine HCl to 8 minutes with lidocaine-CO_2.[131]

DURATION OF ANALGESIA

The longest duration of anesthesia usually occurs following major nerve blocks (Table 23). In general, the agents of moderate duration, e.g., lidocaine and mepivacaine, produce anesthesia of 1–2 hours' duration following minor nerve blockade or epidural administration, whereas analgesia usually persists for 3–4 hours when these compounds are used for major nerve blocks. Similarly, the longer-acting drugs such as tetracaine and bupivacaine cause 2–6 hours of minor nerve blockade or epidural anesthesia as compared to durations of

major nerve blocks of 4–12 hours. This prolonged duration of major nerve blockade is due to several factors. In general, a greater dose of local anesthetic agent is used for major nerve blocks as compared to other types of regional anesthetic procedures (Table 23). The use of larger doses, in part, reflects an attempt to reduce onset time and also to compensate for the technical difficulties inherent in certain major nerve blocks. In addition, the region of the brachial plexus or sciatic and femoral nerves are poorly vascularized relative to other areas such as the epidural space or caudal canal. This results in a slow rate of vascular absorption of local anesthetic agents which permits a greater uptake of drug by the major nerves.[189]

The duration of major nerve blocks will be influenced by the usual factors of dosage, technique, concomitant use of vasoconstrictor agents, and basic pharmacological properties of the various local anesthetic drugs. As indicated previously, a "flooding" technique frequently is employed for procedures such as brachial plexus blockade. The use of large volumes of dilute anesthetic solutions affords a practical method of overcoming technical difficulties. However, as in other forms of regional anesthesia, total dose rather than volume or concentration of anesthetic solution appears to be the prime determinant of analgesic duration. For example, Lund and associates observed no difference in any analgesic parameter when comparing 30 ml of 0.5% etidocaine and 20 ml of 0.75% of this agent for brachial plexus blockade by the supraclavicular approach.[133]

As in infiltration anesthesia, epinephrine will prolong the duration of most local anesthetic agents employed for major nerve blocks. However, the agents of intrinsically longer duration, e.g., bupivacaine, do not benefit as much from the addition of epinephrine as do those local anesthetic drugs of short or moderate activity, e.g., procaine and lidocaine.

Although the analgesia associated with major nerve blockade persists for a longer time than in any other form of regional anesthesia, the variation in total duration of anesthesia is also considerably greater than that observed in other types of conduction blocks. This variability in anesthetic duration is particularly marked when the longer acting compounds are used for major nerve blockade. For example, the mean duration of intercostal or brachial plexus blocks is approximately 600 minutes (10 hours) for bupivacaine, but the standard deviation in both cases exceeds 100 minutes.[184] Brachial plexus blocks varying in duration from 4 to 20 hours have been reported in individual patients with the long-acting local anesthetic agents.[188] To date, no reports of irreversible major nerve blocks have appeared in

the literature following the use of bupivacaine or etidocaine. It would be prudent to forewarn patients receiving these agents for major nerve-blocking procedures about the possibility of prolonged sensory and motor block in the involved region.

CENTRAL NEURAL BLOCKADE

Epidural (Peridural) Anesthesia

Anatomically, the epidural space is that area between the dura mater and the ligaments and periosteum lining the vertebral canal, extending from the foramen magnum to the sacrococcygeal membrane. This space has been described as a "potential" space, since normally it is completely filled with a loose type of adipose tissue, lymphatics, and blood vessels. It is particularly rich in venous plexi. No free fluid exists in the epidural space in contradistinction to the cerebrospinal fluid which is found in the subarachnoid space. However, solutions injected into the epidural space will spread in all directions between the loose tissue structure that occupies this area. Epidural anesthesia is usually subdivided into three categories depending on the site of injection: thoracic epidural, lumbar epidural, and caudal anesthesia. Cervical epidural anesthesia is possible but is rarely performed. Thoracic epidural anesthesia has been employed mainly for the production of a segmental band of analgesia involving the middle and lower thoracic dermatomes. This technique has proven beneficial for the relief of pain following thoracic or upper abdominal surgery. Lumbar epidural anesthesia is useful as an adjunct to surgical procedures involving the lower abdomen, pelvis, perineum, lower extremities, and obstetrical procedures. Caudal anesthesia is usually reserved for pelvic and perineal surgery and for vaginal deliveries.

MECHANISM OF EPIDURAL ANESTHESIA

The anatomy, physiology, and pharmacology of epidural anesthesia have been reviewed in an attempt to define the mechanism of this particular form of conduction blockade.[190–193] The possible sites of action of local anesthetic agents administered epidurally are the paravertebral nerve trunks, the dorsal root ganglia, the dorsal and ventral spinal roots, and the spinal cord (Fig. 4-7). Radiopaque material injected into the epidural space exits through the intervertebral foramina. It is, therefore, possible that anesthetic agents could leave

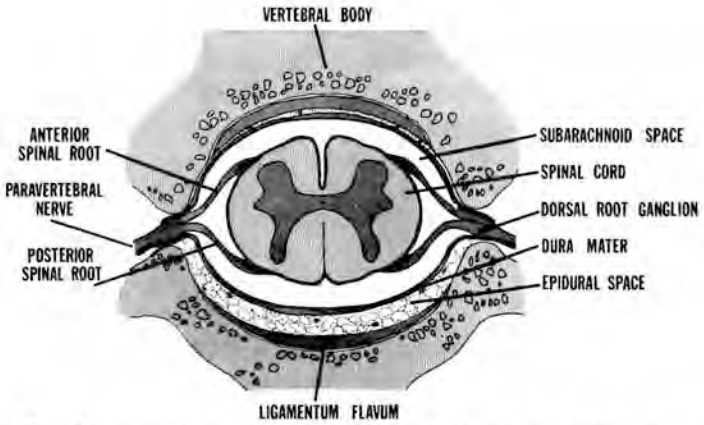

Fig. 4-7. Cross-sectional diagram of vertebral column and spinal cord.

the epidural region via these foramina to inhibit conduction in the paravertebral nerve trunks. Under these conditions, epidural anesthesia would be analogous to multiple paravertebral blocks. However, the intervertebral foramina are patent only in young people, which might suggest a correlation between age and spread of epidural anesthesia.[194] Such a relationship has not been observed by all investigators.[195] Therefore, paravertebral blockade probably plays a minor role in the production of epidural anesthesia and, even then, only in young subjects.

