Comparative Clinical Pharmacology of Local Anesthetic Agents

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THE ABILITY of a chemical compound to alleviate or prevent localized pain is not difficult to evaluate. However, with the knowledge and methodology now available, it is neither adequate nor acceptable to determine simply that a new agent can interfere with the conduction process of nervous tissue. Thus, when a new agent is introduced into clinical practice, information should be available as to its relative potency compared with standard local anesthetic drugs, potential local and systemic toxicity, and other pharmacologic variables such as absorption, distribution, and sites of metabolism.

Since requirements for regional anesthesia vary considerably, depending on the condition of the patient, the type, degree and etiology of the pain, and the surgical procedure, it is unlikely that any single chemical entity will prove adequate for all anesthetic procedures. Thus, selection of the proper agent for a specific indication requires a thorough knowledge of both its specific anesthetic and its general pharmacologic properties. A review of the data currently available from studies of some standard local anesthetic agents and some new agents is presented below. In addition, an attempt is made to define the data that should be available prior to the introduction of a new anesthetic agent into general clinical practice.

Preclinical Pharmacology

Impairment of nerve conduction can be evaluated simply and most directly by means of an isolated nerve technique.[1] The isolated sciatic nerve of the frog has been used most often, but it is possible to use a mammalian nerve, such as the vagus nerve of the rabbit.[2] This procedure can provide information concerning anesthetic potency of a new compound, relative potency compared with standard anesthetics, the time to onset of conduction block, and rapidity of recovery. In addition, characteristics of diffusion across the nerve sheath can be determined by comparing the times to onset of conduction block in an intact isolated nerve and a desheathed isolated nerve.[2] Truant and Takman have presented kinetic plots for blockade of the monophasic A spike of the frog sciatic nerve with procaine, lidocaine, and tetracaine.[3] From these data one can determine the relative potencies of these three agents (procaine = 1, lidocaine = 4, tetracaine = 25), the relative times to onset of nerve blockade (procaine = lidocaine > tetracaine) and the relative durations of action (tetracaine > lidocaine > procaine) (table 1). Similar studies have been conducted with two relatively new local anesthetics, prilocaine and bupivacaine. At equipotent concentrations, prilocaine (20 mM) has an onset time of four minutes and a recovery time of 20 minutes, whereas bupivacaine (5 mM) has an onset time of five minutes and a recovery time of 100 minutes.

In-vivo studies of animals also can provide useful information. Intradermal wheals and sciatic nerve blocks in rats have been employed for many years to evaluate local anesthetic activity of new compounds.[4] Recently, techniques for producing peridural anesthesia in cats have been developed.[5] With these techniques one can compare the frequency of attainment of anesthesia, as well as the times to onset and durations of anesthesia with various agents. In addition, degrees of potential local neural toxicity and systemic toxicity can be evaluated. Table 2 shows relative potencies and durations of anesthesia of various agents *in vivo* in the rat sciatic-nerve preparation and the cat peridural preparation. As can be seen from tables 1 and 2, there is reasonable correlation between data obtained *in*

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vitro and *in vivo* for both potency and duration of anesthesia.

Local anesthetic agents differ from most other drugs in that they are usually applied to the specific areas where they are to exert their primary pharmacologic actions. However, these agents also are absorbed systemically and can affect target organs other than peripheral nerves. The cardiovascular and central nervous systems are particularly susceptible to the actions of local anesthetics, since these drugs tend to exert a generalized effect on all excitable membranes. In this regard, the cardiovascular effects of lidocaine have been well studied, in part owing to the current use of lidocaine as an antiarrhythmic agent.[6, 7, 8]

Since the cardiovascular actions of most local anesthetic agents are similar, lidocaine's properties are representative of the cardiovascular pharmacology of this class of agents. At blood levels (0–5 μg-ml) achieved with normal doses (*e.g.*, 300 mg administered epidurally), changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood levels (5–10 μg/ml) depress cardiac conduction and excitability, which may lead to atrioventricular block and ultimately to cardiac arrest. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and blood pressure.

