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Comparison of length of anesthesia using the vasoconstrictors : epinephrine and phenylephrine with procaine, carbocaine, and lidocaine

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COMPARISON OF LENGTH OF ANESTHESIA USING THE VASOCONSTRICTORS, EPINEPHRINE AND PHENYLEPHRINE, WITH PROCAINE, CARBOCAINE, AND LIDOCAINE

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I. INTRODUCTION

A. Background of local anesthetics.

In a list of medical discoveries which have greatly influenced the course of medical practice one would surely have to include the discovery of local anesthetics.

Niemann was the first to observe in 1860 that an alkaloid, cocaine, when placed on the tongue, caused a sensation of numbness. Although other pioneers are mentioned in connection with experiments with cocaine, it remained for Sigmund Freud and Karl Koller in 1884 to develop the practical application of cocaine as a local anesthetic to medical practice. A short time later Halstead in the United States started investigations which led to the discovery of nerve blocks. In 1905 Einhorn introduced procaine, a synthetic local anesthetic which displayed less toxicity than cocaine and did not promote addiction. Since then, numerous local anesthetics have been synthesized, displaying various degrees of anesthesia, toxicity and duration of action.

Many of the common local anesthetics are esters of amino alcohols and aminobenzoic acid. When injected they are in an ionized form. In this form they are transported to the nerve tissue where the alkaline environment changes the drug

* Carbocaine is the trade name of Winthrop Laboratories for mepivacaine.

to an un-ionized form.[2] Although the mechanism of action of local anesthetics isn't completely understood it is thought that this un-ionized form depolarizes the nerve membrane so that conduction is interrupted. Thus, poor anesthesia is obtained in an infected area because of the acidic environment which keeps the anesthetic ionized. Pain disappears first, then cold, warmth, touch and deep pressure.

It has been noted that the time required for induction of a blockage by a particular drug varies inversely with the concentration of the drug and directly with the square of the radius of the nerve. However, duration of anesthesia is usually affected by concentration also, with the higher concentrations lasting longer than the very dilute solutions. Above certain concentrations (which are actually quite dilute solutions) no practical increase in anesthesia is obtained but increased toxicity with danger to the patient is found.

Most local anesthetics do have certain toxic actions which can produce very serious effects on the patient when used incorrectly. Local toxicity is demonstrated by the damage to tissue due to the effects of the drug at the site of injection. Systemic toxicity is manifest by reactions which are usually due to an increased blood concentration of the anesthetic. This can be caused by giving too great a quantity of anesthetic, too rapid absorption, giving the anesthetic intravascularly, or

insufficient destruction of the anesthetic. A few reactions have been explained on a hypersensitivity and anaphylactoid basis.

One means of better controlling absorption of local anesthetics has been the addition of vasoconstrictor substances to the anesthetic. This causes local vasoconstriction of the vessels, slowing down spread and absorption of the anesthetic. It permits the use of less anesthetic and makes possible more intense and more prolonged anesthesia without an increase in quantity of anesthetic. This results in a decrease in severity and frequency of toxic symptoms due to absorbed anesthetic agents.

Campbell and Adriani[4] found that using 1:100,000 epinephrine with procaine decreased certain signs of toxicity from the procaine by 30%. The optimal concentration of epinephrine to use with local anesthetics was studied by Keesling and Hinds[14] who noted that a solution of 1/250,000 epinephrine was as effective in increasing depth and duration of anesthesia as 1/50,000 or 1/100,000 concentrations. (Lidocaine was the only anesthetic used).

Another advantage to a vasopressor in a local anesthetic is that it decreases hemorrhage at the site of an operation or laceration.

Disadvantages of using a vasoconstrictor could probably be listed as:

1. Danger to tissues if injected into an area with a blood supply consisting of end arteries.

2. Danger of too much epinephrine being mixed with the anesthetic and causing toxic symptoms.

3. Inconvenience of adding a second drug to the local anesthetic being used.

4. Contraindications: Hypertension, severe arteriosclerosis, pheochromocytoma, and thyrotoxicosis.

B. Drug Description.

1. Procaine.

Of the three local anesthetic agents used in this study, procaine is the most common. It is an amino ester made from an amino alcohol and para-amino benzoic acid and is soluble in water to the extent of 1 gram in 1 cc. of water. It is still probably the most widely used of currently available local anesthetics. Procaine produces fairly good anesthesia and has little toxicity except in larger doses. It is not very effective as a topical anesthetic as it is poorly absorbed from the mucous membranes. Procaine is used as the standard for toxicity and potency in comparing injectable anesthetics. A rate of about 1 gram per hour appears to be tolerated by man.

