DURATION OF LOCAL ANESTHESIA[1]

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In regard to duration of action local anesthetics have been classified into three groups—short-acting: procaine, parethoxycaine (Intracaine), piperocaine (Metycaine), and butethamine (Monocaine); intermediate: lidocaine (Xylocaine) and hexylcaine (Cyclaine); long-acting: tetracaine (Pontocaine) and dibucaine (Nupercaine) [Pitkin (1)]. Newer local anesthetics could be added to one or another of these groups with borderline cases more difficult to classify. This is an empirical classification based on a concept of duration of action which is deceptively simple—at effective clinical doses the duration of anesthesia produced by members of the first group (procaine, intracaine, etc.) is considerably shorter than that following the injection of tetracaine and dibucaine (third group). However, for each local anesthetic the doses used clinically have been arrived at by an empirical process of selection in which potency, systemic toxicity, irritancy, time of onset, and even duration of action have been considered. The separation between short- and long-acting compounds is somewhat more difficult in experimental local anesthetic studies and requires the determination of other parameters. The duration of experimental anesthesia increases with the dose, and there are several publications showing a linear relationship between duration in minutes and the logarithm of the concentration (or dose). Since in experimental anesthesia the effective range covers a few to 100 or more minutes, it is possible to find doses of short-acting compounds (procaine, for example) which produce anesthesia of longer duration than that following the injection of a small dose of a long-acting compound like dibucaine. Even if solutions of the same concentration are compared, the results may be misleading if the shorter-acting compound is considerably more potent than the other. It is obvious that comparative duration tests should be carried out with equiactive solutions or doses.

The local anesthetic activity or potency of a compound could be expressed by the reciprocal of its threshold or minimal anesthetic concentration (TAC). The TAC would vary for each type of nerve fiber; in general the TAC would be positively correlated with fiber diameter (2–5). The TAC can be determined on isolated nerve fibers, with an approximation which depends mainly on the concentration intervals of the solutions tested. When a frog's isolated sciatic nerve fiber was blocked by a threshold or slightly higher concentration of cocaine, onset (after drug addition) and

[1] The survey of literature pertaining to this review was concluded in July 1968.

recovery time (after washing) were extremely short—less than a second (6, 7).

It must be assumed that for each nerve fiber *in vivo* blockade by local anesthetics is an all-or-none phenomenon as it is for the fiber *in vitro*. Therefore, for each fiber, no greater blockade can be produced by higher supra-threshold concentrations.

The method for determination of the TAC in isolated mammalian nerve fibers is not practical, but approximations can be obtained by selecting as TAC one of the lowest points in the dose-effect curve obtained by one of several standard tests [intradermal wheal test in guinea pigs (8, 9), sciatic nerve block (10, 11), spinal anesthesia in rabbits (12, 13)].

If activity is the reciprocal of the TAC, the concentration of equipotent solutions would be the same number of times higher than the TAC. The TAC (or a closely related value like the TAC_5) for the known local anesthetics is low. For intradermal anesthesia in guinea pigs the values of the TAC_5 found for procaine and tetracaine were, in terms of the bases, 0.21 and 0.018 per cent, respectively (9).

The concentration of solutions used in the clinic or in duration experiments is considerably higher than the TAC_5.The anesthetic diffuses out of the site of injection or application following concentration gradients. As it spreads, its concentration gradually decreases. Nerve fibers are reached and then blocked when the concentration becomes higher than the TAC (onset). While they remain blocked the solution keeps spreading and the anesthetic concentration continues to decline as a result of this process and to systemic absorption through the blood which bathes the treated area. The duration time is the span between the onset and the point at which the concentration reaches a value below the TAC. It is logical then to assume that if the per cent rate of decline in concentration is the same for two drugs given in equiactive concentrations, their duration of action would be the same. This is the rationale for the use of equiactive concentrations in duration tests which indirectly measure the rate of decline of the concentration at the site of action.

Methods

Any of the various methods devised to measure local anesthesia could be used to determine duration of action. Relatively high equiactive concentrations are required (5 to 20 times the TAC_5); a standard local anesthetic like procaine, mepivacaine, lidocaine, or tetracaine is tested in parallel for comparison, since the object is to determine relative, rather than absolute, duration of action. The standard methods for intradermal (guinea pigs), sciatic nerve block (guinea pigs), or spinal (rabbits) anesthesia may be used.

The results obtained by the corneal anesthetic method are not necessarily applicable to topical anesthesia in other areas or to intradermal or spinal anesthesia. The rate of penetration into the cornea from the applied

aqueous phase determines the amount of anesthetic deposited on the cornea. However, rate of penetration and rate of diffusion may not have the same relationship for all compounds. A modification of Bülbring & Wajda's intradermal test (8, 14) is one of the most practical for measuring relative duration of action. Since two wheals are raised on the backs of guinea pigs, this method permits the parallel testing of an experimental and a control solution (14, 15). In these tests interstitial circulation in the treated areas influences the duration of anesthesia. Tissue clearance of local anesthetics would be equivalent to systemic absorption.

In vitro tests have also been carried out where the recovery time of nerve trunks has been determined after the bathing local anesthetic solution had been replaced by a control saline solution (16–19).

Relationship Between Duration of Anesthesia and Concentration and Volume of the Local Anesthetic Solution

Concentration.—It is well known that the duration of anesthesia increases with the concentration. However, there is no agreement on the exact relationship between these two variables. From the results obtained by Braun (20), Uhlmann (21), and others, Miescher (22) concluded that there was a linear relationship between the logarithm of the duration and the logarithm of the concentration. However, Uhlmann's results, obtained by testing each concentration on two or three rabbits (topical corneal anesthesia), showed that the increase in the increment obtained by doubling the concentration occurred only with the high doses. In the experiments reported by Braun, acoin was injected intradermally in man; in addition to the local anesthetic effect he reported that acoin also produced pain on injection, and intense irritation at high doses. Gradually increasing irritation may have been responsible for the gradual increase in the slope of the duration-log concentration curve.