The dorsal root ganglia would appear to be a logical site of action because of their anatomical location *vis à vis* the epidural space. Tissue distribution studies of local anesthetic agents administered into the subarachnoid space have revealed minimal concentrations of lidocaine in dorsal root ganglia as compared to other subdural neural structures (Fig. 4-8),[196] which suggests that dorsal-root ganglion inhibition is not a primary determinant of epidural anesthesia.

The intradural spinal roots show a high concentration of local anesthetic agent following both subarachnoid and epidural injection.[196, 197] The dermatomal progression of anesthesia following epidural administration is also consistent with conduction blockade of the spinal roots. The anatomical characteristics of the neural membranes in the region of the spinal roots favor the diffusion of anesthetic drugs. In this area, the dura mater is relatively thin, and there are numerous arachnoid villi which increase the surface area available for diffusion of anesthetic agents from the epidural space.[192] The concentration of analgesic drug localized in the dural sleeves containing the spinal roots would soon exceed the minimum effective anesthetic level required for conduction blockade of these spinal roots.

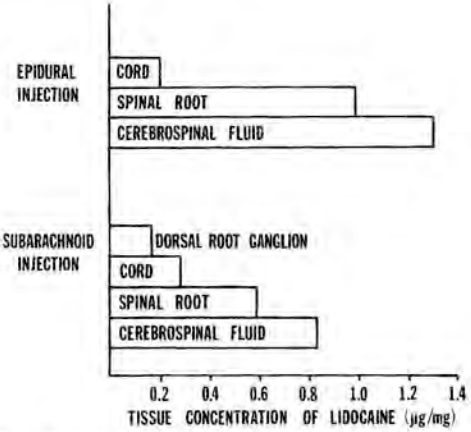

Fig. 4-8. Relative lidocaine tissue concentration following epidural or subarachnoid injection.

The spinal cord itself also takes up anesthetic drug.[196, 197] The concentration within the cord, however, is less than that in the spinal roots. Moreover, a greater quantity of drug is located in the periphery rather than the center of the cord. The dermatomal onset pattern of epidural anesthesia and the physiological differences observed between subarachnoid and epidural anesthesia would indicate that the spinal cord is not the initial site of action following epidural administration. However, the regression of epidural anesthesia does not follow the same segmental distribution observed at the onset of analgesia.[198] During the recovery phase, the cranial level of analgesia appears as a straight line encircling the body like a belt, which would be analogous to a transverse section through the cord. This suggests that spinal cord blockade does occur following epidural administration of local anesthetic agents, but only after inhibition of conduction in the spinal roots. In summary, the mechanism of epidural anesthesia appears to be related primarily to sensory and motor spinal-root inhibition, followed by spinal cord blockade and, possibly, in young people, conduction block in the paravertebral nerve trunks.

FACTORS INFLUENCING QUALITY OF EPIDURAL ANESTHESIA

Epidural anesthesia may be influenced by various factors such as site of injection, speed of injection, patient position, patient height, age, pregnancy, arteriosclerosis, volume and/or concentration of anesthetic solution, and pharmacological properties of the anesthetic agent.

Site of Injection. The dorsal epidural space is narrow from the foramen magnum to the fifth cervical vertebra. There is a gradual increase in the dorsoventral dimensions from C_5 down to the second and third lumbar vertebrae. Below this level the space again narrows.[191] Injections of small volumes of anesthetic solution (3–5 ml) into the relatively narrow midthoracic epidural space result in a discrete, but wide, segmental block. Lumbar epidural administration requires the use of larger volumes (10–30 ml) to achieve satisfactory analgesic results. Cranial spread occurs more easily than sacral spread following lumbar epidural injections, due in part to negative intrathoracic pressure and to the resistance afforded by the narrowing of the epidural space at the lumbosacral junction. A significant delay and/or an absence of analgesia at the first and second sacral segments is frequently observed following lumbar epidural injections. This has been attributed in part to the narrowing of the epidural space at the lumbosacral junction and also to the thickness of spinal roots in this region.[199] Caudal anesthesia usually requires greater amounts of drug, due to loss of solution through the anterior sacral formina and the rapid vascular absorption from this site.[189, 193, 200] Little cranial spread beyond the lumbosacral junction occurs following caudal injections because of the peculiar anatomy of the epidural space in this region.

Speed of Injection. Erdemir, Soper, and Sweet compared anesthetic qualities of 20 ml of 2% lidocaine injected into the lumbar epidural space at a rate of 1 ml/sec and 1 ml/3 sec.[201] Each of 17 subjects was studied on two occasions, so that each individual served as his own control. The slow injection resulted in a duration of motor block 10-minutes longer than achieved by the rapid injection. The level of anesthesia was approximately one dermatome higher following the fast injection. These differences were statistically significant but, obviously, are of little clinical relevance. Rate of injection had no effect on the spread of radiopaque material administered into the epidural space.[195] Probably the most pertinent clinical aspect of varying injection rate is the significantly greater patient discomfort associated with a rapid rate of injection.

Patient Position. Posture has been demonstrated by Bromage to influence the quality of epidural analgesia.[135] This investigator reported that larger quantities of anesthetic drug were required to achieve the same dermatomal level in patients in the sitting position as compared to the horizontal position. Lumbar epidural anesthesia is

often performed with the patient in the sitting position in obstetrics to obtain satisfactory perineal analgesia. However, studies involving spread of radiopaque solutions and radioisotope tracers in the epidural space have failed to demonstrate any effect of posture on spread in the epidural space.[195, 202] This apparent discrepancy may be related to differences in the density of administered material. Most local anesthetic solutions are slightly hyperbaric and so would be influenced by gravity. The radiopaque and radioisotope studies may have utilized isobaric solutions, the movement of which should be independent of the influence of gravity.