The activity of the central nervous system can be altered by local anesthetics. As in the cardiovascular system, CNS effects at nontoxic blood levels are minimal. At toxic blood levels marked CNS effects are observed. The initial change is depression of inhibitory neurons, which is probably responsible for the increase in CNS irritability and convulsions seen with toxic doses of local anesthetics.[9] A further increase in blood levels results in general depression of the central nervous system, leading ultimately to respiratory arrest.

With gas chromatography, autoradiography, and other analytical techniques it is now possible to measure in a very sensitive way the blood and tissue levels of most local anesthetics. For example, a study of the absorption, distribution, and metabolism of lidocaine and prilocaine has revealed that lidocaine is the more rapidly absorbed from highly vascular areas.[10] In addition, tissue distribution patterns are similar for the two agents, with the possible exceptions of lung and brain, where greater amounts of prilocaine were found. Prilocaine also appears to be more rapidly metabolized by liver slices. Such studies are important since they may explain the lower blood level and shorter half-life of prilocaine in human blood as compared with lidocaine. Autoradiographic studies of mice following the intravenous and subcutaneous administration of mepivacaine revealed that the drug accumulated rapidly in the liver, kidneys, salivary glands, and brain.[11] Thus, absorption, distribution, metabolism, and excretion should be investigated during the preclinical pharmacologic evaluation of any new local anesthetic.

The potential toxicity of a new compound should be thoroughly evaluated prior to the start of human pharmacologic investigations. Guidelines for toxicologic studies for various classes of drugs, including local anesthetics, have been defined.[12]

TABLE 1. *In-vitro* Analgesic Properties of Local Anesthetics in the Isolated Frog Sciatic-nerve Preparation

	Concentration (mM)	Relative Potency	Onset* Time (Min)	Duration† (Min)
Procaine	20	1	4	16
Lidocaine	5	4	4	16
Tetracaine	0.8	25	9	130

* Time required to produce a 50 per cent reduction in amplitude of monophasic A spike potential.

† Time for monophasic A spike potential to return to control amplitude following replacement of local anesthetic solution with Ringer's solution.

Clinical Pharmacology

Initial Determination of Local Anesthetic Activity and Potential Tissue Irritation

Initial studies in man of a potential new local anesthetic are usually directed at a simple evaluation of localized sensory analgesia. This can be accomplished by means of intradermal wheals.[13, 14] Since the dosage is small,

TABLE 2. Relative Potencies and Analgesic Durations of Local Anesthetics Determined *in vivo* by Rat Sciatic-nerve Block and Cat Peridural Block Techniques

	Concentration (Per Cent)	Relative Potency	Average Analgesic Duration ± SE (Min)	
			Rat Sciatic Block	Cat Peridural Block
Lidocaine	2	1	125 ± 8	115 ± 7
Mepivacaine	2	1	156 ± 22	—
Prilocaine	2	1	123 ± 6	131 ± 2
Tetracaine	0.5	4	245 ± 39	227 ± 5
Bupivacaine	0.5	4	212 ± 34	248 ± 12

minimal hazards from systemic toxicity are anticipated. To assure that the maximum amount of information is obtained in any studies of man, they should be conducted under carefully controlled conditions. Comparison with a standard local anesthetic agent should be made, and a standard technique, *e.g.*, pin prick, should be used to determine the frequency with which anesthesia is attained, time to onset, and duration of sensory anesthesia. In addition, the site of injection should be examined for swelling, inflammation, and necrosis, as signs of possible local irritation. Results obtained with various agents utilizing the intradermal wheal technique are summarized in table 3.

Upon determination that a compound can produce adequate sensory analgesia without local irritation, limited peripheral-nerve block studies should be initiated. Albért and Löfström have described a method for evaluating the local anesthetic properties of new agents with a standard ulnar-nerve block technique.[15] Sensory analgesia was evaluated by a pinch test and motor block was assessed by finger motility. By means of this technique, the times to onset and durations of sensory and motor anesthesia for a number of local anesthetics have been determined. The results of Albért and Löfström indicate that lidocaine and mepivacaine have similar times to onset of sensory analgesia, whereas procaine has a significantly slower onset. In addition, mepivacaine has a longer duration of anesthetic action than lidocaine which, in turn, produced significantly longer-lasting analgesia than procaine. A measure of relative potencies also could be obtained by such a technique, since at concentrations of 0.5 and 1 per cent the incidence of incomplete blocks was significantly greater with procaine than with lidocaine and mepivacaine.