Most of the published results agree that the duration of anesthesia is related linearly to the logarithm of the concentration (13, 23–25). In the case of spinal anesthesia in rabbits (13), each doubling of the concentration of lidocaine and dibucaine resulted in an approximate average increase of 6 and 58 min, respectively.

The slope of the duration-log concentration curve could be expressed by the increase in minutes produced by each doubling of the concentration. Since for each drug the increase is approximately the same, it is not accurate to state that "doubling the concentration increases the duration by approximately 30 per cent" as was stated in an excellent review on nerve block (26). Obviously the per cent increase in duration would be gradually reduced with each doubling of the concentration.

The linear relationship between duration and the logarithm of the concentration has been established by various experimental tests [rabbit cornea (23, 24, 27), sciatic nerve block (28, 29), spinal anesthesia in rabbits (13, 30), and corneal anesthesia after subconjunctival injection (23)].

When a vasoconstrictor is present in the solution the relationship between duration of action and concentration of local anesthetic is not clear. Sinha (31) found an approximate linear relationship between these two parameters) when he tested cocaine in the presence of epinephrine by intradermal injection in guinea pigs. The slope of the regression line was higher than that obtained with the same concentrations of cocaine alone. No conclusions can be drawn from this result because the vasoconstrictor potency of the solution would be gradually enhanced by the potentiating effect of increasing concentrations of cocaine. In experiments in this laboratory (15) little or no difference in duration of action was found between five solutions of propoxycaine HCl (Ravocaine HCl) 0.125, 0.25, 0.5, 1, and 2 per cent) containing epinephrine 1:100,000 and between five solutions of procaine MCl (0.25, 0.5, 1, 2, and 4 per cent) with epinephrine 1:100,000. Perhaps lower concentrations of the local anesthetics in the presence of epinephrine would have shown an increase in duration positively correlated to the anesthetic strength of the solution. In mixtures of local anesthetics and vasoconstrictors the latter in the concentrations used in the clinic make a greater contribution to the duration of anesthesia than the local anesthetic. When the concentration of the local anesthetic remains constant the duration of intradermal anesthesia in guinea pigs is linearly related to the log of the concentration of the vasoconstrictor (15). The information on the duration of nerve block and spinal anesthesia in man does not permit, to my knowledge, drawing conclusions as to the relationship between duration and concentration. Considerably larger volumes than in experimental anesthesia are injected, the diameter of the nerves involved is larger, and the number of concentrations graded at 0.3 log intervals, between the minimal effective and the tolerated concentrations, is limited. If, as in experimental anesthesia, there is an approximate linear relationship between duration and log of the concentration, it would be unlikely to obtain nerve block or spinal anesthesia lasting many hours with nonirritant concentrations in solutions without vasoconstrictors. The foregoing justifies the conclusion [Sinha (31)] that "the most economical method of producing local anesthesia for a long period is to give repeated injections of drug."

Volume.—In the studies cited above, the volume of the local anesthetic solution remained constant. The relationship between the volume of the solution and the duration of anesthesia is not so well known. Using the intradermal wheal in man, Sinha (31) demonstrated that if the concentration remained constant and the volume increased, there was a parallel increase in duration of action. However, if the amount of anesthetic remained constant and the volume increased, the decrease in concentration was accompanied by a gradual reduction in duration (31).

Causes of differences in duration of anesthesia.—The use of the aforementioned methods reveals differences between compounds; significant differences in the slopes of their duration-log concentration (or dose) curves occur. The cause or causes producing these differences are unknown.

However, duration can be associated with certain properties of compounds and this has permitted a tentative classification into three main groups. This classification will be discussed below.

Any drug injected subcutaneously, intradermally, or intrathecally will be absorbed systemically. Tissue clearance of a number of substances has been studied. In studying nerve recovery time we have a similar situation with the difference that with local anesthetics we measure only the time an all-or-none nerve fiber block takes to disappear.

Greater or lesser affinity for the nerve membrane has been related to greater or lesser duration of action (26). This does not seem likely in view of the rapid disappearance of the effect of cocaine on isolated nerve fibers (6) and the difference in this respect between intact and desheathed nerves (26, 32). It seems more logical to assume that local anesthetics, like other lipid soluble drugs, are adsorbed nonspecifically to membranes (cellular and intracellular) and are also bound to proteins in the tissue fluids. During the recovery time most of the drug is carried away by the paracapillary circulation into the blood stream (33). Only a small proportion is lost through the lymphatics.

After injection or topical application, the concentration of the local anesthetic decreases because of systemic absorption and spreading to adjacent areas. If the circulation is reduced or stopped the spreading increases, and this process can be used to measure indirectly the effect of systemic absoption (34) with normal circulation. Spreading facilitates systemic absorption by exposing a larger capillary surface as a channel for systemic absorption of the local anesthetic.

Recently, evidence has been presented which suggests strongly that the ion is the active form of the local anesthetic (35). However, local anesthetic activity as measured in conventional ways indicates that within certain limits the activity increases with length of a carbon chain in homologous series. It is therefore likely that local anesthetics pass a lipid barrier before reaching the site of action. During the period of recovery the passive transport through this barrier is reversed.

