THE ESSENTIAL CHARACTERISTICS OF LOCAL ANESTHETICS *

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THE object of our experimental research was to find the physiologic and chemical properties possessed by many of the widely used local anesthetics.

Although considerable research has been carried out on local anesthetics, the literature contains no comparative survey of the properties of those local anesthetics which are listed in New and Nonofficial Remedies. For such a comparison we gaged the anesthetic efficiency of 18 widely known local anesthetics by the well known method of corneal anesthesia upon a rabbit's cornea. This method is more specific for local anesthesia than most of the available methods since it completely fails to take effect when distilled water, various dilute acid solutions, alcohol, ether, chloroform or phenol, etc. are instilled in the eye. These and many other substances produce local anesthesia *only by damaging tissues in general* when they are injected subcutaneously or intramuscularly, or when they are allowed to act on dissected tissue. Only those effective local anesthetics which fail to irritate in therapeutic concentrations will anesthetize the eye.

The results obtained are listed in table 1. All tests were performed on groups of rabbits (5 to 11) and the averages taken. We measured (1) the duration of anesthesia after instilling 2 drops (0.3 cc.) of a 1 per cent solution of the respective solutions in the eye, anesthesia being tested by means of a probe pressed on the eye, manifesting itself by absence of the wink reflex; (2) the minimal effective concentration of these local anesthetics for a short-lasting anesthesia of only ten minutes' duration. Obviously, such a short-acting local anesthesia on the eye is inadequate for all practical purposes; a much more lasting, hence penetrating, effect is needed. For this end the local anesthetic concentration must be increased 20 to 100 times (e.g. cocaine in the eye is used in 2 per cent to 10 per cent solutions while our "minimal" anesthetic concentration equals 1:1100). If the "minimal" anesthetic concentration of any drug is greater than about 0.5 per cent, that drug cannot be employed for local anesthesia of the eye.

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THE MOST POTENT LOCAL ANESTHETIC AGENTS

The three most potent drugs on our list are nupercaine, pontocaine and diothane. All of these proved to be very irritant in 1 per cent solution, which concentration is obviously too high for these potent drugs. The highest nonirritant concentration was found to be: 1:5000 for nupercaine, which is 20 times higher than our "minimal" anesthetic concentration; 1:1000 for pontocaine, which is 5 times higher than our "minimal" anesthetic concentration; and 1:1000 for diothane, which is 12 times higher than our "minimal" anesthetic concentration.

TABLE 1

RESULTS OBTAINED WITH 18 LOCAL ANESTHETIC AGENTS*

Anesthetic	No. of animals used	pH	Anesthesia duration in minutes (1%)	Minimum effective conc. for 10 min. anesthesia	Effect of 1% solution	Non-irritant conc.
Alypin HCl	8	6.0	36	1 : 600	non-irritating	
Amylcaine HCl	5	4.9	16	1 : 500	non-irritating	
Apothesine HCl	11	5.1	no anesthesia	6 : 100	non-irritating	
				slightly irritating		
Benzyl alcohol	5	—	no anesthesia	1 : 20	slightly irritating	
				very irritating		
Butyn sulfate	10	6.0	25	1 : 1300	non-irritating	
Cocaine HCl	10	4.7	55	1 : 1100	non-irritating	
Diothane HCl	9	4.7	85	1 : 12000	very irritating, exudation	1 : 1000
Holocaine HCl	6	4.9	59	1 : 500	non-irritating	
Intracaine HCl	5	4.9	16	1 : 200	non-irritating	
Larocaine HCl	8	5.1	43	1 : 750	non-irritating	
Metycaine HCl	9	5.1	56	1 : 2200	non-irritating	
Monocaine HCl	11	4.9	25	1 : 150	non-irritating	
Nupercaine HCl	7	3.5	3000	1 : 100000	very irritating, excessive exudation	1 : 5000
Pontocaine HCl	6	5.3	79	1 : 5000	very irritating	1 : 1000
Procaine butyrate			no anesthesia	2 : 100	non-irritating	
				slightly irritating		
Procaine HCl	5	5.1	no anesthesia	3 : 100	non-irritating	
				non-irritating		
Tutocaine HCl	5	4.9	14	1 : 250	non-irritating	
Quinine urea HCl	5	2.6	no anesthesia	tried 1 : 10, but got no anesthesia	irritating	

* Volume of solutions used was 2 minims (0.3 cc.).

In an attempt to determine to what extent the acidity is responsible for the anesthetic effect of the three strongest anesthetics, as much 10 per cent sodium carbonate was added to the 1 per cent solutions of their hydrochlorides as was possible without producing a precipitate. Very little can be added in this way because of the feeble basic nature of the strong anesthetics and their insolubility. The results are listed in table 2.