Age and Height. Discrepancies also exist between studies in which the influence of age and height on epidural anesthesia has been assessed by clinical means, i.e., analgesic dermatomal levels, and by radiographic observations.[135, 194, 195] Bromage has reported that dose per segment requirements of epidurally administered analgesic agents are directly proportional to patient height and inversely proportional to patient age.[135] Burn, Guyer, and Langdon failed to demonstrate any correlation between age, height, and the spread of radiopaque material in the epidural space.[194] These authors have concluded that the degree of vertical spread in the epidural space is dependent to a greater extent on the soft tissue contents rather than the size of the epidural space and that escape of solution via the intervertebral foramina, even in young people, is of little significance.

Pregnancy. Significantly less anesthetic drug is required in pregnant patients to produce levels of epidural analgesia comparable to those in nonpregnant subjects. For example, similar epidural anesthetic results can be obtained by the use of 6–10 ml of 2% lidocaine (120–200 mg) in obstetrics and 15–30 ml of 2% lidocaine (300–600 mg) in nonparturient patients.[141, 203] This difference is believed related to inferior vena caval compression in pregnancy, which results in a marked distention of the epidural venous plexi. It is possible to mimic this situation in nonpregnant animals by placing an inflatable balloon in the inferior vena cava. Under these conditions, an exaggerated spread of epidurally administered contrast media has been observed.[204] The distended venous plexi would occupy more space, thereby decreasing the diameter of the epidural cylinder and facilitating the vertical spread of epidurally administered anesthetic solution.

Arteriosclerosis. A decrease in the dose per segment epidural requirement of local anesthetic agents has been observed in ar-

teriosclerotic patients.[194] This is probably due to a decreased rate of vascular absorption of anesthetic agents from the epidural space by sclerotic arterioles, which allows more drug to be available for uptake by nerves. Closure of the intervertebral foramina would prevent leakage of drug through this route and also may contribute somewhat to the greater anesthetic spread in older arteriosclerotic patients.

Volume and/or Concentration of Anesthetic Solution. Much has been written about the relative influence of volume and concentration of anesthetic solutions on the quality of epidural anesthesia. Volume will influence the vertical spread of epidural analgesia.[201] For example, 30 ml of 1% lidocaine produced a level of analgesia following lumbar epidural administration, which was 4.3 dermatomes higher than that achieved by 10 ml of 3% lidocaine.[201] However, the essential qualities of epidural anesthesia, i.e., onset, depth, and duration of sensory analgesia and motor blockade are related to the mass of drug (total mg), rather than variations in volume or concentration of solution (Fig. 4-2).[141,193] Since the primary mechanism of epidural anesthesia involves spinal root blockade, the main anesthetic determinant would be the transdural drug gradient which, in turn, is a function of the epidural drug mass, i.e., the product of volume times concentration.

Anesthetic Agent. The basic pharmacological properties of the various local anesthetic agents will influence the dosage requirements and resultant quality of epidural anesthesia. The drugs utilized for epidural anesthesia may be classified according to their intrinsic anesthetic potency and duration of action (Table 24). Procaine, chloroprocaine, lidocaine, mepivacaine, and prilocaine are commonly administered as 1% to 3% solutions, whereas tetracaine, bupivacaine, and etidocaine are employed in concentrations of 0.25% to 1.5%. These agents can be divided into three categories based on analgesic duration: short action (30–90 minutes), e.g., procaine and chloroprocaine; moderate duration (60–180 minutes), e.g., lidocaine, mepivacaine, and prilocaine; long duration (180–360 minutes), e.g., tetracaine, bupivacaine, and etidocaine.[140,205]

Onset of epidural anesthesia may be separated into initial onset, i.e., the time at which analgesia to pin prick is observed at any dermatomal level, and complete onset, i.e., the time required for maximal segmental spread of analgesia. Initial onset usually occurs within 5–10 minutes following epidural administration of the various agents. Complete onset commonly occurs at 10–20 minutes after

Table 24

COMPARISON OF LOCAL ANESTHETIC AGENTS EMPLOYED IN EPIDURAL ANESTHESIA

AGENT	USUAL CONC. (%)	USUAL VOL. (ml)	TOTAL DOSE* (mg)	DURATION (min)
A. Short Duration				
PROCAINE	1-2	15-30	150-600	30-90
CHLOROPROCAINE	1-3	15-30	150-900	
B. Moderate Duration				
LIDOCAINE	1-2	15-30	150-500	
MEPIVACAINE	1-2	15-30	150-500	60-180
PRILOCAINE	1-3	15-30	150-600	
C. Long Duration				
TETRACAINE	0.25-0.5	15-30	37.5-150	
BUPIVACAINE	0.25-0.75	15-30	37.5-225	180-360
ETIDOCAINE	1-1.5	15-30	150-300	

* doses of epinephrine-containing solutions

injection of the anesthetic solution. Differences in epidural onset time between the various agents are significantly less than observed following other regional anesthetic techniques such as brachial plexus blockade (Table 25). For example, an average difference of approximately 10 minutes in onset time was observed between mepivacaine and bupivacaine in brachial plexus blocks, whereas an average difference of only 1.5 minutes existed when these agents were used for epidural anesthesia.[131] Marked variations in onset of epidural anesthesia have been reported by various investigators studying the same agent. Such variations are probably related to the method of evaluation (Table 26).[132, 134, 207-210]

Table 25

COMPARATIVE ONSET TIMES AND ANALGESIC DURATIONS OF VARIOUS LOCAL ANESTHETIC AGENTS IN BRACHIAL PLEXUS BLOCKADE AND EPIDURAL ANESTHESIA**