Usually 1 or 2 per cent solutions are used but 4 per cent is used for some dental extractions.

2. Lidocaine.

Lidocaine (Xylocaine®)* was synthesized by Loefgren in 1943 and is readily water soluble and stable. It was derived from

* Xylocaine is the trade name used by Astra Pharmaceutical Products, Inc., for lidocaine.

acetanilide and is somewhat greater in toxicity and potency than procaine. Maximum doses per injection is generally thought today as one half of that for procaine, or 500 mg. It is effective topically on mucous membranes whereas procaine is not. Lidocaine is usually used in one half to two per cent solutions for infiltration.

3. Carbocaine.

Carbocaine is a comparatively new local anesthetic synthesized in 1956. It has a greater potency and it seems to be less irritating than procaine. Luduena[16] and his group found that carbocaine had twice the duration of action of lidocaine. He also found that carbocaine injected into mice was twice as toxic as procaine but was less toxic than lidocaine. Maximum dose per injection in man is presently recommended at 500-750 mg.

4. Epinephrine (Adrenaline®, Supararenin®)*

This is a substance which is produced in the body by the adrenal medulla. It is also synthetically made in the laboratory. It's action is adrenergic: constriction of most arteries and veins, constriction of mucous membranes, cardio acceleration, relaxed bronchi, etc.

Administration is usually parenteral as there is poor response when administered orally.

Inactivation is usually quite rapid and is thought to be accomplished through several enzyme systems capable of

* Adrenaline is Parke Davis trade name and Suprarenin is the Winthrop trade name for epinephrine solutions.

inactivating the dehydroxyphenyl adrenergic amines.

This is a very potent drug and usual therapeutic doses will produce minor toxic symptoms (anxiety, tremor, headache, palpitations). These do not usually last long and are not thought to be dangerous. Overdosage produces toxic effects which can be fatal, however. These include cerebrovascular hemorrhage produced from the elevated arterial pressure, pulmonary edema from pulmonary arterial hypertension, and ventricular hyperirritability. Dose for any parenteral route other than intravenous is 1 mg. or less. With local anesthetics the concentration of epinephrine is usually 1:100,000 or 1:200,000, although in dental practice a concentration of 1:60,000 is often used.

5. Phenylephrine (Neo-Synephrine®)*

This vasopressor drug is less potent than levarterenal and has a little longer duration of action. Parenteral administration in humans produces peripheral vasoconstriction, increased arterial pressure, and reflex bradycardia. It does not stimulate cardiac tissue to the degree that epinephrine does nor does it produce central stimulation.

Doses often advocated are: 0.5 mg. intravenously, 5 mg. subcutaneously, or 250 mg. orally. In local anesthetics it is used in concentrations of 1:2500 to 1:54,000.

* Neo-Synephrine is the trade name of the Winthrop Laboratories for phenylephrine.

II. PURPOSES OF STUDY

The effects of local anesthetics in inhibiting pain has been studied on nerve specimens, animals and man. Although experiments on laboratory animals and specimens usually produce more accurate values and afford more reliable duplication of results, the findings do not necessarily apply to man. Pain is a subjective phenomenon which is very difficult to study in animals. Therefore, any final test of pain inhibiting drug which is to be used primarily on humans must ultimately be tested on humans.

The purpose of this study was first to compare the length of anesthesia of three local anesthetics; procaine, lidocaine and carbocaine. The second purpose was to compare the three local anesthetics without a vasoconstrictor to similar solutions with (a) epinephrine and (b) phenylephrine added. A third comparison to be noted is what differences, if any, exist between local anesthetics with epinephrine added and anesthetics with phenylephrine added. Interest here is focused particularly on the use of phenylephrine, as this is not commonly used with local anesthetics. Epinephrine is the main vasoconstrictor used with local anesthetics.