With regard to newer agents, prilocaine was compared with lidocaine. The times to onset of anesthesia were similar, but 1 per cent prilocaine without epinephrine produced significantly longer-lasting anesthesia (98 ± 13 min) than did 1 per cent lidocaine without epinephrine (35 ± 14 min).[16] Subsequent evaluation of mepicavaine, tetracaine, and bupivacaine showed that these three agents have similar times to onset of action. However, the action of 0.25 per cent bupivacaine (415 ± 23 min) lasted significantly longer than that of 1 per cent mepivacaine (211 ± 18 min) or 0.25 per cent tetracaine (135 ± 18 min). All solutions tested contained 1: 200,000 epinephrine.[17]

Intercostal nerve block is also an excellent method for studying sensory analgesic properties. Bilateral injections can be made, permitting simultaneous comparison of the properties of a new and a standard agent in the same subject. Moore *et al.* have used this technique to compare the anesthetic properties of lidocaine, mepivacaine, tetracaine, and bupivacaine.[18] At equipotent concentrations, times to onset ranged from a low of 3.6 ± 0.7 minutes for lidocaine to a high of 6.2 ± 2.3 minutes for bupivacaine, whereas durations of anesthesia ranged from a high of 623 ± 106 minutes for bupivacaine to a low of 157 ± 44 minutes for lidocaine. Results obtained by the ulnar-nerve block and intercostal-nerve block techniques are presented in table 4. Results of the two techniques are similar with regard to the analgesic durations produced by the various agents. The one difference concerns

tetracaine, which had a considerably shorter duration of analgesia in the ulnar-nerve block studies than in the intercostal-nerve block studies.

To obtain more objective methods for assessing pain and other indices of anesthetic effect, electrical stimulation has been used, particularly in the evaluation of topical local anesthetic preparations and local anesthetic agents intended for use in dentistry. Adriani *et al.* have evaluated the potencies of a number of topical anesthetics by electrical stimulation of the tip of the tongue.[19] Giddon and associates studied several topical formulations of lidocaine by means of electrical stimulation of the gingiva.[20] The most precise measurements of injected anesthetic agents have been carried out by Bjorn, using electrical stimulation of the dental pulp.[21, 22] By this method the frequency of attaining anesthesia, time to onset, duration, and spread of anesthesia produced by various local anesthetics have been evaluated and described.[22]

In addition to providing information about potencies *in vivo* of local anesthetics and defining their pharmacologic properties, these standardized techniques provide valuable information on the advisability of combining a vasoconstrictor agent with a local anesthetic. For example, Albért and Löfström [23] found that addition of 1:200,000 epinephrine to 1 percent lidocaine increased the duration of anesthetic action from 35 ± 14 minutes to 190 ± 14 minutes. On the other hand, addition of 1:200,000 epinephrine to 1 per cent prilocaine and 1 per cent mepivacaine prolonged anesthetic durations from 98 ± 13 minutes to 186 ± 11 minutes and from 111 ± 15 minutes to 211 ± 18 minutes, respectively. Thus, lidocaine benefits more from addition of a vasoconstrictor drug than do prilocaine and mepivacaine. This finding suggests that lidocaine possesses a greater vasodilating action than prilocaine or mepivacaine, or that the latter agents have stronger antiepinephrine effects.