ANESTHETIC TECHNIQUE	ANESTHETIC AGENT	USUAL CONC.(%)	AVERAGE ONSET TIME (min ± S.E.)	AVERAGE ANALGESIC DURATION (min ± S.E.)
BRACHIAL PLEXUS BLOCK 40-50 ml	LIDOCAINE	1.0	14.04 ± 3.83	195 ± 26.3
	MEPIVACAINE	1.0	14.84 ± 6.22	245 ± 26.8
	BUPIVACAINE	0.25	23.26 ± 7.93	575
	ETIDOCAINE	0.5	8.77	572
EPIDURAL ANESTHESIA 20-30 ml	LIDOCAINE	2.0	15	100 ± 20*
	MEPIVACAINE	2.0	15	115 ± 15
	BUPIVACAINE	0.5	16.5	195 ± 30
	ETIDOCAINE	1.0	10.85	170 ± 57

* 2-segment regression

** Data derived from ref. 128, 185

Table 26

COMPARATIVE EVALUATION BY VARIOUS INVESTIGATORS OF THE ANESTHETIC PROPERTIES OF 0.5% BUPIVACAINE WITH EPINEPHRINE 1:200,000 IN EPIDURAL ANESTHESIA

INVESTIGATOR (REFERENCE NO.)	EVALUATION TECHNIQUE	INITIAL ONSET	COMPLETE ONSET	2 SEGMENT REGRESSION	TOTAL REGRESSION
132	PIN PRICK	6.3±1.2	—	228 ± 23	—
134	PIN PRICK	9.0±1.0	18.0±2.0	160 ± 20	315±22
188	PIN PRICK	5.8	18.2	196 ± 31	—
206	TIME OF POST-OP PAIN	—	—	—	423±15
207	PIN PRICK POST-OP PAIN	12.2±1.1	28.3±2.03	—	261±23
208	PIN PRICK	7	21	210	330
209	ALLIS CLAMP	5.4±1.7	19.6±5.5	332±169	459±82
210	PIN PRICK	9.2±4.0	19.8±6.2	156 ± 68	284±111

Analgesic duration is commonly divided into (a) 2-segment regression, i.e., the time required for analgesia to regress 2 dermatomes from the highest level of block, and (b) total duration, i.e., the time for complete disappearance of analgesia from all dermatomes. The time interval between 2-segment regression and total recovery from analgesia is considerably longer for the long-acting agents as compared to the agents of moderate total duration (Fig. 4-9).[211] In general, the duration of epidural anesthesia is markedly shorter than the duration of major nerve blockade. However, the difference in duration between epidural and major nerve blockade is less for agents such as lidocaine and mepivacaine than for those compounds possessing an intrinsically longer duration of action, e.g., bupivacaine and

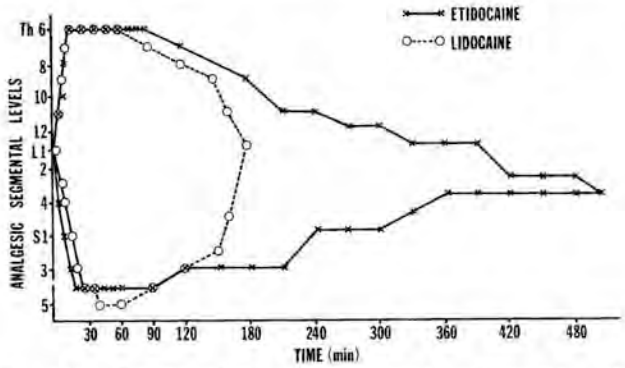

Fig. 4-9. Comparative time-segment diagrams for lidocaine and etidocaine following epidural administration.

tetracaine (Table 25). Considerable variation also exists in the values for anesthetic duration reported by different investigators for the same agent, which again reflects differences in the method of analgesic evaluation (Table 26).[132, 134, 206–210]

Duration of anesthesia may be influenced by the concomitant use of vasoconstrictor agents. In general, the duration of agents of short or moderate activity is significantly prolonged by the use of epinephrine-containing solutions, whereas the long-acting agents benefit little from the addition of epinephrine.[141, 145, 209] The optimal concentration of epinephrine required to retard the vascular absorption of local anesthetic agents from the epidural space and so prolong the duration of anesthesia may vary depending on the relative vasodilator properties of the different analgesic drugs. The optimal concentration of epinephrine for each anesthetic agent has not been well elucidated. A 1:200,000 (5 μg/ml) concentration of epinephrine usually is employed with all epidurally administered anesthetic drugs. This concentration of epinephrine has been demonstrated to be optimal for lidocaine and etidocaine.[212, 213]

With regard to the use of other vasoconstrictor agents, phenylephrine has been compared with epinephrine as an additive to solutions of lidocaine for epidural anesthesia.[214] A concentration of 50 μg/ml (1:20,000) of phenylephrine added to 2% lidocaine produced a duration of epidural analgesia which was approximately 45 minutes shorter than that achieved by a 2% lidocaine solution with epinephrine 1:200,000 (5 μg/ml). This shorter analgesic duration of the lidocaine-phenylephrine solution was correlated with a higher peak blood level of lidocaine, which suggests that the vasoconstrictor effect of phenylephrine was not comparable to that of epinephrine at the concentrations studied.