III. METHOD

Early in the study, it was hoped that we could use a small electric nerve stimulator with a method of injecting materials around the nerve which was to be blocked. However, this necessitated 10 different injections into the area around the same nerve, each of which required considerable time as well as a danger of injury to the nerve with so many injections.

Therefore, we decided to use intracutaneous injections into the anterior surface of the forearms.

A. Test substances (10 different items)

1. Procaine, lidocaine, carbocaine, 1% solutions.
2. Procaine, lidocaine, carbocaine, 1% solutions with 1:200,000 epinephrine added.
3. Procaine, lidocaine, carbocaine, 1% solutions with 1:25,000 phenylephrine added.
4. Saline, normal.

These test drugs were prepared by Dr. J. Jones and placed in bottles which had only an alphabetic letter on them. The exact contents of each bottle was known only to Dr. Jones until the study was completed. The pH of each test drug was determined before and after testing with little change noted.

B. Procedure

One milliliter from each bottle was injected, subcutaneously, using 25 gauge needles, into a cleaned area on the anterior forearms of each volunteer, care being taken that the injection

sites were properly spaced to avoid overlapping of anesthesia. Each wheal was marked with the letter indicating which test drug had been injected. The same drugs were not used in exactly the same areas on each volunteer but were rotated around the various areas.

C. Testing the degree of anesthesia.

Each volunteer was given essentially the same amount of information about the study and instructions they were to follow. None of them knew what were in the test bottles. Each volunteer was asked to check the various test sites every 5 minutes in order to ascertain when the anesthesia wore off. They were instructed to use 25 gauge needles in testing for loss of pain and to use approximately the same amount of pressure on each test site in determining anesthesia. Mimeographed sheets were made and on which the volunteers marked the (a) time when the injection was made; (b) time of onset of anesthesia; (c) time when some pain first came back into the area and (d) that time when pain sensation had completely returned.

Any toxic signs or symptoms, whether local or of a more systemic nature, were to be noted.

IV. RESULTS AND DISCUSSION

Anesthesia was almost invariably complete immediately after the injection of one milliliter of the test drug. The area of anesthesia was usually limited to the area of the original wheal formation.

When 2 milliliters of test drug was used, considerable overlapping of anesthesia was noted, particularly distal to the wheal. Also greater burning was noted upon injection of the drug. Therefore, 1 milliliter was used throughout the study.

The length of time from the onset of anesthesia until the first detectable pain sensation was noted in each case and an average length of anesthesia in minutes determined for each test drug (Table I). When these are compared with the average length of anesthesia from onset until complete return of pain sensation to pin prick (Table 2), it is noted that most volunteers detected some return of pain from 20 to 60 minutes before pain sensation had completely returned. This is indicative of the diffusion of the anesthetic into the tissues and blood stream and gradual return of normal function to the nervous tissue involved.

Table 2 gives the range of values as well as the mean anesthesia time for each test drug. These values are the number of minutes from onset of anesthesia until complete return of pain sensation to pin prick.

A comparison of the average length of anesthesia of procaine, carbocaine, and lidocaine show that anesthesia lasted about 66% longer in the cases of lidocaine and carbocaine over procaine.

However the range of values was considerably wider with lidocaine and carbocaine. This does not agree with Luduena[16] and his group who found that carbocaine had twice the duration of action of lidocaine. Lidocaine is thought to be about twice as potent as procaine. Our results show procaine with a mean length of anesthesia of 61.5 minutes and lidocaine with a mean length of anesthesia of 102.6 minutes.

When epinephrine was added to carbocaine a 50% increase in the average length of anesthesia time was noted. In comparing carbocaine with epinephrine and carbocaine without epinephrine, we have a standard error of the difference between the two means of 17.4 minutes and a relative deviate of 2.76. This shows we are out on the far sides of our distribution curve a distance of 2.76 standard errors. In a normal distribution 99% of the values lie within 2.6 standard errors of the mean. This would give us a probability (P) of less than 0.01, in which case we can conclude that something other than chance caused the difference in our two samples. In this case the presence of epinephrine is the one known differing factor and we can conclude that it probably caused the increased length of anesthesia time.