Human Tolerance Studies

The early stages of the clinical pharmacologic evaluation should include tolerance studies in volunteers. These studies are best done by administering the drug intravenously and concomitantly measuring blood levels. Subjects of these studies should be observed carefully, and objective measurements should be made of CNS and cardiovascular function (*e.g.*, electroencephalography, electrocardiography, cardiac output) and clinical chemistries (*e.g.*, CBC, BUN, SGOT, alkaline phosphatase, bilirubin) to detect changes in organ function. Such studies should be of a dose–response type and should attempt to establish the relationship between dose administered, blood levels obtained, and changes in CNS, cardiovascular, or other organ functions. Various types of tolerance studies with local anesthetic agents have been conducted.[24, 25] In general, these studies indicate good correlation between rate of tissue distribution, rate of chemical degradation, and systemic toxicity. Thus, Foldes *et al.* have shown that local anesthetics of the ester type, which are hydrolyzed in blood, tend to be less toxic than the agents of the amide type, which are nonhydrolyzable and depend on enzyme systems

Table 3. Analgesic Durations of Local Anesthetics Determined by the Intradermal Wheal Technique in Man

	Concentration (Per cent)	Average Analgesic Duration (Min)	
		Study 1[13]	Study 2[14]
Procaine	0.5	—	20(15–30)
Lidocaine	0.5–2.0	108.5±13.7	75(30–340)
Mepivacaine	0.5	—	108(15–240)
Prilocaine	2.0	100.8±20.6	—
Bupivacaine	0.5	252.8±34.3	—

Table 4. Durations of Analgesia with Local Anesthetics Determined by Standard Ulnar-nerve Block and Intercostal-nerve Block Techniques*

	Concentration (Per cent)	Average Analgesic Duration ± SE (Min)	
		Ulnar-nerve Block[16,17]	Intercostal-nerve Block[18]
Lidocaine	1	190 ± 14	157 ± 44
Mepivacaine	1	211 ± 18	196 ± 50
Tetracaine	0.25	135 ± 18	429 ± 93
Bupivacaine	0.25	415 ± 23	623 ± 106

* All solutions contained epinephrine, 1:200,000.

in the liver for metabolism.[24] Furthermore, those ester-type agents which undergo rapid hydrolysis tend to be less toxic than the more slowly hydrolyzed agents. A similar study comparing prilocaine with lidocaine demonstrated that prilocaine, which disappears from blood more rapidly and is metabolized more rapidly, is less toxic to the CNS and cardiovascular systems. A comparative study of the tolerances to intravenous administration of mepivacaine and bupivacaine, the newest local agent available at this time, was conducted by Jorfeldt and colleagues.[26] At equipotent doses there was no difference between the systemic toxicities of mepivacaine and bupivacaine, and their rates of disappearance from blood were similar.

Drug Disposition

As with most drugs, the clinical efficacy and potential toxicity of local anesthetic agents are affected by such factors as systemic absorption from the site of injection, distribution, metabolism, and excretion. Gas chromatography has made possible the sensitive measurement of concentrations of local anesthetics in blood and tissues. A number of human studies in which blood levels of local anesthetics have been measured have been reported recently. These studies show that absorption of local anesthetics varies both as a function of the site of injection and according to the pharmacologic vascular properties of the agent. Braid and Scott have presented detailed information about factors influencing the systemic absorption of local analgesic agents.[27] Their results indicate that rate of absorption is mainly a function of:

1) Pharmacologic characteristics of the drug. Thus, the rate of absorption of lidocaine was significantly greater than that of prilocaine, the difference being attributed to the greater vasodilator property of lidocaine.

2) The site of injection. Absorption occurred more rapidly and to a greater extent following intercostal regional block than following peridural block. A similar study with bupivacaine revealed more rapid rates of systemic absorption following axillary plexus blocks as compared with peridural blocks.[28]

3) Presence of a vasoconstrictor drug. The rate of systemic absorption of lidocaine decreased significantly when epinephrine was added to the anesthetic solution.

These findings have practical anesthetic implications, since slower vascular absorption should allow more of the local anesthetic to be available for diffusion to the nerve, usually resulting in a greater incidence of attaining nerve block, more profound block, and longer-lasting anesthesia. In addition, slower absorption and a lower peak blood level of the anesthetic should decrease its potential systemic toxicity. However, when absorption is retarded by a vasoconstrictor agent, the potential toxicity of the vasoconstrictor agent itself must be considered.