Epidural anesthesia has proven to be a useful technique for differential nerve blockade and for unmasking subtle differences between agents that are not seen in other forms of regional anesthesia. As indicated previously, nerve fibers have been classified according to their conduction velocity as A, B, and C fibers (Table 27).[215] The A fibers are further subdivided into alpha, beta, gamma, and delta in order of decreasing conduction velocity. A fibers consist of both sensory- and motor-myelinated fibers. The A delta fibers are believed responsible for fast pain sensation. B fibers are found in myelinated preganglionic autonomic nerves. C fibers consist of unmyelinated sensory and postganglionic autonomic fibers. In general, the conduction velocity of these different fibers is directly proportional to their size, i.e., the fast-conducting A fibers are largest, whereas the slow-

conducting C fibers are smallest. It appears that the size of the nerve fibers influences the minimum anesthetic concentration required for conduction block, i.e., the larger fibers have a higher Cm. On the basis of this anatomical and physiological knowledge, it is possible to administer varying doses of local anesthetic agents epidurally in order to selectively block different nerve fibers. For example, sympathetic nerve blockade may be performed with 5–7 ml of 0.5% to 1.0% lidocaine or mepivacaine, whereas 15–20 ml of 1% to 2% solutions are required for complete sensory and motor block.[182] The onset and duration of sympathetic, sensory, and motor block differ following epidural anesthesia. The onset of sympathetic and sensory block occurs most rapidly, followed by motor blockade, while regression occurs in the opposite direction, i.e., motor function returns initially, followed by sensory and sympathetic activity (Table 27). Sympathetic block following epidural administration of local anesthetic drugs mainly involves inhibition of the preganglionic sympathetic B fibers. The A delta fibers conduct rapid and sharp pain impulses and, due to their larger size and higher Cm requirements, may become unblocked sooner than B fibers. Thus, sensory activity may return sooner than sympathetic tone. Hypotension may occur if patients are ambulated too soon following epidural anesthesia, in the mistaken impression that sympathetic activity has fully returned when sensation appears completely recovered.[216]

An interrelationship exists between the anatomy of the epidural space, the morphology of nerve fibers involved in epidural anesthesia, and the physicochemical properties of the local anesthetic agents employed for this procedure. This is best exemplified by comparing the epidural anesthetic results obtained with bupivacaine and

Table 27

CLASSIFICATION OF NERVE FIBERS ACCORDING TO ANATOMICAL AND PHYSIOLOGICAL PROPERTIES

CLASS	DIAMETER (microns)	MYELINATED	FUNCTION	CONDUCTION VELOCITY (m/sec)	C_m	ORDER OF BLOCK	ORDER OF RECOVERY
A Fibers	2-22	+		10-120	HIGHEST	3	1
α			MOTOR				
β			MOTOR				
γ			MOTOR				
δ			SENSORY				
B Fibers	1-3	+	PREGANGLIONIC AUTONOMIC	10-20	INTERMEDIATE	2	2
C Fibers	0.5-1	−	SENSORY POSTGANGLIONIC AUTONOMIC	0.5-2.0	LOWEST	1	3

etidocaine. These two agents possess the same intrinsic anesthetic potency as determined on an isolated nerve.[114, 115] However, in the epidural space of man, a 1% concentration of etidocaine is equivalent to 0.5% bupivacaine in terms of sensory blockade.[210] This difference is probably attributable to the very high lipid solubility of etidocaine which results in an uptake and sequestration of this compound by the extensive adipose tissue in the epidural space. The high lipid solubility and lower pK_a of etidocaine are probably responsible for the rapid diffusion of this agent through the dura and myelin covering of A fibers, which leads to a more rapid onset of motor blockade.[210] Moreover, the profoundness and longer duration of motor block observed with etidocaine suggests an accumulation in the lipid myelin sheaths of the A fibers.[188, 210]

Spinal Anesthesia

This form of regional anesthesia represents the oldest and still the most commonly employed type of central neural blockade. This procedure was described in the last decade of the nineteenth century by Halsted and his associates and by August Bier. In recent years, this form of central neural blockade has been the subject of much controversy related, particularly, to the potential hazards and complications associated with spinal anesthesia. Several studies of a prospective and retrospective nature have been published in which the hazards of subarachnoid blockade have been evaluated.[217–220] Noble and Murray reviewed the experiences of 27 Canadian university-affiliated hospitals in which a total of 78,746 spinal anesthetic procedures had been conducted between the years of 1959 and 1969.[221] These authors concluded that the hazards of spinal block are no greater than that of any other anesthetic technique and that the procedure should be retained as part of the armamentarium of the anesthesiologist.

COMPARISON OF EPIDURAL AND SPINAL ANESTHESIA

Moore and co-workers compared both forms of central neural blockade involving approximately 20,000 patients and stated that both these techniques are safe, provided the physician performing the procedure evaluates his own capabilities and the patient's physical status.[222] The anesthetic characteristics of subdural and extradural procedures differ somewhat (Table 28). The onset time for subarachnoid blocks is appreciably shorter than that observed following

Table 28

COMPARISON OF SPINAL AND EPIDURAL ANESTHESIA

PROCEDURE	AGENTS*	USUAL CONC. (%)	USUAL VOL (ml)	TOTAL DOSE (mg)	TONICITY RELATIVE to CSF	GLUCOSE CONC.	COMPLETE ONSET (min)	DURATION (min)
SPINAL ANESTHESIA	LIDOCAINE	1.5, 5.0	1-2	15-100	hyperbaric	7.5%	3-6	30-90
more controllable more predictable less segmental	TETRACAINE	0.25, 0.5, 1.0	1-4	5-20	isobaric hypobaric hyperbaric	5% (hyperbaric sol'n only)	5-12	75-150
EPIDURAL ANESTHESIA	LIDOCAINE	1.0, 1.5, 2.0	10-30	100-300	isobaric	—	10-20	45-120
less controllable less predictable more segmental	TETRACAINE	0.25, 0.5	10-30	25-150	isobaric	—	15-25	120-240

*values are based on anesthetic solutions without epinephrine

epidural administration. Moore and associates reported an average onset time of 5–12 minutes for spinal block as compared to 15–25 minutes for epidural anesthesia.[222] Other investigators have reported an immediate onset with agents such as lidocaine and mepivacaine administered into the subarachnoid space.[223, 224] The more rapid onset of spinal anesthesia is understandable, since minimal diffusion barriers exist in the subarachnoid space. This lack of a diffusion barrier is readily apparent when the biotoxin substances, tetrodotoxin and saxitoxin, are employed for regional anesthesia. In the subarachnoid space, the biotoxins show a rapid onset of action and a high frequency of satisfactory analgesia. However, when these agents are administered extradurally either for epidural anesthesia or for peripheral nerve blocks in animals, the onset of anesthesia is extremely prolonged, and, generally, the incidence of satisfactory analgesia is very poor.