Procaine with epinephrine added showed a mean anesthesia time increase from 61.5 minutes to 214.0 minutes. Comparing the procaine with epinephrine (test item) with the procaine without epinephrine (control sample) we find that our relative deviate is 4.8 which statistically is very significant. (When out 3

standard errors from the mean, 99.73% of the values are included). Here also we can conclude that random sampling or chance couldn't have caused this large a variation between the two test items.

Lidocaine with epinephrine showed about 100% increase in mean anesthesia time. However, there was a wide dispersion of the values so that there was a standard error of the mean of 42 minutes with a standard error of the difference between the 2 means (lidocaine with and without epinephrine) of 46.0 minutes. The relative deviate was 2.3 which would give a probability of about 0.03. (When out two standard errors you are at the 95 percentile and have a probability of 0.05 which has borderline significance). A probability of 0.03 is statistically significant and we would conclude that the epinephrine added to the lidocaine probably caused the increase in anesthesia time.

When phenylephrine was added to carbocaine the mean anesthesia time increased from 103.5 minutes to 238.7 minutes. The relative deviate was 6.5 which is very significant statistically.

Procaine with phenylephrine added increased very little in mean anesthesia time (61.5 to 76.7). In comparing procaine with and without phenylephrine the relative deviate was 1.36. This would be about the 75th percentile. Thus, in future samples of these test items there would be 25% of them with differences as great as or greater than those in our actual study and could be due to chance. Therefore, the small increase in mean anesthesia time observed with the phenylephrine added to the procaine is not

statistically significant and could be due to chance.

Lidocaine increased in mean anesthesia time from 102.6 minutes to 220.4 minutes with phenylephrine added. It had a relative deviate of 4.03 which indicates that this difference in anesthesia time between the lidocaine containing phenylephrine and the lidocaine without phenylephrine is significant and is probably due to the phenylephrine and not due to chance.

In comparing the two vasoconstrictors used in this study, it can be seen that when added to lidocaine the mean anesthesia times are about the same but the range of values of the lidocaine and epinephrine causes it to have less statistical significance than the lidocaine with phenylephrine added.

The large difference in mean anesthesia time between the two vasoconstrictors added to procaine has already been mentioned. The lack of response of phenylephrine with procaine will have to remain unexplained for the present.

Carbocaine with phenylephrine showed a significantly longer mean anesthesia time than when epinephrine was added. Further studies involving various concentrations of these two vasoconstrictors as well as different concentrations of the anesthetics would help in explaining differences noted in mean anesthesia time. No similar studies using phenylephrine with local anesthetics were found in order to compare results. One volunteer had anesthesia of the area in which normal saline was injected. This could have been caused by injecting the saline around the cutaneous nerve

supplying this area with enough pressure to cause a disruption of nerve impulses. His anesthesia lasted for 101 minutes. When this test was repeated a few weeks later he experienced no anesthesia.

No systemic reaction to the test items were noted. The only local "reactions" noted were small red papules on certain wheals of some volunteers. No consistency involving certain test drugs causing these small red papules was noted.

V. CONCLUSIONS

Lidocaine and carbocaine exhibited about a 70% greater mean anesthesia time than procaine. These two anesthetics (lidocaine and carbocaine) had mean anesthesia times which were within one minute of each other indicating similar potency at these concentrations and for subcutaneous injections.

When epinephrine was added to the local anesthetics, they all had significant increases in duration of anesthesia, although larger increases were noted with lidocaine and procaine, the latter not being statistically as significant due to the wide range of the observations.

Phenylephrine is not considered as potent a vasoconstrictor as epinephrine but significant increases in duration of anesthesia were noted when phenylephrine was added to carbocaine and lidocaine. The mean anesthesia time of the carbocaine and phenylephrine was about 50% more than when epinephrine was added to the carbocaine. The reason for phenylephrine producing these results with carbocaine but causing little increase in duration of anesthesia when added to procaine remains unexplained.

From this study we can conclude that phenylephrine added to carbocaine or lidocaine (in the amounts used) does as well in prolonging local anesthesia time as when epinephrine is added as the vasoconstrictor. It also can be concluded that little, if any, change is noted in duration of anesthesia when phenylephrine is added to procaine.

