

REGIONAL ANESTHESIA WITH TETRACAINE

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*Tacoma, Washington**(Continued from the September 1950 Issue)*CLINICAL INVESTIGATION OF THE PHARMACOLOGIC
PROPERTIES OF TETRACAINE

The anesthetic properties and toxicity of tetracaine have been particularly studied during this entire period by close observation of the routine clinical cases and by special investigation done in selected cases. In the routine cases the time required for onset of complete analgesia, the duration of the block, the presence or absence of toxic manifestations and the complete reversibility of action were observed and noted. Soon after we started to use tetracaine, special investigations were also initiated. The first of these, which has recently been published (90), was done on a group of 125 patients in whom comparative studies of 2 per cent procaine, 0.15 per cent tetracaine and 1.5 per cent metycaine administered for brachial plexus block were made with conditions controlled as well as can be done clinically. Subsequently similar controlled studies were done on selected patients who received several blocks for the relief of postoperative pain or for diagnostic or therapeutic purposes. In such cases the blocks were performed on successive days with tetracaine with and without epinephrine, thus affording an opportunity to use patients as their own controls. They were observed by trained personnel who noted the onset and the duration of anesthesia, variations in blood pressure, respiration, pulse and presence of any toxic manifestations. In addition, studies of the anesthetic properties have been made by intracutaneous injections in volunteers and the relative toxicity of the drug has been studied by intravenous administration in a small group of subjects.

Anesthetic Properties

Onset of Analgesia.—The initial study of brachial plexus blocks indicated that the time of onset of analgesia when 0.15 per cent tetracaine was employed was about 25 per cent longer than that when 2 per cent procaine was used, which actually amounts to about five minutes. It must be noted, however, that in this comparative study the concen-

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tration of tetracaine was about one-thirteenth that of procaine. It has been shown by Moore (98) and confirmed by the present study that if the relative concentration of tetracaine is increased to one-fifth to one-eighth that of procaine, the time of onset of analgesia is about the same with both drugs.

An analysis of all the cases herein reported indicates that the onset of analgesia with dilute solutions (0.05 to 0.15 per cent) when the infiltration technic is used occurs within five to eight minutes; when small nerves, such as the intercostal, radial, ulnar, median, phrenic and sympathetic, are blocked, complete analgesia occurs within fifteen minutes, but when large nerve trunks, such as the brachial plexus or the sciatic nerve, are blocked, the onset is delayed and fifteen to thirty minutes is required. The time of onset, depends not only upon the concentration of the drug and the size of the nerve but also upon the proximity of the needle to the nerve tissue, and whenever possible paresthesia has been elicited in order to indicate that the point of injection was near the nerve.

Duration of Analgesia.—Again referring to the initial study, it was then determined that 0.15 per cent tetracaine caused analgesia which was three to four times as long as that obtained with 2 per cent procaine. In an effort to confirm these results, the original study has been extended, as previously stated, and the duration of analgesia has been observed in all patients, but has been closely investigated and recorded in 735 procedures. In this latter group the anesthesiologists frequently tested the analgesia during the operation and also every fifteen to thirty minutes during the postoperative period until it disappeared. The objective duration was computed from the time the block was complete to the time the patient first detected pin prick, while the subjective duration was calculated from the time of onset to the time the patient first felt pain in the operative site. In some cases the block was executed several hours before the scheduled time of operation either to determine the operability after long periods of analgesia or because of convenience to the anesthesiologist. As has been previously mentioned, this group included therapeutic blocks for the relief of pain in which several procedures were performed with and without epinephrine. The results obtained are shown in table 7 in which the minimum, maximum and average time for both objective and subjective analgesia are recorded. It is important to point out that in most instances the minimum figures are those obtained with dilute solutions or with solutions which contained no epinephrine. We believe that average values of about five to six hours represent the true index of the duration of analgesia that may be obtained with optimal doses of tetracaine. The comparatively short duration of cervical plexus block may be explained by the fact that in these cases the solutions are injected diffusely into vascular tissue in which absorption of the drug is rapid, an observation which has been made by others (19, 27, 28, 29)