TABLE 2

THE ACTION OF THE STRONGEST LOCAL ANESTHETICS AFTER NEUTRALIZATION OF THEIR HYDROCHLORIDES IN SOLUTION BY CAUTIOUSLY ADDING SODIUM CARBONATE

1% solution of the anesthetic	After neutralization			Before neutralization		
	pH	Irritation	Duration, minutes	pH	Irritation	Duration, minutes
Nupercaine HCl	4.9	slight	132	3.5	excessive	3000
Diothane HCl	5.1	*excessive*	71	4.7	excessive	85
Pontocaine HCl	6.2	slight	44	5.3	excessive	79

The conclusion that diothane is particularly harmful to tissue is supported also by practical experience, since it has been observed to produce tissue edema, a property which is not exhibited by other local anesthetic agents to the same extent at corresponding concentrations (personal communication by Dr. E. A. Tyler, Hahnemann Hospital of Philadelphia).

It is noteworthy that *after neutralization the anesthetic potency of nupercaine is considerably diminished* (see table 2). This finding seems to indicate that the anesthetic action of this potent drug is, to some extent, the result of an irritation caused by the free hydrochloride in it. As is well known, the anesthetic power of procaine hydrochloride is augmented by the addition of sodium bicarbonate, indicating that in this case the base is the sole anesthetic agent, but not so for nupercaine.

THE "INTERMEDIATE" CLASS OF LOCAL ANESTHETICS

Ten of the 18 local anesthetics which we investigated had "minimal anesthetic concentrations" of from 1:150 to 1:2200. These well known drugs are listed according to potency in table 3. None of them is irritant in 1 per cent solution.

TABLE 3

LOCAL ANESTHETICS WITH AN INTERMEDIATE ACTION

Drug	Minimal anesthetic concentration
Metycaine	1 : 2200—strongest of this group, an efficient nonirritant local anesthetic
Butyn sulfate	1 : 1300
Cocaine HCl	1 : 1100—the only reliably vasoconstricting local anesthetic in this list
Larocaine HCl	1 : 750
Alypin HCl	1 : 600
Amylcaine HCl	1 : 500
Holocaine HCl	1 : 500—irritation frequently reported although not observed in our tests
Tutocaine	1 : 250 weakest of this group; monocaine has some vasoconstrictor action but
Intracaine	1 : 200 has not been widely introduced to date
Monocaine	1 : 150

THE WEAK LOCAL ANESTHETICS

This class includes: quinine urea hydrochloride, benzyl alcohol, the two procaine salts which we studied, as well as apothesine. All these drugs are too feeble for efficient surface anesthesia as their "minimal anesthetic concentration" is higher than 0.5 per cent. The feeblest local anesthetic in this list is quinine urea hydrochloride, the old-time drug which seems to rely on the reputation of quinine as a cure-all, hence also a local anesthetic! In our experiments it failed to exhibit any local anesthetic effect on the rabbit's cornea in a concentration of 1 per cent. At 10 per cent concentration, violent irritation occurred, but even then no anesthesia was obtained.

In order to determine whether quinine has any local anesthetic effect we applied it to the sciatic nerve of the frog in situ, in the well known manner. Six eviscerated frogs were used in each series. After

TABLE 4

TIME VALUES FOR DISAPPEARANCE OF REFLEX

Drug and its concentration	pH	Duration of anesthesia, minutes
Quinine urea HCl, 1%	3.0	41.0
Quinine urea HCl, 2%	3.0	44.3
Quinine urea HCl, 10%	2.6	9.8
Procaine HCl, 1%	5.3	8.5
HCl, n/1000	3.0	44.3
NaCl, 0.7%	7.0	42.0
HCl, 0.025 n	2.6	20.4

determining the threshold for reflex stimulation, a cotton plug soaked with a 1 per cent solution of quinine urea hydrochloride was placed in the emptied abdominal cavity upon the exposed sciatic nerves. The time was observed within which the reflex disappeared. For comparison, a parallel series with 6 frogs was run in which the quinine urea hydrochloride was replaced by a 1/1000 normal solution of hydrochloric acid which has the same pH, namely 3. Another control was run using pledgets of isotonic saline solution, and also a series employing 1 per cent solution of procaine hydrochloride. The time values for the disappearance of the reflex are set forth in table 4.