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The use of epinephrine, of necessity, must be limited in patients with hypertension, arteriosclerosis, cardiac arrhythmias, angina, coronary thrombosis and diseases of hypermetabolism such as thyrotoxicosis. The fact that phenylephrine prolonged the anesthesia time as long as epinephrine indicates that the local anesthetic is not absorbed any faster with the former vasopressor as with the latter. This would indicate that phenylephrine should be used in place of epinephrine in patients with the before mentioned disease states.

Further investigations should include larger populations as well as using different and varied concentrations of the vasoconstrictors and the anesthetics. As was stated earlier, pain is a subjective finding, the detection and degree of which is difficult to determine and evaluate. If changes in pain sensation are carefully noted and recorded however, statistically significant data can be obtained.

SUMMARY

It has been known for many years that vasoconstrictors prolong the duration of anesthesia when added to local anesthetics. However, there are few studies involving specific anesthetics with specific vasoconstrictors and their effect on humans. Epinephrine is the vasoconstrictor usually used with local anesthetics. Other vasoconstrictors are rarely used for this purpose.

The object of this study was to find out what differences existed between three local anesthetics, procaine, lidocaine and carbocaine as to duration of anesthesia, both with and without vasoconstrictors added. Using two different vasoconstrictors, epinephrine and phenylephrine, a further comparison could then be drawn between these two for effectiveness in prolonging anesthesia.

The method consisted of intracutaneous injections in the forearms of ten volunteers who then measured degree and length of anesthesia by checking for pain by pin prick. Ten injections of 1 cc. each were made on each volunteer; a 1% solution of each anesthetic (procaine, lidocaine and carbocaine), a 1% solution of each anesthetic with 1/200,000 epinephrine added, 1% solutions of each anesthetic with 1/25,000 phenylephrine added, and an injection consisting of 1 cc. of normal saline.

Lidocaine (102.6 minutes) and carbocaine (103.5 minutes) had about twice the mean anesthesia time as procaine.

When epinephrine was added, an increase of mean anesthesia

time ranged from a 50% increase for carbocaine to a 250% increase for procaine. Lidocaine with epinephrine had a marked increase in mean anesthesia time but the values fell over such a wide range that its statistical significance was not as great as when procaine and carbocaine solutions with epinephrine were compared to solutions without epinephrine.

Procaine with phenylephrine showed little increase in mean anesthesia time. Lidocaine and carbocaine however, showed increases in duration of anesthesia time as great or greater than when epinephrine was used. These were also statistically significant.

This study indicates that phenylephrine, when used with lidocaine or carbocaine and in the concentrations used in this study, would perform as well as epinephrine and would be particularly useful with those patients who have hypertension, thyrotoxicosis, arteriosclerosis and other disease states in which the use of epinephrine is rather limited.

ACKNOWLEDGEMENTS

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Typing and clerical work were done by Connie French and my wife, Donna, of which I am very grateful.

A final acknowledgement would be to the volunteers who endured both needles and intrusions on their busy schedules. Any accuracy of our data is a reflection of the carefulness and dedication with which they carried out their part of the project.