TABLE 7
DURATION OF ANALGESIA

Type of Block	No. of Blocks	Objective Analgesia			Subjective Analgesia		
		Minimum	Maximum	Average	Minimum	Maximum	Average
Block of Cranial Nerves	37	2 hr. 30 min.	6 hr. 45 min.	4 hr. 53 min.	2 hr. 30 min.	10 hr. 30 min.	6 hr. 50 min.
Cervical Plexus Block	28	1 hr. 35 min.	5 hr. 30 min.	3 hr. 55 min.	1 hr. 35 min.	6 hr. 30 min.	4 hr. 40 min.
Brachial Plexus Block	108	1 hr. 50 min.	12 hr. 50 min.	6 hr. 10 min.	1 hr. 50 min.	13 hr. 50 min.	8 hr. 55 min.
Elbow Block	6	4 hr.	8 hr. 30 min.	6 hr. 40 min.	4 hr.	8 hr. 30 min.	7 hr. 30 min.
Radical Mastectomy Block (Brachial, Cervical, Intercostal)	47	2 hr. 30 min.	6 hr. 30 min.	4 hr. 50 min.	2 hr. 30 min.	9 hr. 30 min.	6 hr. 40 min.
Bilateral Intercostal-Posterior Splanchnic	77	2 hr. 30 min.	7 hr. 15 min.	5 hr. 33 min.	2 hr. 30 min.	8 hr. 45 min.	5 hr. 30 min.
Paravertebral Block	61	3 hr. 15 min.	5 hr. 55 min.	5 hr. 38 min.	3 hr. 15 min.	7 hr. 45 min.	6 hr. 25 min.
Intercostal Block	130	3 hr.	8 hr. 30 min.	5 hr. 50 min.	3 hr.	9 hr. 15 min.	6 hr. 10 min.
Sciatic-Femoral Block	12	3 hr.	6 hr. 15 min.	4 hr. 27 min.	3 hr.	7 hr. 15 min.	5 hr. 20 min.
Peridural Block	78	2 hr. 15 min.	8 hr.	3 hr. 52 min.	2 hr. 15 min.	9 hr.	4 hr. 50 min.
Stellate Ganglion Block	29	3 hr. 20 min.	10 hr. 30 min.	6 hr. 29 min.	3 hr. 20 min.	10 hr. 30 min.	6 hr. 59 min.
Lumbar Sympathetic Block	62	3 hr. 45 min.	9 hr. 15 min.	7 hr. 18 min.	3 hr. 30 min.	10 hr.	7 hr. 30 min.
Total Average	735	2 hr. 30 min.	7 hr. 59 min.	5 hr. 27 min.	2 hr. 38 min.	9 hr. 17 min.	6 hr. 20 min.

NOTE: The duration of analgesia was established by observation and pinprick tests made every fifteen to thirty minutes. The end of analgesia has thus been determined within an error not exceeding fifteen minutes.

and is important to keep in mind from the standpoint of toxicity. In blocking the brachial plexus, on the other hand, the solution is deposited within a comparatively closed space and consequently slowly absorbed, causing longer analgesia.

Recently additional comparative studies have been made on the duration of procaine and tetracaine analgesia by intracutaneous injections in human beings, a method introduced by Braun (99) and widely used by Sollman (100) Hirshfelder (7) Bieter (19) and many others. Such a method affords an opportunity to study the time of onset, duration, presence or absence of pain when the initial wheal is made, the efficiency of epinephrine to prolong analgesia and the degree of local tissue reactions. This study, the results of which are shown in table