It appears that quinine urea hydrochloride has an anesthetic action only at the very irritant concentration of 10 per cent, at which point its pH is 2.6. But a solution of hydrochloric acid having the same hydrogen ion concentration is also "anesthetic," obviously through irritation exclusively. In concentrations of 1 to 2 per cent, which are used clinically, the drug has no more anesthetic effect than ordinary saline solution, or slightly acidulated water (1/1000 normal hydrochloric acid). This finding is in accordance with Sollmann's statement that the anesthesia produced by quinine urea hydrochloride is "indeed due

to necrosis of the axis cylinders and sheaths with subsequent regeneration (1)."

Another ineffective local anesthetic agent which we studied was benzyl alcohol, listed in New and Nonofficial Remedies as "a local anesthetic used by injection and by application to mucous membranes. . . . It is practically nonirritant and nontoxic in the ordinary doses . . . is usually used in the form of a 1 to 4 per cent solution."

We found benzyl alcohol in 1 per cent concentration slightly irritant but devoid of any anesthetic action on the rabbit's eye. In order to obtain anesthesia of ten minutes' duration it was necessary to raise the concentration to 4 per cent, but at this level the irritation was marked. Since benzyl alcohol can be contaminated with benzoic acid, which might be the cause of the irritation, we added some sodium carbonate to it, but the alkalinized 4 per cent solution proved to be quite as irritating and poorly anesthetic as the 4 per cent solution without the sodium carbonate. Benzyl alcohol would not, therefore, deserve to be classified as a local anesthetic agent.

Quinine and benzyl alcohol, the most ineffective local anesthetics in our list, are chemically the only drugs which have no ester structure. Somewhat stronger than these are several local anesthetics, chemically characterized as "ester" structures, as for example, apothesine hydrochloride, procaine hydrochloride, procaine butyrate. Yet in all of these drugs the minimal anesthetic concentration is so high that it cannot be raised 20 to 100 times for reliable anesthesia.

These anesthetics can be used only in infiltration anesthesia, nerve block and so forth. Apothesine is, moreover, slightly irritating at the "minimal" anesthetic concentration of 6 per cent. The slightly irritant effect of procaine butyrate can probably be attributed to the butyric acid; procaine hydrochloride seems preferable. This finding is in agreement with a recent study by M. L. Tainter (2) who showed that procaine hydrochloride is the local anesthetic of choice for injection.

CONVULSIVE POWER AND INTERNAL TOXICITY

Most local anesthetic agents are convulsive poisons, although in many cases their action may be so rapid that there is respiratory paralysis, collapse and death before convulsions have had time to develop. Our problem was to determine, quantitatively as far as possible, whether convulsive power and anesthetic potency run a parallel course. When trying to determine the convulsive potency of a drug it must be realized that the susceptibility to convulsive poisons varies widely for different animals of the same species. It is necessary, therefore, to observe the incidence of convulsions in a group of animals, preferably guinea pigs which survive even severe and lasting attacks. Experiments of this kind have been carried out in this laboratory for several years for the purpose of determining the inhibition of convul-

sions by other salts (3). Recently, H. Wastl (4) has continued this line of research studying the anticonvulsive action of a large number of calcium salts, on the convulsions produced by procaine, butyn, pontocaine, and other local anesthetics.

The same method has been used for a comparison of different local anesthetics without addition: the smallest dose capable of producing convulsions in 90 to 100 per cent of a group of 10 guinea pigs was determined. These observations were carried out in the winter of 1939–40 by Mr. Landay and Mr. Lieberman in our laboratory under the same conditions (see table 5).

TABLE 5

CONVULSIVE DOSES IN RELATION TO ANESTHETIC EFFICIENCY

(*a*) *Strong acting local anesthetics:*

Drug	Convulsive dose	Min. anesth. dose	Ratio of anesth. : conv. dose
Nupercaine HCl	15 mg./Kg.	1 : 100000	1 : 1500000
Pontocaine HCl	10 mg./Kg.	1 : 5000	1 : 50000
Diothane HCl	150 mg./Kg.	1 : 12000	1 : 1800000 (irritant)

(*b*) *Local anesthetics with an intermediate action:*

Drug	Convulsive dose	Min. anesth. dose	Ratio of anesth. : conv. dose
Alypin HCl	50 mg./Kg.	1 : 600	1 : 30000
Amylcaine HCl	60 mg./Kg.	1 : 500	1 : 30000
Butyn sulfate	20 mg./Kg.	1 : 1300	1 : 26000
Cocaine HCl	30 mg./Kg.	1 : 1100	1 : 33000
Holocaine HCl	25 mg./Kg.	1 : 500	1 : 12500
Intracaine HCl	50 mg./Kg.	1 : 200	1 : 10000
Larocaine HCl	30 mg./Kg.	1 : 750	1 : 22500
Monocaine HCl	90 mg./Kg.	1 : 150	1 : 13500
Metycaine HCl	30 mg./Kg.	1 : 2200	1 : 66000
Tutocaine HCl	75 mg./Kg.	1 : 250	1 : 18750