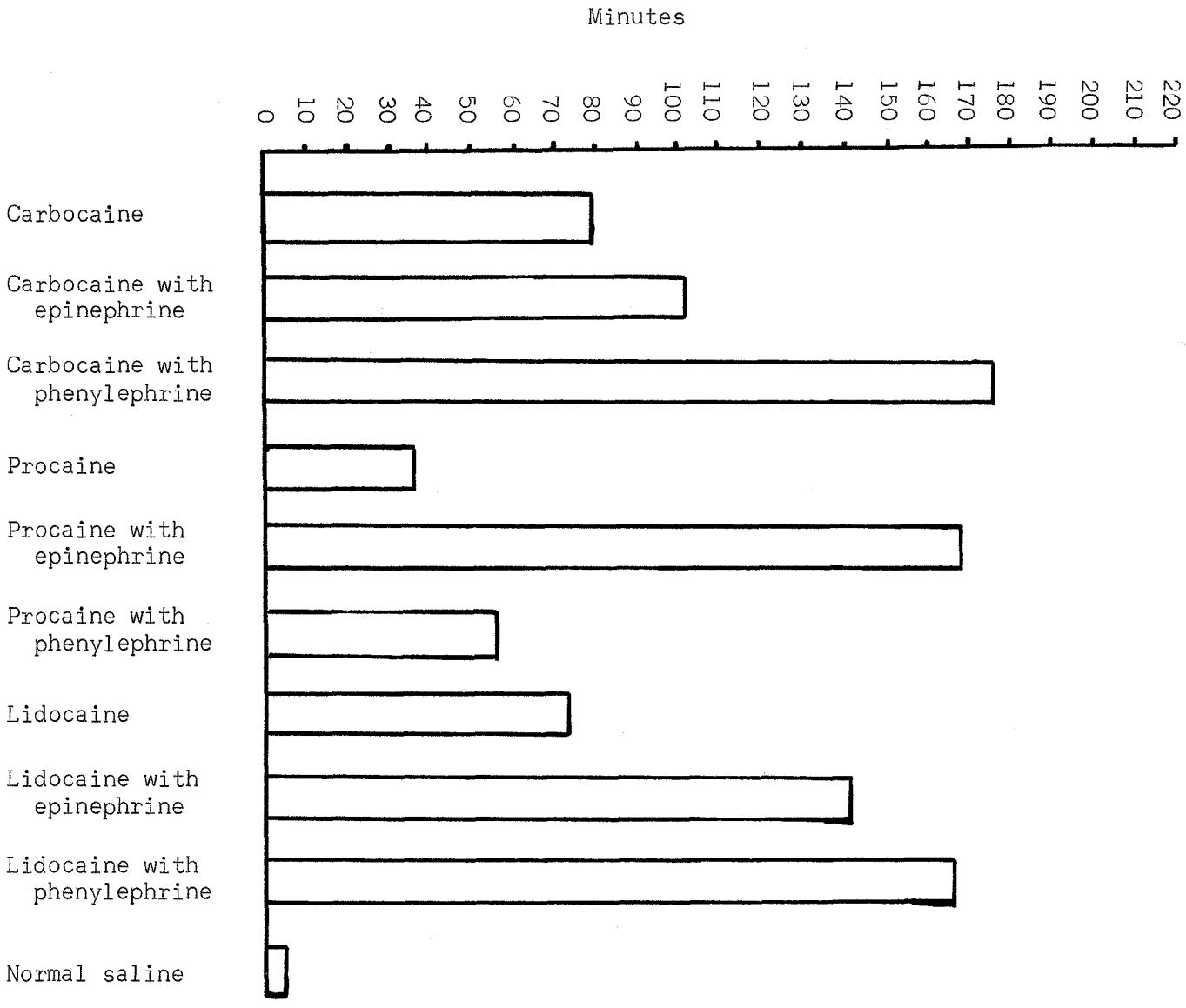

TABLE 1. Average length of anesthesia in minutes from onset of anesthesia until the first detectable pain sensation to pin prick.

Test Drugs	Range of Values	Mean (min.)
Carbocaine	36 - 151 (min.)	103.5
Carbocaine with epinephrine	65 - 226	152.0
Carbocaine with phenylephrine	136 - 317	238.7
Procaine	35 - 92	61.5
Procaine with epinephrine	94 - 426	214.0
Procaine with phenylephrine	37 - 119	76.7
Lidocaine	33 - 179	102.6
Lidocaine with epinephrine	68 - 444	209.8
Lidocaine with phenylephrine	105 - 327	220.4
Normal saline	0 - 104	12.6