TABLE 8
DURATION OF ANALGESIA
A COMPARISON OF VARIOUS DRUGS

Method	Drugs Compared	No. of Cases	Duration of Analgesia		
			Minimum	Maximum	Average
Brachial Plexus Block in Man	2% procaine with 1:200,000 epinephrine	50	40 min.	4 hr. 25 min.	1 hr. 31 min.
	0.15% pontocaine with 1:200,000 epinephrine	50	1 hr. 50 min.	12 hr. 50 min.	6 hr. 18 min.
	1.5% metycaine with 1:200,000 epinephrine	25	1 hr.	3 hr. 20 min.	1 hr. 56 min.
Intracutaneous Injection in Man (Compared in the same Individuals)	1% procaine without epinephrine	18	20 min.	1 hr. 25 min.	40 min.
	0.1% pontocaine without epinephrine		35 min.	1 hr. 25 min.	1 hr. 12 min.
	1% procaine with epinephrine		1 hr.	4 hr.	2 hr. 35 min.
	0.1% pontocaine with epinephrine		3 hr. 30 min.	6 hr. 15 min.	4 hr. 26 min.

8, has corroborated the clinical findings. The onset of analgesia with 0.1 per cent tetracaine was as quick as with 1 per cent procaine, both caused no pain during the formation of the wheal and no tissue reaction was observed with either drug. A comparative study on the duration of analgesia showed that 0.1 per cent tetracaine solution afforded analgesia which was twice as long as that exerted by 1 per cent procaine. In other words, one-tenth the dose exerted analgesia which was twice as long. The efficacy of epinephrine to prolong analgesia was originally recognized by Braun (17, 99) and since has been acknowledged by most laboratory investigators and clinicians. One clinical investigator (98), however, believed that in the case of tetracaine the addition of epinephrine does not prolong the analgesia sufficiently to make much difference. This is contrary to the findings of others (3, 7,

10, 11, 12, 13, 19, 22, 34, 47, 82, 101) and those of the author who not only investigated this problem by intracutaneous methods, as shown in table 8 but also with therapeutic blocks, in which cases tetracaine was administered to the same patient with and without epinephrine on different days. In such instances as with the studies with intracutaneous wheals, it was conclusively shown that epinephrine prolonged analgesia two to four times. In addition, I am firmly convinced that it decreases the toxicity of local drugs. Tetracaine alone is a powerful vasodilator and should never be employed without epinephrine except in special cases. Blaustein (102) has shown that the use of epinephrine with local drugs does not significantly disturb the diabetic patient and should be used to obtain maximal action and decrease the absorption. Even diagnostic sympathetic blocks may be done with solutions containing epinephrine without affecting the results.

Reversibility of Action.—In all of the cases herein presented, the effects of tetracaine blocks disappeared without leaving any trace of its action and no neurologic complications or sequelae have occurred.

Toxicity of Tetracaine

Some of the authoritative teachings and opinions in regard to the unusual toxicity of tetracaine have made us particularly cognizant of the possible occurrence of toxic reactions, and consequently great emphasis has been placed during the present investigation on the prevention and immediate diagnosis and therapy of such reactions. Particular stress has been laid upon proper administration to avoid quick absorption or inadvertent intravascular injections because we believe this is the best means of obviating these unpleasant and often alarming experiences. The administration of barbiturates prior to and during injection, originally advocated by Tatum et al. (103), may also be employed as an aid in the prevention of mild or moderate reactions, but should not be completely relied upon to prevent severe reactions. If barbiturates are used as substitutes for proper administration, they may mask and possibly aggravate rather than prevent the depression which follows these complications. In the event that reactions occur it is essential that they are immediately recognized and treated if the danger inherent to such complications is to be avoided.