Literature data and results obtained in this laboratory suggest that the duration of local anesthesia is associated with one or more of the following three properties, suggesting three different mechanisms: (*a*) molecular "amphypathy"; (*b*) self-depression of absorption due to irritancy; (*c*) self-depression of absorption not due to irritancy.

Molecular "amphypathy".—"Amphypathy" is a name coined by Hartley (36) to describe "the occurrence in a single molecule or ion, with a suitable degree of separation, of one or more groups which have an affinity ("sympathy") for the phase in which the molecule or ion is dissolved, together with one or more groups which are antipathetic to the medium (i.e., which tend to be expelled by it). It is convenient to refer to these two groups as "lyophilic" and "lyophobic", respectively, (or "hydrophilic" and "hydrophobic" if the solvent is water)" (37).

Local anesthetics possess hydrophilic and hydrophobic groups. In homologous series with the increase in size of the hydrophobic portion of the molecule, local anesthetic activity, systemic toxicity, irritancy, surface activity, and oil/water partition coefficient increase. The duration of action of the members of a homologous series, tested at anesthetic equiactive, sub-irritant concentrations, also increases.

In a study on cat sciatic nerves, compounds which were not homologues were investigated, which permitted a comparison of various parameters, including duration of action (18). The results are summarized in Table I. Each solution was tested on eight nerves. If we consider only the greatest differences in duration, the increment in duration parallels the increment in irritancy. It must be kept in mind that the concentrations used were well below the threshold irritant concentration as determined by the trypan blue test; therefore, these differences were not due to tissue irritation. Irritancy in local anesthetics, and possibly in other basic organic compounds, is directly correlated with surface activity (38), a property dependent on the "amphypathy" of the compounds. Among the biological properties which increase with length of carbon-chain in homologous series, only irritancy appears to be consistently correlated with duration of action; toxicity is positively correlated with local anesthetic activity, not with irritancy (39). In the series of diethylaminoethoxy-5-Br-anilines (40) and the 2-alkoxy analogues of procaine and thiocaine (9, 13), the increase in local anesthetic activity continued up to the *n*-hexoxy compound (higher homologues were not tested). The duration of anesthesia, as determined by the slope of the duration-log concentration curve, increased in the same manner (9, 13, 40). However, Miescher (41) reported that the duration of topical anesthesia on the rabbit's cornea produced by members of a dibucaine series increased up to the 2-*n*-butoxy analogue and then decreased. Surface activity increased up to the heptyloxy or octyloxy homologues (41). Uhlman (21), who also found maximal anesthetic potency with the *n*-butoxy homologues as Buchi & Perlia found in other series (42), used the same concentration (0.1 per cent) in all cases in his duration tests and therefore the *n*-butoxy homologue solution had the maximal anesthetic strength (21, 41). On the other hand, Profft & Jumar (43) found a gradually increasing duration of topical anesthesia on the tongue up to the *p*-*n*-octyloxy compound in a series of Falicaine homologues.

In the light of the work of Ritchie & Greengard (35) and others, which indicate that the local anesthetic cation is the active form, it may be concluded that this difference in activity in homologous series is not a measure of drug-receptor affinity. The affinity may be nearly the same for all the members of a series, but as indicated by Ritchie & Greengard, a higher lipid/water partition coefficient would permit the passage of a greater proportion of the anesthetic through a barrier (perineurium or endoneurium, or both,) before reaching the site of action (axon membrane). If the hy-

TABLE I

DURATION OF LOCAL ANESTHESIA
Cat Sciatic Nerve (18)

Compound	Molecular Wt of Base	Local Anesthetic Activity Molar Procaine Ratios	Irritancy		Duration Test	
			Molar Procaine Ratios	Threshold Irritant Conc. 4 m*M*	m*M* Conc.[a]	Recovery Time (min)
Procaine HCl	236.3	1	1	176	71	16
Lidocaine	234.33	3.3	2.8	62	20	23
Propoxycaine HCl	294.40	11	2.3	75	6.5	33
WIN 3766[b]	310.40	96	12	15	0.74	60–150
Dibucaine HCl	343.40	20	31	5.6	3.5	180–240

[a] Equiactive concentrations. (Local anesthetic activity was determined by the intracutaneous wheal test.) The concentrations are 8 to 9 times higher than the Threshold Anesthetic Concentration 5 (TAC_5).

[b] WIN 3766 = 2-propoxythiocaine.

drophobic portion of the molecule is already large in relation to the hydrophilic group (for example, giving a distribution of 90 to 1 between the barrier biophase and the aqueous phase), no further important increase in passage would be obtained by bringing the proportion to 95 (or more) to 1 by additional hydrophobic group substitution. Also, if at equilibrium the proportion dissolved in the aqueous phase is very small, diffusion through the interstitial fluid would be very slow and more drug would have to be injected to obtain a supra-threshold concentration at the site of action. It must be kept in mind that in most of the experimental tests designed to determine local anesthetic activity, the local anesthetic, after injection or application, is not placed in immediate contact with nerve fibers. Even in topical anesthesia some penetration must be accomplished in order to obtain complete anesthesia. This is illustrated in the studies of Profft & Jumar (43) showing that the highest *p*-alkoxy analogues of Falicaine (*p*-alkoxy piperidino propiophenones) produce only mild or moderate anesthesia of the tongue, the maximal degree of anesthesia being reached only after a period of 40 to 50 min.

Although we cannot exclude the possibility that a large hydrophobic chain may reduce the affinity of the molecule to the local anesthetic receptor, the decline in local anesthetic activity after a maximal value may be due to a gradual decrease in transport through the intercellular aqueous phase. Studies of homologous series on isolated nerve fibers, eliminating the penetration factor, could establish whether or not the changes in potency produced by lengthening of alkyl side chains are or are not due to changes in affinity to the local anesthetic receptor.