The duration of spinal anesthesia is generally shorter than that of epidural anesthesia. For example, an average duration of spinal anesthesia of 156–190 minutes has been reported for tetracaine as compared to a value of 334 minutes when this agent was used for epidural analgesia.[225] This difference in duration is probably due, in part, to the smaller total dosage of drug employed for spinal anesthesia as compared to epidural anesthesia (Table 28).

The area of anesthesia produced by spinal blockade is more predictable, controllable, and less segmental than that obtained with epidural administration of analgesic drugs.[222] The use of anesthetic solutions of varying tonicity and the ease of altering anesthetic level by patient posture accounts for the greater predictability and controllability

of spinal anesthesia. The uptake of larger amounts of anesthetic drug by the spinal cord probably is responsible for the absence of a segmental pattern of anesthesia following subarachnoid injection.

FACTORS AFFECTING SPINAL ANESTHESIA

The analgesic properties of subarachnoid blockade may be influenced by a number of factors that can be related to the patient, anesthetic solution, and anesthetic technique.

Patient Factors. Patient position during and immediately following subdural administration of a local anesthetic agent will influence the spread of spinal anesthesia.[226] Since hyperbaric anesthetic solutions are commonly used for subarachnoid blocks, the spread in cerebrospinal fluid will be affected by gravity. For example, the patient in a sitting position at the time of injection will experience a lower level block than the patient who is supine.

A decrease in the spinal fluid capacity of the subarachnoid space will markedly affect the degree of analgesia and the dose requirements for satisfactory spinal anesthesia. Inferior vena cava compression, usually due to pregnancy, is the most common cause of engorgement and distention of the vertebral system, which will decrease the capacity of the subarachnoid space for spinal fluid. Subarachnoid administration of 4 mg of tetracaine usually produces analgesia to the T_{11} dermatomal level in normal subjects. This same dose of tetracaine will result in a T_{7-8} level of anesthesia in pregnant patients or subjects in whom inferior vena cava pressure has been experimentally elevated by abdominal compression.[227] These data support the general clinical impression that the dosage requirements for spinal anesthesia are significantly lower in pregnant patients than in nonparturient subjects.

Anesthetic Factors. Although most anesthetic drugs may be used for spinal anesthesia,[226] essentially only two agents are prepared in a form specifically intended for subarachnoid administration. Lidocaine is available as a hyperbaric solution in concentrations of 1.5% and 5.0% with 7.5% glucose. Tetracaine, which is the most commonly used spinal agent, is available both as niphanoid crystals and as a 1% solution which may be diluted with 10% glucose to obtain a 0.25% or 0.5% hyperbaric tetracaine solution. Hypobaric and isobaric solutions of tetracaine also have been utilized for specific operative situations, e.g., anorectal or hip surgery in which it may be advantageous to maintain the patient in a head-down position.[228, 229]

Lidocaine essentially provides a short duration of spinal anes-

thesia, whereas tetracaine is considered to be an agent of long duration. An average total analgesic duration of 94 minutes has been reported following the use of 1 ml of 5% lidocaine (50 mg)[130] with variations in duration of 30 to 150 minutes when doses of 50–250 mg are employed.[223, 230] However, surgical anesthesia for 30 to 75 minutes is usually obtained with the routine use of 1–2 ml of 5% lidocaine (50–100 mg). Tetracaine in doses of 4–20 mg has been reported to provide 75 to 105 minutes of surgical anesthesia for intraabdominal procedures and 120 to 150 minutes of surgical anesthesia for perineal and lower-extremity procedures.[222]

As in other forms of regional anesthesia, vasoconstrictor agents may prolong the duration of spinal anesthesia. The addition of 0.25–0.3 mg of epinephrine to lidocaine or tetracaine solutions will produce a 50% prolongation of spinal anesthesia.[223, 231] Measurements of spinal fluid concentrations of lidocaine following subarachnoid administration have revealed that epinephrine slows the rate of disappearance of anesthetic drug from spinal fluid, probably because of its vasoconstrictor effects.[223] An increase in the duration of subarachnoid block has also been reported following the addition of 5 mg of phenylephrine to tetracaine.[231]

Technical Factors. The site of injection will influence the analgesic dermatomal level. The L_{3-4} interspace is commonly used for the subarachnoid administration of anesthetic drugs. Injection at higher vertebral interspaces is associated with a higher level of block. The speed of injection, needle direction, and type of spinal needle may influence the level of spinal anesthesia.[225] Use of a unidirectional needle positioned in a cephalad direction will produce a higher level of sensory analgesia. Injection of tetracaine at a rate of 1 ml/sec produced a level of analgesia which was approximately 2 dermatomal levels higher than was achieved with an injection rate of 0.2 ml/sec. Moreover, the use of a unidirectional needle resulted in a higher analgesic level than that obtained with a conventional needle, regardless of injection rate.[225]

TACHYPHYLAXIS

The continuous infusion or intermittent injection of local anesthetic agents into the epidural or subdural space has been employed for prolonged surgical procedures or to provide an extended period of postoperative pain relief. However, tachyphylaxis, or rapid tolerance, has been observed to occur following the continuous or repeated

administration of local anesthetic agents into the subarachnoid or epidural space.[232-234] Tachyphylaxis is defined as a rapidly developing decreased analgesic response to a constant repeated dose of a specific local anesthetic drug. Bromage and associates have carefully described the development of tachyphylaxis in a group of patients undergoing epidural anesthesia.[233] A progressive decrease in duration and spread of anesthesia was observed as the interval between the return of sensation and the subsequent injection was increased from 10 to 60 minutes, reaching a constant degree of tachyphylaxis when the interanalgesic interval exceeded 60 minutes. A constant 30% reduction in response to each successive injection occurred at maximum tolerance.