To evaluate tetracaine and record toxic reactions properly, we have classified them as mild, moderate and severe. A mild reaction occurs when the amount of drug in the general circulation is just above physiologic limits, causing stimulation of the cardiovascular, respiratory and central nervous systems, manifested by mild nausea, palpitation, vertigo, tinnitus, hypertension, tachycardia and hyperpnea. Moderate reactions are caused by greater concentrations and are characterized by a progressive aggravation of these signs and symptoms, and in addition the patients may vomit and have muscular twitchings which

usually progress to convulsions. If, however, the toxic dose of the drug in the circulation is very large, the reaction progresses to a severe degree causing depression manifested by hypotension, bradycardia, profuse sweating and other signs of circulatory and respiratory collapse including respiratory depression which may progress to paralysis, unconsciousness and even death. If the absorption of the drug following administration is very fast, the toxicity may progress so rapidly that collapse and death occur before convulsions have had time to develop, which emphasizes the importance of preventing such reactions. These are true toxic manifestations and should be distinguished from those resulting from hypersensitivity and allergy which rarely occur.

An analysis of all of the 4082 regional procedures reported reveals that no severe and only one moderate reaction occurred. In this instance a brachial plexus block was administered to a 6 year old child by an inexperienced intern who inadvertently injected 100 cc. of 0.15 per cent (150 mg.) solution of tetracaine. Within five minutes convulsions developed which fortunately were immediately recognized and successfully treated with oxygen and a small amount of pentothal sodium. This amount of tetracaine was about 4 mg. per pound of body weight which was obviously a severe overdose. In addition to this moderate reaction, 2.1 per cent of the patients complained of transient palpitation, apprehension and slight dizziness which in some instances disappeared without treatment, while in others small amounts of barbiturates were given. Some of these mild reactions may have been the result either of apprehension or of epinephrine which has been shown to cause such symptoms. The validity of these statistics could be questioned when one considers that the barbiturates, which were given prior to or during the block to allay apprehension or obviate discomfort, may have masked some reactions were it not for the fact that none of the many patients who did not receive barbiturates had reactions.

The importance of investigating both toxicity and anesthetic properties by the same method has been recently emphasized by several authors (36, 47) who pointed out that in order properly to evaluate the clinical usefulness of a local drug for a particular type of regional analgesia, its relative toxicity and relative potency must be determined by a particular method of injection. If, for example, the drug is to be evaluated for its use in infiltration analgesia, it is necessary to study toxicity and anesthesia with subcutaneous infiltration rather than to investigate potency by topical application and toxicity by intravenous infusion. With this thought in mind, I have recently attempted to establish toxicity values for tetracaine with subcutaneous injections in man by administering therapeutic blocks with large doses of this drug to a selected group of patients. In a few of these cases procaine blocks were administered on different days in order to obtain relative values.

The blood pressure, pulse, respiration and color were noted before and every five minutes after the block was completed for a period of one hour or longer because, as has been indicated, alterations of these are the first signs of toxicity.

In the first group of 50 cases 1 mg. of tetracaine or 10 mg. of procaine per pound of body weight was used to complete the block and in none were any alterations noted. In a second group 1.5 mg. of tetracaine or 15 mg. of procaine per pound of body weight was administered and in this group, two had moderate reactions with procaine but none with tetracaine. Recently, 2 mg. of tetracaine per pound of body weight was administered to a few patients, limiting the total dose to a maximum of 250 mg., and thus far no reactions have been observed, but because this group is small the results are of no statistical significance. *I would like to emphasize strongly at this point that these doses are much larger than necessary and, although they have been employed for investigative purposes, I strongly recommend that they not be used clinically.*