The tissue distribution of a local anesthetic is important, since it may influence systemic toxicity. Several studies have compared the plasma/erythrocyte distributions of local anesthetics. Lidocaine had a greater plasma/erythrocyte ratio (1.34) than prilocaine (0.88).[25] When the plasma/erythrocyte ratios of lidocaine (2.1), mepivacaine (2.6), and bupivacaine (7.8) were compared,[29] the degree of plasma-protein binding apparently was correlated with the plasma/erythrocyte ratio. Thus, bupivacaine, which had the greatest capacity for plasma-protein binding, also had the highest plasma/erythrocyte ratio. The peripheral arteriovenous differences for several local anesthetics also have been determined.[25] Simultaneous measurements of samples from the brachial artery and the antecubital vein show significant arteriovenous differences for lidocaine and prilocaine. The venous–arterial blood concentration ratios were 0.73 ± 0.03 for lidocaine and 0.47 ± 0.03 for prilocaine. Thus, the rate of diffusion into muscle appears to be considerably faster for prilocaine than for lidocaine, which again would account, in part, for the lower blood levels of prilocaine. Recently, a detailed clinical evaluation of bupivacaine was presented by Moore and colleagues.[30] In this study peak arterial levels of bupivacaine were 20–40 per cent higher than simultaneous venous levels.

Most of the agents used clinically, *e.g.*, lidocaine, mepivacaine, prilocaine, and bupivacaine, are amides. Studies in animals have

TABLE 5. Placental Transmission of Local Anesthetics

	Route of Administration	Number of Patients	Maternal Arterial or Venous Blood Levels (μg/ml)	Umbilical Vein Levels (μg/ml)	UV/M Ratio	Reference
Bupivacaine	Epidural	12	0.26 (0.12–0.41)	0.11 (0.04–0.25)	0.44 (0.14–0.86)	37
	Epidural	23	0.26 (0.10–0.76)	0.08 (0.02–0.25)	0.31 (0.10–0.67)	38
Lidocaine	Epidural	6	1.81 (0.25–3.46)	1.00 (0.25–3.46)	0.57 (0.42–0.70)	37
	Epidural	13	2.82 (1.1–4.7)	1.43 (0.6–2.2)	0.56 (0.25–1.00)	39
	Intravenous	9	2.8 ± 1.1	1.6 ± 0.94	0.55 (0.26–0.97)	40
	Epidural	7	2.2 (0.2–5.3)	0.9 (0.2–1.6)		
	Epidural	27	2.7 (0.2–5.5)	1.3 (0.4–3.4)	Average 0.52	41
	Paracervical	23	3.5 (0.7–6.0)	1.3 (0.2–3.4)	± 0.23	
	Epidural	19	1.39 ± 0.51	0.83 ± 0.35	0.60 ± 0.14	42
	Epidural	27	1.23 ± 0.09	0.8 ± 0.06	0.67	43
	Epidural	46	2.6 ± 1.3	1.8 ± 0.9	0.69	44
Mepivacaine	Epidural	5	6.9 (3.9–8.6)	4.9 (2.5–7.9)	0.69 (0.49–0.92)	45
	Epidural	56	2.91 ± 0.28	1.9 ± 0.16	0.71 ± 0.04	46
Prilocaine	Epidural	43	1.1 (0.0–2.7)	1.3 (0.4–3.5)	1.18	47
	Epidural	35	1.03 ± 0.07	1.07 ± 0.14	1.03	43
	Epidural	40	1.5 ± 1.0	1.5 ± 0.8	1.00	44

revealed the liver to be the prime site of metabolism for this amide-type anesthetics. Recent studies in man also indicate that the liver is the main site of metabolism. Harrison *et al.* measured the arterial–hepatic-vein levels of lidocaine; from these values and the estimated hepatic blood flow, they calculated that 70 ± 16 per cent of injected lidocaine is metabolized in the liver.[31] In addition, the rate of disappearance of lidocaine from blood decreased when this agent was administered to patients whose livers had been removed during the course of liver transplantation. This would be supportive evidence for the liver as a prime site of metabolism.[32] It is important to identify the main site of metabolism, since a patient with severe hepatic disease will be more sensitive to the systemic toxicity of an agent detoxified primarily in the liver, as are the amide-type local anesthetics. The precise metabolism in man of amide-type local analgesic agents remains unclear. The metabolic pathways of lidocaine and mepivacaine in several animal species have been described.[33, 34] However, confirmatory studies in man are lacking.