The etiology of local anesthetic tachyphylaxis has not been completely resolved. Cohen and associates have proposed that the development of tolerance following repetitive subarachnoid administration is related to changes in the pH of cerebrospinal fluid (CSF).[234] A significant increase in the H^+ content of CSF was observed when multiple subarachnoid injections of acidic solutions of lidocaine and procaine were made. This greater H^+ content (lower pH) of CSF would tend to increase the amount of the ionized form of a local anesthetic agent and conversely produce a relative decrease in the base form, which is responsible for diffusion through the nerve membrane. Such an alteration would be manifested clinically as a reduced analgesic response. Consistent with this hypothesis was the observation that a correlation existed between the rate of development of tachyphylaxis and the pK_a of the local anesthetic agent. For example, tolerance occurred more rapidly when an agent with a lower pK_a, e.g., mepivacaine was used. The relative proportion of base and cationic form of such a drug would be affected to a greater degree by alterations in the pH of CSF than would an agent with a higher pK_a. These studies suggest that the development of tachyphylaxis may be retarded by the use of agents with intrinsically longer durations of action, use of agents with higher pK_a values, and use of a buffer to prevent the decrease in pH of cerebrospinal fluid.

TOPICAL ANESTHESIA

Topical anesthesia is an extremely complex subject, due to a number of complicating factors such as lack of reliable objective techniques for evaluating anesthetic activity, variability in application site, and diversity of anesthetic application forms.[235]

Site of Application

Anesthetic agents have been applied topically to such diverse sites as skin, eye, tympanic membrane of the ear, gastrointestinal tract, gingival mucosa, tracheobronchial tree, genitourinary tract, and rectum. Endotracheal instillation of local anesthetic agents for endoscopy and bronchoscopy represents one of the most common uses of topical anesthesia.[236] Cocaine, tetracaine, lidocaine, and prilocaine have been reported to be efficacious for topical anesthesia of the oropharynx, larynx, and tracheobronchial tree.[237-239] Onset of anesthesia usually occurs in 5–10 minutes, and analgesic duration as judged by suppression of the cough reflex persists for approximately 30 minutes with lidocaine and prilocaine.[239] The duration of cocaine and tetracaine probably averages 60 minutes, although definitive values based on control studies are lacking.

Attempts have been made to utilize local anesthetic drugs orally for the treatment of conditions such as peptic esophagitis and duodenal ulcers.[240, 241] The rationale for the oral use of local anesthetic agents is the ability to inhibit the formation or release of gastrin by a blockade of vagal nerve endings. The extremely low gastric pH renders most of the conventional local anesthetic agents orally ineffective. However, oxethazaine was introduced as a local anesthetic compound that was active in a low pH environment.[242] Oxethazaine has been reported to be effective for the treatment of peptic esophagitis and duodenal ulcers,[240, 241] but it has not been possible to demonstrate a gastrin inhibitory effect with the drug.[243]

Topical anesthesia is frequently employed as an adjunct to various diagnostic urologic procedures to obviate the need for general anesthesia. The urethral instillation of lidocaine incorporated in a highly viscid gel has been demonstrated to produce a significant increase in pain threshold as evaluated by an electrical stimulation technique.[244]

Mucous membranes such as the gingiva are a common site for the application of topical anesthetic agents. Adriani and associates have conducted a series of studies to determine the topical anesthetic properties of various drugs on mucous membranes and the factors which influence their action.[245-248] A standardized technique involving electrical stimulation of the tip of the tongue was utilized to evaluate over 40 drugs. Tetracaine, cocaine, dibucaine, lidocaine, and dyclonine were found to be the most potent and effective topical anesthetic agents.[246, 247] Marked differences were found in the anesthetic properties of different agents when topical administration was compared to administration by injection. For example, tetracaine and

Table 29

COMPARATIVE TOPICAL AND INJECTABLE ANESTHETIC ACTIVITY OF VARIOUS LOCAL ANESTHETIC AGENTS

AGENT	EFFECTIVE ANESTHETIC CONCENTRATIONS	
	INJECTABLE	TOPICAL
PROCAINE	1.0 – 4.0%	10 – 20%
TETRACAINE	0.25 – 1.0%	0.2 – 1.0%
LIDOCAINE	0.5 – 2.0%	2.0 – 4.0%
MEPIVACAINE	0.5 – 2.0%	12 – 15%

lidocaine provide effective anesthesia by surface application and local injection, whereas procaine and mepivacaine are very effective anesthetic agents when administered by injection, but display poor topical anesthetic properties (Table 29).

An increase in dose will shorten the onset and prolong the duration of surface anesthesia as observed in other forms of regional anesthesia (Fig. 4-10). The onset of anesthesia with cocaine is reduced from 4 to 0.3

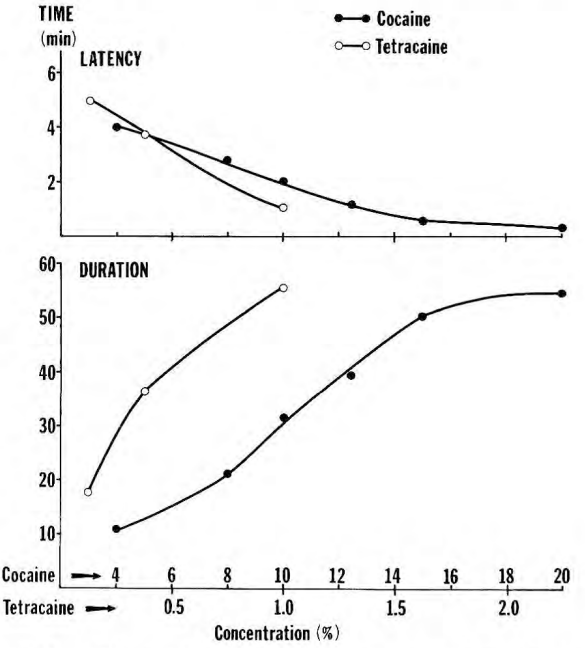

Fig. 4-10. Effect of anesthetic concentration on the onset and duration of topical analgesia.