(*c*) *Local anesthetics too weak for surface anesthesia:*

Drug	Convulsive dose	Min. anesth. dose	Ratio of anesth. : conv. dose
Procaine HCl	200 mg./Kg.	1 : 33	1 : 6600
Apothesine HCl	75 mg./Kg.	1 : 16.6	1 : 1350

It appears from these findings that the ratio of anesthetic potency to convulsive dose is approximately 1:10,000 to 1:75,000 for many of these drugs, although their minimal anesthetic concentration varies to a much greater extent, namely, 1:200 to 1:5,000. There is, therefore, *a roughly parallel course of anesthetic potency and convulsive power.* Not included in this listing are: all those local anesthetics which have an irritant action, such as nupercaine and diothane. Their minimal

anesthetic concentration is much lower, obviously because of the irritation which they produce. Apparently these drugs owe only a part of their anesthetic power to a specific action on the nerve cells; on this assumption we may explain their considerably smaller ratio of anesthetic to convulsive dose. The second exception to the general rule of roughly parallel course of anesthetic and convulsive power is found with the weak acting drugs: procaine, apothesine, quinine urea hydrochloride and benzyl alcohol.

The last two drugs are not true local anesthetics but rather irritants, as explained previously. Accordingly they do *not* readily produce convulsions: benzyl alcohol under no conditions, quinine urea hydrochloride only in the large dose of 300 mg./Kg. In the case of procaine and apothesine a very high ratio of anesthetic to the convulsive dose is found by our method, because these drugs are actually not surface anesthetic agents; hence our minimal anesthetic concentration is exceptionally high, and, consequently, also the above ratio.

RELATION OF CONVULSIVE TO LETHAL DOSE

As a survey of the literature showed, our "convulsive" doses are in every instance much smaller than the minimal lethal doses estimated by various methods. Usually the convulsive dose is only one-half to one-quarter of the lethal dose. An exception to this rule can be found in the case of nupercaine in which the convulsive and lethal dose coincide. This coincidence may be another factor in the exceptionally low ratio of anesthetic to convulsive dose for this drug (see table 5).

THE RELATION OF CHEMICAL CONSTITUTION TO CHEMICAL ACTION

Practically all efficient local anesthetics have a typical chemical make-up: they are ester-like combinations of an amino alcohol with p-aminobenzoic acid or with another benzoic acid derivative.

Aminobenzoic acid is contained in six drugs on our list—procaine, butyn, monocaine, amylcaine, larocaine and tutocaine. The amino alcohols contained in them differ by the length of their carbonic chains: procaine and monocaine have the shortest chains both in the alcohol and in the terminal groups attached to the amine; in the other drugs the length of the alcoholic carbon chain is increased; in butyn the terminal groups on the amino-N are extended. With increasing length of carbonic chain, the oil solubility, hence the penetration through cell membranes and the activity of any drug, increases. The same is true for local anesthetic agents. In this connection it should be remembered that the p-aminobenzoic acid, which is in loose chemical combination in all these drugs, is really a vitamin, being one of the B complex.

Unmodified benzoic acid in loose combination with an amino alcohol, or a similar basic compound, is found in alypin, cocaine, and mety-

caine. The basic compounds connected by an ester bond to the benzoic acid in these drugs are widely different; some of them are highly complex, as in cocaine or substituted piperidine in metycaine, while in alypin the basic compound is an alcohol with 2 amino groups. Cocaine is so well known that it does not need any further discussion. Apothesine has cinnamic acid in the place of benzoic acid, but such a substitution has no advantage. Intracaine has p-ethoxy benzoic acid in this place, also without a striking improvement.

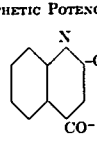
However, in *pontocaine* a new activating substitution has been introduced. Instead of amino benzoic acid, this compound has butylamino benzoic acid. The substitution of a butyl group in this particular location of the molecule appears to raise the anesthetic potency and the toxicity considerably, much more so than an equivalent substitution in the amino alcohol part of the molecule. This conclusion seems justified since pontocaine has an amino alcohol with even fewer carbon atoms than that in procaine. The increase in potency can therefore be due only to the four carbon chains attached to the p-aminobenzoic acid. In New and Nonofficial Remedies (1941) the close chemical relationship of procaine and pontocaine is emphasized, by stating:

Pontocaine hydrochloride is a local anesthetic with actions similar to those of procaine hydrochloride but it is effective when applied to mucous membranes in lower concentrations.