The urinary excretion of local analgesic agents by man has been studied in recent years. Beckett *et al.* found less than 1 per cent unchanged lidocaine in the urine of patients within 24 hours after an intravenous injection.[35] Studies of the renal clearances of lidocaine and prilocaine in man revealed that the clearances of these agents were inversely proportional to the *p*H of urine, which suggested that urinary excretion occurred by nonionic diffusion.[36]

Some mention should be made of a specialized category of drug disposition, namely, distribution across the placenta in pregnant women. Much information about maternal–fetal blood levels of local anesthetics has been made available in recent years (table 5). The values for the umbilical vein/maternal blood level ratios (UV/M) of anesthetics reported by various investigators have been remarkably similar. For example, in six separate studies the lidocaine UV/M ratios ranged from 0.52 to 0.69. In four of these studies, mean values ranged only from 0.52 to 0.57.

It is generally accepted that local anesthetic agents cross the placenta by passive diffusion. However, the rate and degree of diffusion vary significantly among agents. Thus, bupivacaine has the lowest UV/M ratio (0.31–0.44); prilocaine has the highest (1.00–1.18). The UV/M ratios of lidocaine and mepivacaine are similar, occupying intermediate positions

TABLE 6. Comparative Evaluation of Agents Used for Peridural Anesthesia*

	Concentration (Per Cent)	Average Onset Time (Min) (Mean ± SD or SE)	Average Analgesic Duration (Mean ± SD or SE)	Reference
Lidocaine	2	5.5 ± 1.2	97 ± 19.2	54
	2	5.07 ± 0.58	156.6 ± 0.58	55
Prilocaine	2	7.3 ± 1.5	97 ± 10.5	54
	2	6.5 ± 0.8	135 ± 5	56
Mepivacaine	2	6.5 ± 0.5	149 ± 9	56
Tetracaine	0.25	14.5 ± 0.65	334 ± 15.1	57
	0.5	6.6	145.7 ± 22.4	58
Bupivacaine	0.5	5.8	196 ± 31.3	58
	0.5	8.1 ± 0.8	208 ± 22	56
	0.5	6.27 ± 1.19	228 ± 23	55
	0.5	10.8 ± 0.65	423 ± 15.1	57

* All solutions contained epinephrine, 1:200,000.

(0.52–0.71). Numerous factors probably influence placental diffusion. The data in table 5 indicate that the UV/M ratio is not affected by route of administration or maternal blood level. Thus, for example, the UV/M ratios of mepivacaine in two separate investigations were similar (0.69 and 0.71), whereas maternal blood levels showed a twofold difference (2.9 and 6.9 μg/ml). An inverse correlation between the protein-binding capacities of the agents and their UV/M ratios does exist. Of the agents in table 5, bupivacaine had the highest protein-binding capacity (84 per cent) and the lowest UV/M ratio (0.31–0.44); prilocaine has the lowest protein-binding capacity and highest UV/M ratio (1.00–1.18). Again, values for protein-binding and UV/M ratios of lidocaine and mepivacaine are intermediate. Thus, the protein-binding capacity of a local anesthetic may be one of the main factors in the regulation of its diffusion across the placenta.

Drug Interactions

The interactions of various drugs used concomitantly are a major concern in medicine. Unfortunately, little information about the interrelationships between anesthetics and other classes of drugs in man is available at present. Studies to determine the possible interactions of local anesthetics and other classes of drugs have been conducted in animals. These studies have revealed:

1) Neuromuscular blockade is enhanced by some local anesthetics.[48] For example, apnea produced by succinylcholine can be significantly prolonged by lidocaine.[49]

2) In dogs, iproniazid, isoniazid and chloramphenicol can prolong the toxic symptoms of local anesthetics, whereas phenobarbital can reduce their cumulative toxicity.[50]

3) Promethazine and meperidine may enhance the potential convulsive action of local anesthetics.[51]

Thus, local anesthetics interact with other classes of drugs. In addition, since the local anesthetics most commonly used are metabolized primarily in the liver, drugs which are enzyme inducers may influence the rate of metabolism, and subsequently the pharmacologic and toxicologic properties of amide-type local anesthetics.