The pKa of the commercial anesthetics varies within a relatively narrow range. At the pH of the tissue fluids the undissociated form may act as the solute spearhead to penetrate lipid barriers. It would tend to be squeezed out of the aqueous phase and to accumulate at interfaces. This process would also occur with the ionic form in the case of those compounds with large hydrophobic groups. The ionized form would facilitate solution in water and transport through aqueous phases or channels, including diffusion to adjacent areas and systemic absorption. However, the relative concentration of the two forms in the aqueous phase would remain constant.

It seems logical to assume that the greater the surface activity of a compound, the higher would be its accumulation at interfaces inside and outside cells and nerve fibers in the injected area. This would be mainly nonspecific adsorption. At equilibrium there would be a constant ratio between the concentration at various interfaces and the concentration in the aqueous phase. This ratio would be higher the greater the surface activity. The half-life of the drug molecule-receptor (specific or nonspecific) complex is probably very short, playing no important part in the overall duration of anesthesia. A reduction of the amount adsorbed can occur only by reduction in the concentration in the aqueous phase. *In vivo*, the amount of drug absorbed sys-

temically would be a direct function of the rate of paracapillary circulation in the injected area, most of it going into the blood stream, 1 per cent or less absorbed through the lymphatics (33, 44). The fact that a great increase in duration is produced by the addition of a vasoconstrictor to the solutions indicates the preponderant part played by local circulation in reducing the concentration of the drug at the site of action.

According to Pappenheimer the rate of diffusion through the capillary endothelial cells increases with lipid solubility (45) and being lipid soluble substances, local anesthetics pass rapidly through the capillary wall. We may deduce that this process does not play a part in producing the differences in duration of action, since increases in hydrophobic groups increase the duration of action of local anesthetics, not the opposite. The conclusion that long-acting local anesthetics resist systemic absorption by adsorption to nonspecific receptors appears to be supported by the results of duration-of-action tests run with mixtures of propoxycaine (2-propoxy procaine), and procaine (15). The intradermal anesthesia in guinea pigs produced by 0.25 per cent propoxycaine HCl is considerably longer than that following the injection of 1 per cent or 2 per cent procaine HCl. However, the duration of action of a solution containing 0.25 per cent propoxycaine + procaine HCl (1 or 2 per cent) is significantly shorter than that produced by 0.25 per cent propoxycaine alone. A possible explanation is that procaine in a larger concentration competes for nonspecific receptors for which the difference in affinity may be small. This would facilitate the spreading and the systemic absorption of the more active compound [propoxycaine is 7 to 8 times more active than procaine (9)].

Self-depression of absorption due to irritation.—The group of compounds where the differences in duration of action are associated only with parallel variations in surface activity and irritancy includes the majority of the experimental and commercial local anesthetics. Irritancy would be associated with duration of action through the common link of surface activity, but irritation would not be the cause of changes in duration, since the latter are observable with nonirritant concentrations. With a moderate or high degree of irritation, which, for example, the higher members of most homologous series can produce, another factor appears to intervene to reduce the systemic absorption of the drug. This is most likely due to self-depression of absorption. "Self-depression of subcutaneous absorption is the delay caused by endogenous liberated compounds, such as histamine and 5-hydroxytryptamine" [Schou 33)]. So far this phenomenon has been demonstrated in rats but the results of local anesthetic tests strongly suggest that a similar phenomenon occurs in other species after subcutaneous and intradermal injection. Once the threshold irritant concentration is exceeded, an abnormal increase in capillary permeability is produced, which permits the passage into the interstitial fluid of a colloidal dye, such as trypan blue (46). This nonspecific response of the tissue to all kinds of irritant sub-

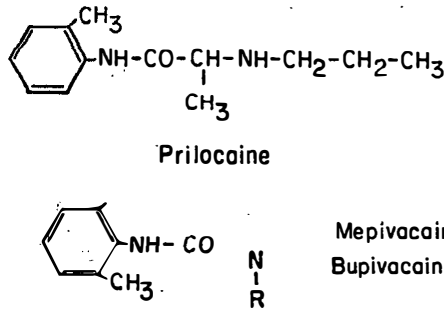

FIG. 1. Chemical structures of prilocaine, mepivacaine, and bupivacaine.

stances appears to be due to the local release of histamine or another endogenous substance, or both, although it is possible that a direct effect on the membrane of the endothelial capillary cell is contributory. Whatever the intimate mechanism, a moderate or high degree of increased capillary permeability results in local edema which by compression of capillaries would tend to slow down or stop capillary flow and consequently paracapillary circulation. This phenomenon is clearly evident when trypan blue is injected intravenously after the intradermal injection of an irritant substance. At a certain degree of irritation [score of 16, Hoppe, Alexander & Miller (46)] the center of the wheal remains colorless, surrounded by a blue ring. At lesser degrees of irritation the whole wheal becomes blue, the intensity of the color varying with the concentration of the test compound. This result indicates that with edema, in spite of the increased capillary permeability, the dye in the blood stream cannot reach the center of the wheal. It is logical to assume that the rate of systemic absorption of a local anesthetic in the center of the wheal would be extremely low; its concentration would be reduced mainly by spreading.

An example of the association of irritation with duration of action is provided by the studies of Seevers & McIntyre (47). Testing logarithmically graded concentrations by intradermal injection in guinea pigs, they obtained reasonably linear concentration-effect (duration) curves for the lower three or four doses of the less irritant compounds when the duration was plotted against dose on semilog paper. A departure from linearity occurred when the mean duration of action of the highest dose was plotted. With one of the more irritant compounds the duration of anesthesia was increased from 72 min to 6 to 18 hr by doubling the concentration. In other cases this increase in dosage resulted in increases in duration from 21 to 96 min to more than 24 hr. In general, the compounds were found to be irritant when tested on the rabbit cornea (47).