It has *not* been sufficiently understood so far that a substitution of this particular kind, namely in the amino group, increases the convulsive action to a marked extent. In fact, pontocaine is the most active convulsant of all local anesthetics as far as we know, being about 20 times more toxic than procaine, and 3 times more so than cocaine.

TABLE 6

SUBSTITUTION IN THE ACID RADICAL AND ITS INFLUENCE ON ANESTHETIC POTENCY

		
p-aminobenzoic acid,	butyl aminobenzoic acid,	butyloxyquinoline carbonic acid,
contained in *procaine.*	contained in *pontocaine;* potency stepped up 150 times.	contained in *nupercaine;* potency stepped up 1,000 times.

In *nupercaine* the development to greater potency is advanced much further. In place of an aminobenzoic acid, this drug has the high molecular quinoline carbonic acid with an attached butyloxy group, the result being an enormously more active compound (see table 6). But

nupercaine also differs chemically in regard to the compound attached to the acid radical. While in procaine and pontocaine we find at that place two amino alcohols of closely related make-up (di-ethyl-amino-ethanol or di-methyl amino-ethanol), nupercaine has a diamine: diethyl-ethylene diamine. Obviously it is necessary to attach a more highly basic radical to the butyloxy quinoline carbonic acid in order to obtain a basic compound, although nupercaine is only feebly basic.

Although all the compounds studied so far have chemically an ester structure, only four drugs on our list differ greatly in chemical structure from the majority: benzyl alcohol, quinine urea hydrochlorides, holocaine (phenacaine) and diothane. Of these, benzyl alcohol and quinine urea hydrochloride may be disregarded since they act chiefly through irritation, as stated; hence they are not true local anesthetics.

Holocaine is a derivative of phenetidine; hence it is an ether but not an ester. Although irritation was not observed, it is not quite safe in that respect. Goodman and Gilman describe it as "slightly irritant and anesthesia is preceded by smarting (5)." Moreover, the ratio of anesthetic to convulsive dose is more unfavorable for this drug than for most others of the intermediate class.

Diothane differs from the majority in that it is a phenyl urethane derivative. This drug is relatively less convulsive in relation to its considerable anesthetic power than any other drug on our list, but this advantage is entirely offset by the marked irritation which it produces.

The conclusion may be drawn, therefore, that *no* compound without an ester structure can be an efficient nonirritant local anesthetic agent.

RECOMMENDATIONS REGARDING THE USE OF THE MOST POTENT ANESTHETICS

The American Medical Association has recommended that the use of cocaine be limited to topical application. Since pontocaine and nupercaine are more potent and toxic than cocaine they should be subjected to the same restriction, although cautious intraspinal use might be indicated. (Diothane, an equally potent drug, is difficult to recommend for any use because of the damage it produces to tissues.) Fatalities from these drugs have been reported. Such a restriction is *not* equally urgent in the case of larocaine, metycaine and butyn since their minimal lethal doses are higher than that of cocaine. However, we found that small doses produced convulsions with these potent local anesthetics. (Holocaine is rarely injected because of the possibility of irritation.)

SUMMARY AND CONCLUSIONS

The result of our work may be condensed into the statement that efficient local anesthetic agents have so far been obtained only as ester compounds of benzoic acid, amino benzoic acids, or some related substituted benzoic acid; in one instance (nupercaine) quinoline carbonic

acid was substituted. These acids are combined with some amino alcohol or a related compound (for nupercaine a diamino radical) which supplies the basic properties. The ester-like loose combination between the acid and the amino alcohol is the essential indispensable characteristic.

Physiologically all efficient local anesthetics have been found to be convulsants and stimulants of the cerebral cortex, the convulsive power being approximately parallel to the efficiency of the local anesthetic in most cases.

The most notable exception to these rules is diothane, which is chemically different and an efficient local anesthetic, with a relatively lower convulsant power, but these advantages are more than offset by the irritation caused by this drug and the possibility of tissue edema.

Apparently it is more than a casual coincidence that all efficient local anesthetics are convulsants. They must possess a marked affinity to the nerve cells in order to depress selectively the terminal nerve fiber without injuring other cells.

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MEETING OF THE NEW ENGLAND SOCIETY OF ANESTHESIOLOGY

WHITE AUDITORIUM, MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASS.

December 8, 1942—8 P. M.

The Anesthetist and Fluid Balance.

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