Clinical Efficacy

Acceptance of a local anesthetic into clinical practice depends ultimately on the characteristics of the agent when used in routine clinical procedures. Peridural administration of local anesthetics probably affords the most critical appraisal of a new compound under practical clinical conditions, since it is possible to determine carefully the time to onset, duration, and

spread of sensory and motor anesthesia, as well as other factors such as degree of abdominal muscle relaxation.

Bromage *et al.* have described a comprehensive method for evaluating the analgesic profile of a local anesthetic following peridural administration.[52] In addition, Bromage has reviewed the physiology and pharmacology of peridural analgesia.[52] Factors such as age and physical status of the patient exert considerable influence on the pharmacologic action of a drug injected peridurally. Thus, it is important that any study using this technique to evaluate the analgesic profile of an agent be well designed and carefully controlled.

Local anesthetics have been evaluated following peridural administration in many studies (table 6). Although there are obvious differences among these studies with regard to the absolute values of times of onset and durations of analgesia, these probably are attributable to differences in techniques for evaluating the end-points for anesthetic onset and disappearance. However, these studies do establish certain differences among the agents evaluated. Thus, it would appear that the currently used local anesthetics can be separated into two groups based on duration of analgesia. Lidocaine, mepivacaine, and prilocaine have analgesic effects of moderate duration; tetracaine and bupivacaine can be classified together as long-acting agents.

Summary

In recent years a number of well designed studies have elucidated the anesthetic and pharmacologic properties of various local analgesic agents. Thus, such variables as frequency of attainment of anesthesia, time to onset, and duration of sensory and motor anesthesia have been evaluated for some of the standard agents, *e.g.*, lidocaine and mepivacaine, as well as for several of the newer local anesthetics, such as prilocaine and bupivacaine. In addition, elaborate human tolerance studies including electroencephalographic recordings and hemodynamic measurements have delineated the potential systemic toxicities of local anesthetics. Furthermore, with the advent of specific and sensitive analytical methodology, *e.g.*, gas chromatography, precise determinations of the blood levels of various agents have been made and these levels correlated with toxicologic effects.

The ability to measure tissue levels of local anesthetics accurately has made possible a variety of clinical pharmacologic investigations. Thus, rates of absorption from various sites of administration, protein-binding capacities, rates of disappearance from blood, patterns of tissue distribution, sites and rates of metabolism, and excretory processes of many local anesthetics are now known.

Certain interesting correlations emerge from this wealth of data. For example, a consideration of intrinsic potency, diffusion characteristics, protein-binding capacity, and duration of analgesia indicates that agents with high protein-binding capacities tend to possess greater intrinsic potency and produce longer-lasting analgesia, but diffuse more slowly to the receptor sites, as indicated by longer times to onset of anesthetic action (table 7). On

TABLE 7. Relative Potencies, Protein-binding Capacities, Anesthetic Onset Times, and Analgesic Durations of Local Anesthetics

	Relative Potency*	Protein Binding† (Per Cent)	Average Onset Time‡ (Min)	Average Analgesic Duration‡ (Min)
Lidocaine	1	52	5.0–5.5	97–156
Mepivacaine	1	65	6.5	149
Prilocaine	1	—	6.5–7.3	97–135
Tetracaine	4	—	6.6–14.5	145–334
Bupivacaine	4	84	5.8–10.8	196–423

* Relative potencies as determined from studies of isolated frog sciatic nerve.
† Protein-binding data derived from Tucker *et al.*[29]
‡ Average onset times and analgesic durations were derived from data on peridural anesthesia in man in table 6.

the basis of these observations, modern local anesthetics can be classified as either: A) agents of rapid onset, moderate potency, and moderate duration, *e.g.*, lidocaine, mepivacaine, prilocaine; or B) agents of moderate time to onset, high potency, and long duration, *e.g.*, tetracaine, bupivacaine.

With the present scientific techniques it should be possible to elucidate the anesthetic, pharmacodynamic, and pharmacokinetic properties of any future local anesthetics, to provide a more scientific basis for their introduction into clinical practice.

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