The duration of anesthesia of "more than 24 hr" may indicate injury to the nerve fibers and may be similar in nature to the anesthesia reported with procaine dissolved in propylene glycol or other irritant solvents (48,

49). The long-lasting local anesthesia produced by a Cl-ethyl analogue of lidocaine (2-ethyl-2-Cl-ethyl amino 2′, 6′-acetoxylidide) reported by Ehrenpreis et al. (50) may have the same mechanism of action. According to these authors the above compound would produce a long-lasting change in the anesthetic receptor, similar to that produced in the sympathetic α-receptors by dibenamine and its congeners. However, they also reported that skin necrosis in guinea pigs had followed the intradermal injection of the compound. Skin necrosis indicates a high degree of irritation; even smaller concentrations would result in a reduction of the systemic absorption.

Until long-lasting anesthesia is obtained with nonirritant concentrations of the compound studied by Ehrenpreis et al., the existence of the claimed long-lasting change in the local anesthetic receptor remains in doubt.

The effect which results from sensory nerve fiber injury does not represent a case of self-depression of absorption since the anesthesia produced would persist long after the local anesthetic had disappeared from the site of injection.

Self-depression of absorption not due to irritation.—So far, only three compounds can be included in this group: L(+)-prilocaine, (+)-mepivacaine, and (−)-bupivacaine.

The reason why only optically active compounds are members of this group is that only by comparison with their corresponding enantiomorphs is it possible to make evident a duration of action influenced by a mechanism other than the two discussed previously.

L(+)-Prilocaine (51), (+)mepivacaine (Table II), and (−)-bupivacaine (52) are significantly longer active than their optical isomers (Figs. 2 and 3 when both members of the pair are tested at the same concentration. The results obtained with the mepivacaine isomers are shown in Tables II and III. The local anesthetic activity of bupivacaine isomers is approximately the same. The dextro-isomer is somewhat more toxic than its enantiomorph when administered intravenously or subcutaneously to rats and mice (52).

It is interesting to note that no difference was found between racemic and dextro-bupivacaine in regard to duration of intradermal anesthesia in the guinea pig, which suggests that the presence of the dextro form had blocked the effect of the active enantiomorph on duration.

The difference in duration of action was also evident when the isomers of bupivacaine were tested by intraspinal injection in rabbits (52).

The additional length of action of one of the isomers of the three aforementioned compounds cannot be attributed to differences in "amphypathy" since the proportion between hydrophilic and hydrophobic groups is the same for both isomers, and it cannot be due to irritation because the differences in duration also occur when the strength of the solutions is well below the threshold irritant concentration. L-(+)-Prilocaine in comparison with its optical isomer delays the clearance of radioactive sodium in-

TABLE II

DURATION OF LOCAL ANESTHETIC ACTION OF (+)- AND (−)-MEPIVACAINE

Test	Duration of Action (min)	
	dextro	levo
Spinal anesthesia 2 per cent solution (10 rabbits)	47±2.8	37±2.4
Spinal anesthesia 4 per cent solution (10 rabbits)	59±3.3	49±4.6
Intradermal anesthesia 2 per cent solution (10 guinea pigs)	81	58
Intradermal anesthesia 2 per cent solution (10 guinea pigs)	80	62
Intradermal anesthesia (1 per cent+ epinephrine 1:200,000)	124	94
Intradermal anesthesia (1 per cent+epinephrine 1:200,000)	134	97

jected intramuscularly in the same solution as $^{22}NaCl$ (51), and (−)-bupivacaine reduces the systemic absorption of phenol red when the two drugs, in the same solution, are injected intradermally in the guinea pig (52). These results indicate that in both cases a reduction in local circulation rate is the most probable cause for the longer action of one of the optical isomers. This reduction in circulation is most likely the result of weak or moderate vasoconstriction. Goldman, Killey & Wright (53) have shown that racemic prilocaine injected under the skin of the rabbit ear produces vasoconstriction, and Pohto & Scheinin (54) have demonstrated that vasoconstriction in the dental pulp follows the injection of racemic mepivacaine (Carbocaine). A similar vasoconstrictor effect on the skin was reported by du Mesnil de Rochemont & Hensel (55) after the intradermal injection of racemic mepivacaine, but not of procaine or lidocaine.

The duration of intradermal anesthesia in guinea pigs produced by (+)-mepivacaine was reduced by adrenolytic drugs (phentolamine and piperoxan) but the difference in duration of action between the two optical isomers of mepivacaine was not changed by the previous systemic injection of phentolamine or by the addition of phentolamine to the local anesthetic solutions (52).