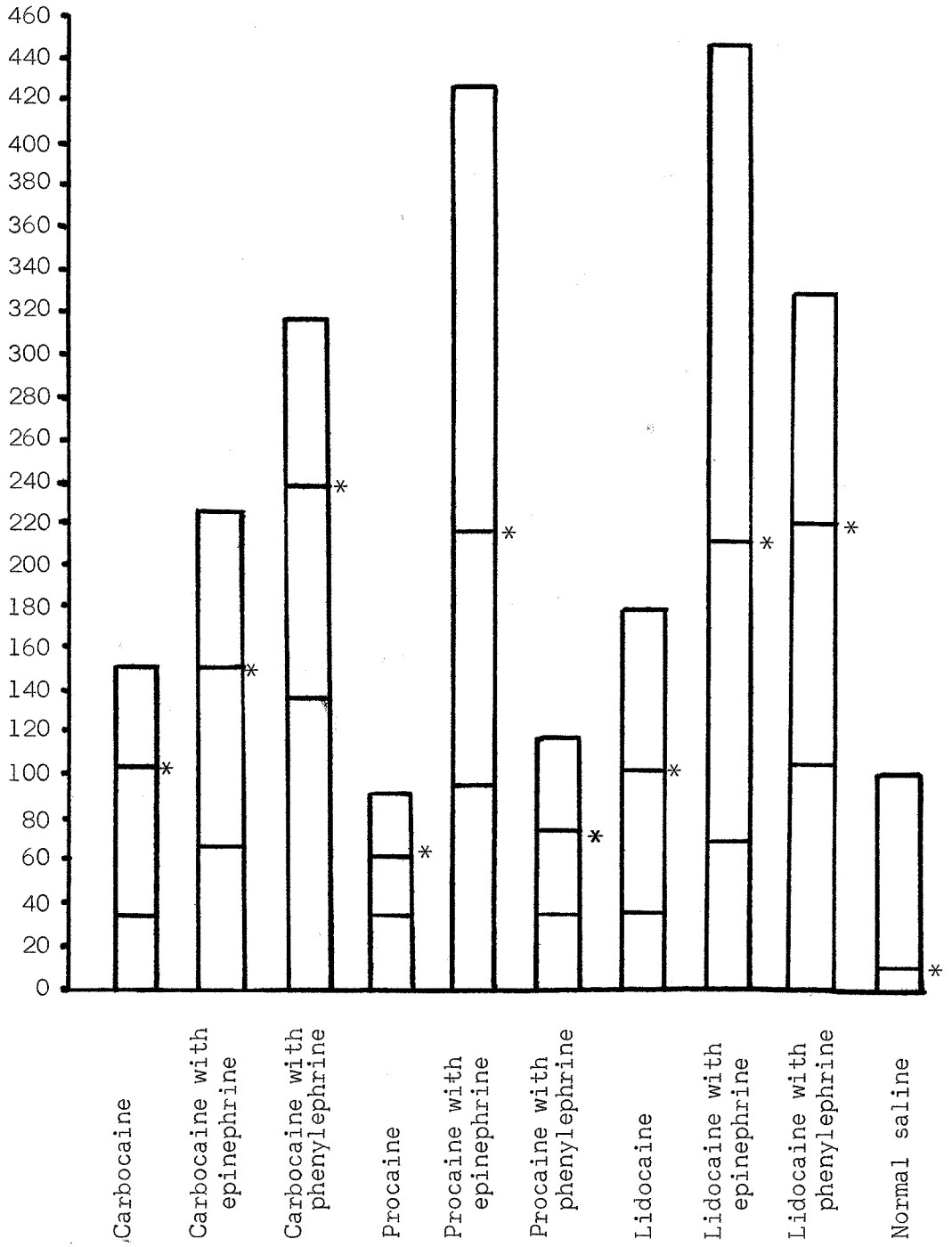

TABLE 2. Length of anesthesia in minutes from onset of anesthesia until complete return of pain sensation to pin prick. (Range of values and mean* for each drug given in table and graph form).

	Mean	Standard Deviation	Standard Error of the Mean	Standard Error of the Difference Between Means	Relative Deviate
Procaine	61.5	20.5	6.5	31.3	4.8
Procaine with epinephrine	214.0	96.4	31.0		
Lidocaine	102.6	58.4	18.7	46.0	2.3
Lidocaine with epinephrine	209.8	130.3	41.9		
Carbocaine	103.5	37.1	12.0	17.4	2.76
Carbocaine with epinephrine	152.0	40.1	12.9		
Procaine	61.5	20.5	6.5	11.0	1.36
Procaine with phenylephrine	76.7	27.4	8.7		
Lidocaine	102.6	58.4	18.7	29.0	4.03
Lidocaine with phenylephrine	220.4	69.3	22.3		
Carbocaine	103.5	37.1	12.0	21.3	6.5
Carbocaine with phenylephrine	238.7	56.0	18.1		

TABLE 3. Statistical Data (mean, standard deviation, standard error of the mean, standard error of the difference between two means are all given in minutes).

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