In another small group of patients and volunteers the toxicity of this drug by intravenous infusions was investigated in an effort to determine the subtoxic intravenous dose. This investigation which has been done with temerity, caution and preparation has been conducted as follows: The subject was first given 0.5 per cent procaine solution intravenously fairly rapidly until toxic manifestations, such as nausea, vomiting or muscular twitchings, were observed by the patient or the investigators. At the first sign of toxicity the infusion was stopped and the total dose of procaine and the time required to initiate the reaction were computed. Whenever possible, this was repeated in the same patient to obtain averages for procaine. On the later date the infusion was repeated with 0.15 per cent tetracaine solution administered at approximately the same rate of flow; it was immediately terminated at the first sign of toxicity and the dose-time computed. This was also repeated to obtain average values for tetracaine. In this small group the average intravenous dose of procaine which could be administered before toxic reactions occurred ranged between 16 and 20 mg. per pound of body weight per twenty minutes, while that of tetracaine ranged between 1.2 and 1.7 mg. per pound of body weight per twenty minute period. It is of interest to note that some of the patients received 100 to 150 mg. of tetracaine intravenously within twenty minutes without signs of toxicity.

The results obtained from these investigations indicate that the dose of tetracaine necessary to cause minimal toxic reactions is about one-tenth to one-twelfth that of procaine. This could be interpreted to mean that the former is ten to twelve times as toxic as the latter, giving tetracaine a relative toxicity ratio of 10 to 12. It must be noted, however, that the investigations also show that when it is employed in one-twelfth to one-fifteenth the dose of the standard drug, it causes

analgesia which is two to four times as long. From these figures the corrected toxicity ratio of tetracaine is computed to be 0.8 and the anesthetic index is 1.2.

DISCUSSION

The many advantages of properly administered and completely effective regional analgesia are recognized and appreciated by all those anesthesiologists and surgeons who have had sufficient experience with it, and yet in spite of these advantages its use in recent years has been rather limited in most American clinics. There are probably several reasons for this situation, not the least important of which is the high standard of general anesthesia obtained by the rapidly developing specialty of anesthesiology whose progress in improving the administrator and administration coupled with the introduction of certain adjuvants as curare has made general anesthesia more suitable for poor risk patients. A more important factor, however, is the uncertainty of effectiveness and duration of regional analgesia which in many instances has made it unpopular with surgeons, anesthesiologists and patients.

Whether the block is sufficiently effective or complete for the proposed operation depends a great deal upon the administrator, whereas the duration depends mainly on the drug employed. The short action of procaine analgesia has in the past caused many anesthesiologists to dismiss completely the use of block analgesia and consequently become less familiar with it. This is unfortunate because the well rounded anesthesiologist should be able to administer regional anesthesia equally as well as general, not only because the former is of value in surgical patients but also because the anesthesiologist is being called upon more and more to aid his colleagues in the diagnosis and therapy of certain diseases by nerve blocking.

I am thoroughly convinced that the substitution of tetracaine for procaine in regional analgesia will do much to obviate the uncertainty of duration, for its action lasts sufficiently long to allow slow administration, which is important in teaching residents, and to perform prolonged procedures without haste on the part of the surgeon. In addition, the busy anesthesiologist can perform the block when it is most convenient for him, even if it is necessary to administer it one or two hours before operation. This increased duration of analgesia is also of great value in therapeutic blocks in which the prolonged action obviates more frequent injections and eliminates the use of the undependable oil preparations. These advantages of tetracaine, initially appreciated by the early German investigators, have been repeatedly demonstrated and emphasized by most laboratory and clinical investigators who, in addition, have shown that in doses used for clinical analgesia, tetracaine is no more toxic than procaine, and some believe that it is less so. Certainly, the general opinion that this drug is too