minutes and the duration prolonged from 10 to 55 minutes as the cocaine concentration is increased from 4 to 20%. The addition of vasoconstrictor drugs, colloids, detergents, cations, and spreading agents did not influence either the intensity or duration of topical anesthesia.[246, 247]

The topical application of local anesthetic agents to intact skin generally fails to produce a measurable degree of cutaneous analgesia unless high concentrations of certain compounds are maintained in contact with the skin for relatively long periods of time (30–60 minutes). Twenty percent benzocaine and 30–40% lidocaine have been reported to produce anesthesia of intact skin.[249, 250] In the case of lidocaine, the use of an occlusive bandage to ensure cutaneous contact for approximately 60 minutes was required to demonstrate surface analgesia. Thus, the onset of anesthesia is slow and the duration and depth of anesthesia is marginal. The lack of cutaneous efficacy may be related either to an inability of the presently available agents to penetrate the epithelial barriers of intact skin or to a rapid vascular absorption following diffusion through the epidermis such that insufficient drug is taken up by the nerve endings in the dermis.

TOPICAL ANESTHETIC APPLICATION FORMS

The composition of topical anesthetic preparations varies markedly, depending on the intended site of application (Table 30). For example, lidocaine is prepared in the following forms for topical use: a 4% aqueous solution for endotracheal instillation; a 2.5–5.0% ointment containing polyethylene and propylene glycol for anesthesia of mucous membranes; a 2% jelly containing carboxymethylcellulose for intraurethral use; a suppository of 100 mg lidocaine for rectal application, and a 10% aerosol for anesthesia of the gingival mucosa. Other agents such as tetracaine, benzocaine, and dibucaine are also prepared in various forms for topical anesthesia. The comparative efficacy of various application forms has been evaluated by means of an electrical stimulating device attached to the gingival mucosa. Giddon and co-workers reported that lidocaine incorporated into a dissolvable film produced a significantly greater increase in pain threshold than the same dose of lidocaine applied either in the form of an ointment, liquid, or spray.[251] The main purpose of these various topical admixtures is to maintain the anesthetic agent in contact with the surface intended to be anesthetized. The various ingredients in the topical anesthetic preparation are not believed to enhance the basic conduction-blocking properties of the anesthetic drug.

Table 30

VARIOUS PREPARATIONS INTENDED FOR TOPICAL ANESTHESIA

ANESTHETIC INGREDIENT	CONCENTRATION %	PHARMACEUTICAL APPLICATION FORM	INTENDED AREA OF USE
BENZOCAINE	1-5	Cream	Skin and mucous membrane
	20	Ointment	Skin and mucous membrane
	20	Aerosol	Skin and mucous membrane
COCAINE	4	Solution	Ear, nose, throat
DIBUCAINE	0.25-1	Cream	Skin
	0.25-1	Ointment	Skin
	0.25-1	Aerosol	Skin
	0.25	Solution	Ear
	2.5	Suppositories	Rectum
DYCLONINE	0.5-1	Solution	Skin, oro-pharynx, tracheo-bronchial tree, urethra, rectum
LIDOCAINE	2-4	Solution	Oro-pharynx, tracheobronchial tree, nose
	2	Jelly	Urethra
	2.5-5	Ointment	Skin, mucous membrane, rectum
	2	Viscous	Oro-pharynx
	10	Suppositories	Rectum
	10	Aerosol	Gingival mucosa
TETRACAINE	0.5-1	Ointment	Skin, rectum, mucous membrane
	0.5-1	Cream	Skin, rectum, mucous membrane
	0.25-1	Solution	Nose, tracheobronchial tree

SUMMARY

1. Local anesthetic activity varies as a function of the regional anesthetic procedure, clinical status of the patient, anesthetic agent, and composition of anesthetic solution.
2. Regional anesthesia may be classified anatomically as follows: (a) infiltration anesthesia (extravascular or intravascular); (b) peripheral nerve blockade (minor or major nerve block); (c) central neural blockade (epidural or subarachnoid block); and (d) topical anesthesia.
3. In general, onset of anesthesia occurs most rapidly during infiltration techniques and subarachnoid administration followed in order of increasing onset time by minor nerve blockade, epidural block, and topical application to mucous membranes. The longest latency is observed in peripheral nerve blockade involving major nerve trunks and plexi. Duration of anesthesia is most prolonged when major nerve blockade is performed, followed in order of decreasing duration by epidural and infiltration procedures, minor nerve and subarachnoid blocks, and topical application.
4. The local anesthetic agents commonly employed for regional

anesthesia may be classified according to their relative duration of activity; agents of short duration, e.g., procaine and chloroprocaine; agents of moderate duration, e.g., lidocaine, mepivacaine, and prilocaine; and agents of long duration, e.g., tetracaine, bupivacaine, and etidocaine.

5. In general, the onset, duration, and quality of regional anesthesia are enhanced by an increase in dose achieved either by an increase in concentration or volume of anesthetic solution and by the concomitant use of a vasoconstrictor drug, epinephrine. However, the local anesthetic properties of the intrinsically more potent and longer-acting agents are influenced less by the addition of epinephrine, particularly when such agents are employed for central neural blockade of the epidural type.
6. The properties of topical anesthesia are influenced by the site of application, the pharmaceutical administration form, and the local anesthetic agent. Tetracaine, cocaine, dibucaine, benzocaine, dyclonine, lidocaine, and prilocaine demonstrate effective topical anesthetic activity, whereas procaine and mepivacaine provide weak surface anesthesia. Intact skin is generally resistant to the anesthetic effect of the conventional agents.