In preliminary experiments similar effects were produced by cyprohepta-

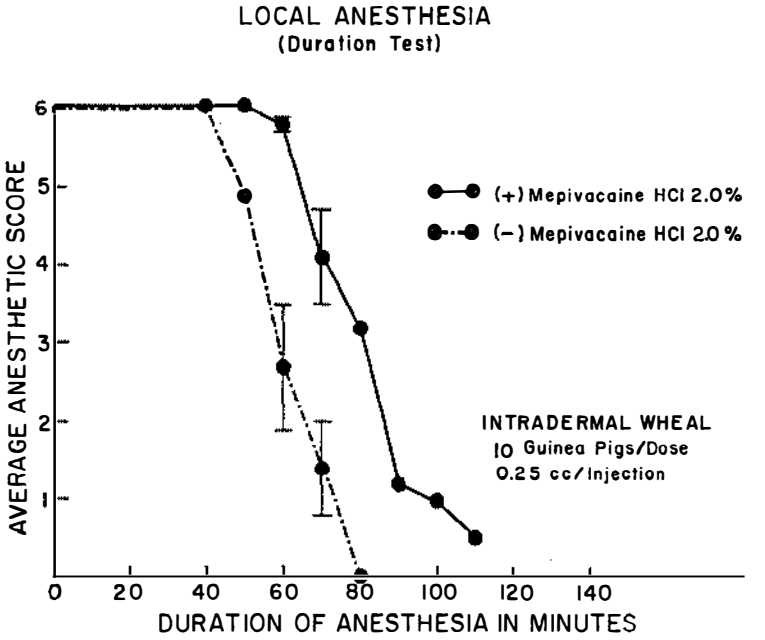

FIG. 2. Duration of anesthesia produced by the two optical isomers of mepivacaine.

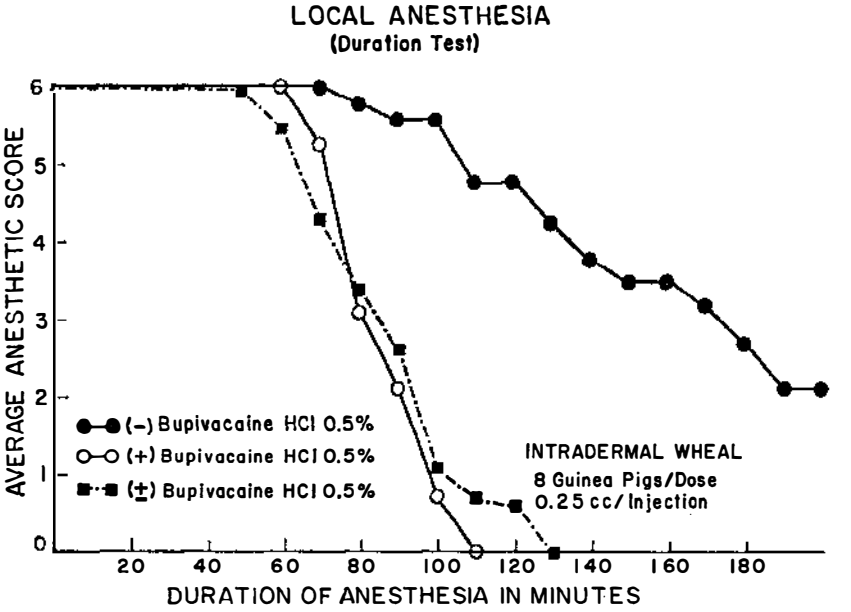

FIG. 3. Duration of anesthesia produced by levo-, dextro-, and racemic bupivacaine.

TABLE III

TOXICITY AND IRRITANCY OF DEXTRO- AND LEVO-MEPIVACAINE

Toxicity		Mepivacaine						
		dextro	levo			racemic		
Species	Route of Administration	LD_{50} (mg/kg)	LD_{50} (mg/kg)	Ratio[a]	99 per cent Confidence limits	LD_{50} (mg/kg)	Ratio[a]	99 per cent Confidence limits
Mouse	i.v.	31.4	31.6	0.99		31.6	0.99	
Rat	i.v.	36.5	38.0	1.01		29.8	1.25[a]	
Mouse	subc. (1st test)	349	226	1.68	(1.34–2.09)			
Mouse	subc. (2nd test)	432	241			273	1.59	(1.16–2.19)
Rat	subc. (1st test)	496	346					
Rat	subc. (2nd test)	601	434	1.42	(1.15–1.75)		1.19[b]	
			IRRITANCY (Trypan Blue Test)					
Rabbits (intradermal)		TIC_4 1.95 per cent	TIC_4 1.90 per cent			TIC_4 1.95 per cent		

[a] ED_{50} of (+)-mepivacaine = 1.

[b] The racemate was tested on another batch of mice. The two isomers were tested in parallel on mice from the same batch.

dine, a potent antihistamine and antiserotonin compound, administered in the same manner as phentolamine. Cyproheptadine, on the other hand, did not change the duration of action of procaine, lidocaine, or tetracaine, when injected intradermally in the same solution (52). These results may indicate that the additional property which makes mepivacaine longer acting than lidocaine is shared, although to a different degree, by the two optical isomers.

As shown in Tables II and III (+)- and (−)-mepivacaine have the same intravenous toxicity, the same irritancy (trypan blue test) and the same local anesthetic activity as determined by the magnitude of the threshold anesthetic concentration. They differ significantly in regard to duration of anesthesia and subcutaneous toxicity. Injected subcutaneously (+)-mepivacaine is less toxic than its optical isomer. A lower rate of systemic absorption of the former could explain both results (52).

The long-acting isomers of mepivacaine and bupivacaine have not been studied clinically, except for a comparative intradermal test which showed no significant difference between *levo*- and *dextro*-mepivacaine (56). However, there is considerable information on the clinical effects of the racemic forms of these two compounds. In experimental animals (57, 58) and in man (59, 60) mepivacaine is longer-acting than lidocaine, although the irritancy of mepivacaine is lower (58). Racemic bupivacaine (Marcaine) was found by Henn & Brattsand (61) to be as long acting as tetracaine when infected intradermally in man. In equiactive anesthetic concentrations and in the presence of epinephrine, bupivacaine was longer acting than mepivacaine (62–65) and tetracaine (65), as a local anesthetic in man.