toxic to employ for infiltration and block analgesia is not founded upon either laboratory or clinical evidence. After a careful review and analysis of the literature and personal experience with over 4000 cases, I am unable to determine why such misconceptions exist which, for the past twenty years, have deprived patients, surgeons and anesthesiologists of the advantages of prolonged tetracaine analgesia. One possible explanation may be that experimental results in animals have not been properly analyzed and clinicians have made little effort either to confirm or to refute them by trial on human beings, which in the final analysis is the most important method of testing drugs. Some clinicians have considered only the absolute toxicity of tetracaine and have often quoted these figures when discussing this drug or disputing its use as a substitute for procaine regional analgesia. It is, of course, true that in equal milligram doses tetracaine is much more toxic but, as has been repeatedly pointed out, it can be used in much smaller doses which actually afford better analgesia and less toxicity. It is also true that reports have appeared in the literature regarding severe toxic reactions and fatalities which have occurred during topical application and subarachnoid injection of tetracaine (104-110) but none can be found in regard to its use in infiltration and block analgesia. I am of the opinion that several factors have played a major role in causing such reactions and, of these, overdosage is probably the most important. I have not infrequently witnessed the topical administration of $1\frac{1}{2}$ to 2 ounces of 2 per cent tetracaine (800 to 1200 mg.) without epinephrine prior to endoscopy. This drug without a vasoconstrictor is a powerful vasodilator and when it is applied to a vascular area such as the mucous membrane, it is absorbed very rapidly and, if large amounts are employed, toxic reactions may occur. Greater care, therefore, should be utilized when applying this or any other drug to mucous membranes of the nose, throat, tracheobronchial tree and urethra, a fact which has been strongly emphasized by many authors, including Bieter (19), Adám (28, 29) and Mayer (111). Fatalities which have occurred during spinal anesthesia most likely have been the result of intercostal and diaphragmatic paralysis as shown by CoTui (44), Bieter (19, 45) and many others, and, therefore, cannot be considered as true toxic reactions.

The conspicuous absence of fatalities of severe reactions among the 40,000 or more cases found in the literature and the 4000 cases herein reported has thoroughly convinced us that, if tetracaine is administered properly, its toxicity is not greater than any other local drug and, therefore, it may be employed for infiltration and block analgesia without fear.

SUMMARY AND CONCLUSION

In an effort to assess the efficacy, toxicity and other physical, chemical and pharmacologic properties of tetracaine for its use in infiltration

and block analgesia, the entire known literature on this subject has been reviewed.

The literature of the laboratory investigations reveals that tetracaine has an anesthetic potency greater than 1 and a corrected toxicity ratio of less than 1 when it is compared to the standard drugs, procaine and cocaine. This is further corroborated by many publications on the clinical use for infiltration and block analgesia.

An analysis of the use of this drug for 4082 regional anesthetic procedures administered to 2913 patients by the author and his associates during a three-year period has been presented. It has been shown that the drug is useful in administering a variety of regional procedures for many operations.

The anesthetic properties and toxicity have been investigated in 735 cases with conditions which have been controlled as well as they can possibly be clinically. In a small group the potency has been studied by the intracutaneous method and the toxicity by the intravenous method. The results obtained are in accord with those obtained by the many laboratory and clinical investigators who have studied tetracaine. These results indicate that this drug is approximately six to ten times as toxic, but also ten to fifteen times as potent as procaine. When used in one-tenth the dose of procaine, tetracaine affords anesthesia which lasts two to three times as long without exerting any toxic effects provided, of course, that it is administered properly.

It must be reemphasized that this drug is a powerful agent and for clinical practice it should be used in dilute solutions with the total dose never exceeding 1 mg. per pound of body weight. Toxic reactions occur from overdosage and are the same as those which occur with procaine and, if treated properly, will cause no complications. Tetracaine appears to have a wide margin between the toxic and the lethal dose and respiration always fails before circulation fails.

In view of these findings I believe that tetracaine merits more use by other clinicians so that many more cases can be accumulated to confirm its usefulness.

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THE CONNECTICUT STATE SOCIETY OF ANESTHESIA: NOTICE OF MEETING

The Connecticut State Society of Anesthesia will hold its quarterly meeting on December 13, 1950 at 8:00 p.m. at the University Club in Bridgeport, Connecticut. Dr. Charles Burstein, Director of Anesthesiology at the Hospital for Special Surgery, and Assoc. Professor of Anesthesiology at New York University Medical School, will be the guest speaker. His topic will be "The Value of Electrocardiography During Anesthesia."