The results obtained with the isomers of mepivacaine and bupivacaine strongly suggest that the long duration of anesthesia that the racemic forms produce in man is due mainly to one of the optical isomers. The comparative studies carried out with these isomers and those reported in the literature (51) strongly suggest that optical isomerism does not influence local anesthetic receptor-drug affinity. In other words the active site of the receptor is not or does not include a molecule containing an asymmetric carbon. Although (+)-prilocaine is more active than its antipode even at concentrations close to their threshold level (intradermal and corneal anesthesia), the two isomers are equally active on the isolated sciatic nerve (51). Also, (−)-bupivacaine is slightly more active and less toxic (intravenously) than its optical isomer (52). In both pairs the difference in activity was small and the difference in toxicity in the second pair was only of 20 to 40 per cent. It appears more probable that the mechanism responsible for the longer duration of action of one of the isomers involves a site of action containing an optically active molecule, and that this has a slight influence in the activity and toxicity readings. In other words, the two isomers would have the same affinity for the receptor, but the concentration at the receptor site would be higher, the lower the rate of systemic absorption.

A duration of action which is longer in relation to its molecular amphypathy (and indirectly to its irritancy) may occur in other homologues of mepivacaine, especially the N-ethyl and the N-propyl, and perhaps in other local anesthetics which do not possess an asymmetric carbon. Since cocaine has vasoconstrictor action it is most likely that this property influences its duration of action. However, cocaine is not a long-acting local anesthetic.

Esterases and duration of anesthesia.—Procaine and other local anesthetic esters are hydrolyzed by plasma cholinesterase (66–68). The rate of hydrolysis of 2-chloroprocaine by this enzyme was considerably higher than that of procaine and tetracaine (69). Foldes & McNall (70) have suggested that in certain areas with a rich vascular supply, hydrolysis of 2-chloroprocaine could account for its short duration of action.

It is most likely that hydrolysis of procaine and especially 2-chloroprocaine occurs at the site of injection, but the per cent inactivated, due to the large amount of drug, may be too small to produce significant reductions in duration of action. Foldes & McNall's own clinical studies (70) showed that (*a*) a pronounced increase in intradermal anesthesia was produced by adding epinephrine to the solution of 2-chloroprocaine, indicating that in the absence of vasoconstriction systemic absorption was the main mechanism for the removal of 2-chloroprocaine; (*b*) no differences in dental nerve block duration were observed when the effect of a solution of 2-chloroprocaine containing epinephrine was compared to that of a similar solution which contained, in addition, a plasma cholinesterase inhibitor.

LITERATURE CITED

1. Pitkin, G. P., *Conduction Anesthesia,* 2nd ed., 289–90 (J. P. Lippincott, Philadelphia, 1005 pp., 1953)
2. Gasser, H. S., Erlanger, J., *Am. J. Physiol.,* **88,** 581–91 (1929)
3. Nathan, P. W., Sears, T. A., *J. Physiol. (London),* **140,** 53–54 (1958)
4. Nathan, P. W., Sears, T. A., *J. Physiol. (London),* **157,** 565–80 (1961)
5. Greene, N. M., *Anesthesiology,* **19,** 45–50 (1958)
6. Kato, G., *Cold Spring Harbor Symp. Quant. Biol.,* **4,** 202–13 (1936)
7. Tasaki, I., *Nervous Transmission,* 90–106 (Charles C Thomas, Springfield, Ill., 164 pp., 1953)
8. Bülbring, E., Wajda, I., *J. Pharmacol. Exptl. Therap.,* **85,** 78–84 (1945)
9. Luduena, F. P., Hoppe, J. O., *J. Pharmacol. Exptl. Therap.,* **117,** 89–96 (1956)
10. Loomis, T. A., Spielmeyer, R., *Yale J. Biol. Med.,* **18,** 165–69 (1946)
11. Luduena, F. P., Hoppe, J. O., *J. Pharmacol. Exptl. Therap.,* **104,** 40–53 (1952)
12. Bieter, R. N., Cunningham, R. W., Lenz, O., McNearney, J. J., *J. Pharmacol. Exptl. Therap.,* **57,** 221–44 (1935)
13. Luduena, F. P., *Arch. Intern. Pharmacodyn.,* **109,** 143–56 (1957)
14. Luduena, F. P., *J. Dental Res.,* **36,** 613–22 (1957)
15. Luduena, F. P., *ibid.,* **39,** 947–54 (1960)
16. Bennett, A. L., Wagner, J. C., McIntyre, A. R., *J. Pharmacol. Exptl. Therap.,* **75,** 125–36 (1942)
17. Truant, A. P., Lanzoni, V., *Federation Proc.,* **16,** 341 (1952)
18. Brown, T. G., Jr., Luduena, F. P., *Anesthesiology,* **14,** 555–66 (1953)

19. Knox, R. P., North, W. C., Stephen, C. R., *Anesthesiology,* **22,** 987–94 (1961)
20. Braun, H., *Local Anesthesia,* 105–08 (Lea & Febiger, Philadelphia, 411 pp., 1924)
21. Uhlmann, F., *Arch. Intern. Pharmacodyn.,* **36,** 253–71 (1929)
22. Miescher, K., *Helv. Med. Acta,* **7** *(Suppl. 6),* 126–48 (1941)
23. Gerlough, T. D., *J. Pharmacol. Exptl. Therap.,* **41,** 307–16 (1931)
24. Sinha, H. K., *J. Pharmacol. Exptl. Therap.,* **57,** 199–220 (1939)
25. Leser, A. J., *J. Pharmacol. Exptl. Therap.,* **68,** 389–94 (1940)
26. de Jong, R. H., Wagman, I. H., *Anesthesiology,* **24,** 684–727 (1963)
27. Luduena, F. P., Hoppe, J. O., *J. Am. Pharm. Assoc.,* **44,** 393–96 (1955)
28. Beyer, K. H., Latven, A. R., Freiburger, W. A., Parker, M. P., *J. Pharmacol. Exptl. Therap.,* **93,** 388–400 (1948)
29. Luduena, F. P., Hoppe, J. O., *J. Pharmacol. Exptl. Therap.,* **104,** 40–53 (1952)
30. Gonzalez, E., Luduena, F. P., *J. Med. Chem.,* **3,** 555–60 (1961)
31. Sinha, H. K., *J. Pharmacol. Exptl. Therap.,* **66,** 42–53 (1939)
32. Wilbrandt, W., de la Cuadra, J. L., *Helv. Physiol. Pharmacol. Acta,* **5,** 265–71 (1947)
33. Schou, J., *Pharmacol. Rev.,* **13,** 441–64 (1961)
34. Selye, H., *European J. Pharmacol.,* **1,** 262–68 (1967)
35. Ritchie, J. M., Greengard, P., *Ann. Rev. Pharmacol.,* **6,** 405–30 (1966)
36. Hartley, G. S., *Aqueous Solutions of Paraffin-Chain Salts,* **45** (Hermann et Cie., Paris, 69 pp., 1936)
37. Moilliet, J. L., Collie, B., *Surface Activity* (E. and F. N. Spon Ltd., London, 379 pp., 1951)
38. Luduena, F. P., Hoppe, J. O., Nachod, F. C., Martini, C. M., Silvern, G. M., *Arch. Intern Pharmacodyn.,* **101,** 17–37 (1955)
39. Luduena, F. P., Hoppe, J. O., Borland, J. K., *J. Pharmacol. Exptl. Therap.,* **123,** 269–77 (1958)
40. Luduena, F. P., Hoppe, J. O., Page, D. F., Clinton, R. O., *J. Med. Chem.,* **3,** 545–53 (1961)
41. Miescher, K., *Helv. Chim. Acta,* **15,** 163–90 (1932)
42. Büchi, J., Perlia, X., *Arzneimittel-Forsch.,* **10,** 1–8 (1960)
43. Profft, E., Jumar, A., *Pharmazie,* **11,** 313–16 (1956)
44. Stone, P. W., Miller, W. B., *Proc. Soc. Exptl. Biol. Med.,* **71,** 529–34 (1949)
45. Pappenheimer, J. R., *Physiol. Rev.,* **33,** 387–423 (1953)
46. Hoppe, J. O., Alexander, E. B., Miller, L. C., *J. Am. Pharm. Assoc.,* **39,** 147–51 (1950)
47. Seevers, R. F., McIntyre, A. R., *J. Pharmacol. Exptl. Therap.,* **62,** 252–62 (1938)
48. Margolis, G., Hall, H. E., Nowill, W. K., *Arch. Surg.,* **67,** 715–30 (1953)
49. Luduena, F. P., *Intern. Encyclopedia Pharmacol. Therap.* (In press)
50. Ehrenpreis, S., Lynes, T. E., Stubbins, J. H., Manning, M. D., Edwards, S., *Federation Proc.,* **27,** 407 (1968)
51. Åkerman, B., Persson, H., Tegner, C., *Acta Pharmacol. Toxicol.,* **25,** 233–41 (1967)
52. Luduena, F. P., Bogado, E. F. (To be published)
53. Goldman, V., Killey, H. C., Wright, C., *Acta Anaesth. Scand., Suppl.,* **21,** 353–65 (1966)
54. Pohto, M., Scheinin, A., *Bibliotheca Anat.,* **1,** 46–49 (1961)
55. du Mesnil de Rochemont, W., Hensel, H., *Arch. Exptl. Pathol. Pharmakol.,* **239,** 464–74 (1960)
56. Ekenstam, B. T. af, Egner, B., Pettersson, G., *Acta Chem. Scand.,* **11,** 1183–90 (1957)
57. Henn, F., *Acta Anaesth. Scand.,* **4,** 125–54 (1960)
58. Luduena, F. P., Hoppe, J. O., Coulston, F., Drobeck, H. P., *Toxicol. Appl. Pharmacol.,* **2,** 295–315 (1960)
59. Sadove, M. S., Vernino, D., Lock, F., Kolodny, S., *J. Oral Surg.,* **20,** 399–404 (1962)
60. El-Shirbiny, A. M., Rasheed, M. H., Elmaghraby, A., Motaweh, M., *Acta Anaesth. Scand., Suppl.* **23,** 442–48 (1966)
61. Henn, F., Brattsand, R., *Acta Anaesth. Scand., Suppl. 21,* 9–30 (1966)
62. Ekblom, L., Widman, B., *Acta Anaesth. Scand., Suppl. 21,* 33–43 (1966)
63. Hollmén, A., *Acta Anaesth. Scand., Suppl. 21,* 53–65 (1966)
64. Telivuo, L., *Ann Chir. Gynaecol. Fenniae,* **52,** 513–20 (1963)

65. Albert, J., Lofstrom, B., *Acta Anaesth. Scand.*, **9,** 1–12 (1965)
66. Foldes, F. F., Aven, M. H., *J. Pharmacol. Exptl. Therap.*, **105,** 253–58 (1952)
67. Foldes, F. F., Aven, M. H., *ibid.*, 259–64
68. Kalow, W., Maykut, M. O., *J. Pharmacol. Exptl. Therap.*, **116,** 418–32 (1956)
69. Foldes, F. F., Davis, D. L., Plekss, O. J., *Anesthesiology,* **17,** 187–95 (1956)
70. Foldes, F. F., McNall, P. G., *Anesthesiology,* **13,** 287–96 (1952)