A COMPARISON OF DEPTH OF ANESTHESIA AND TOXICITY OF 2 AND 4 PER CENT PROCAINE HYDROCHLORIDE SOLUTIONS

by

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INTRODUCTION

Procaine with added vasoconstrictor agent is capable of providing satisfactory anesthesia for operative and surgical procedures in dentistry and possesses less toxicity than most other compounds. The question of the optimal concentration of the drug to be used in dentistry is still being argued. Following Mayer's[1] recommendation of 1924 that 1 per cent procaine was the highest feasible concentration the Council on Pharmacy and Chemistry of the American Medical Association has recommended in its New and Nonofficial Remedies the use of procaine solutions not stronger than ½ per cent for infiltration anesthesia. The Council on Dental Therapeutics[2],[3] has held for many years that no solutions of procaine stronger than 2 per cent ought to be used in dentistry routinely; this stand somewhat contradicts the recommendation of the N.N.R.

There are many occasions where the 2 per cent solution proves ineffective in dentistry[4],[5] and it would seem logical to obtain better anesthesia by increasing the concentration. However fears are expressed that the use of a stronger solution, for instance of 4 per cent, would be more likely to provoke reactions or cause irritation or damage to the tissues. On the other hand, evidence has accumulated in the past tending to show that 4 per cent solutions may be used safely and with distinct

advantages in certain instances(6),(7),(8),(9). The author believes, on the basis of clinical experience that there are definite indications for the use of the stronger procaine concentration. It would appear desirable to use procaine solutions of 2 different strength in routine dental practice, probably 2 per cent and 4 per cent. The 4 per cent solution of procaine has been selected as the strongest suitable for dental anesthesia since it is the highest concentration which, allowing for added vasoconstrictor, does not become hypertonic.

Review of the recent literature on procaine suggests the need for a careful and objective reappraisal of this problem, particularly in view of newer knowledge of the intravenous administration and toxicity of procaine(10),(11),(12). The necessary steps in such an evaluation would be: (a) an objective estimation of the completeness or depth of pulpal anesthesia following the administration of the 2 and 4 per cent solutions in search of measureable advantages of the higher concentration, and (b) an investigation of the influence of varying concentrations of procaine on its toxicity.

PART I

EFFECTIVENESS OR DEPTH OF ANESTHESIA OF 2 AND 4 PER CENT PROCAINE HYDROCHLORIDE SOLUTIONS AS USED FOR PULPAL ANESTHESIA BY SUBMUCOUS MAXILLARY INFILTRATION.

The experimental approach in such an evaluation would involve the measurement of two elements. The first is the alteration in the rapidity of onset and the duration of anesthesia produced by varying strengths of procaine. This has been rather thoroughly studied(13),(14),(15),(16), as has been the influence of added vasoconstrictors on these factors(17),(18),(19),(20),(21),(22). The other factor is depth or completeness of anesthesia. Since neither time of onset nor duration of action necessarily parallel the depth of local anesthesia, it was decided to attempt to measure this latter variable.

EXPERIMENTAL

Several new experimental procedures for comparing the effectiveness of analgesic agents have been introduced recently. One of these is the determination of the changes in the strength of electric shocks required to elicit a response when applied to an amalgam filled tooth of a dog(23). Since it was desired to compare the effectiveness of various concentrations of local anesthetic agents given by submucous infiltration to produce dental pulp

anesthesia, the following procedure for testing the depth of anesthesia was devised.

Healthy adult dogs of either sex were used. The animal was lightly anesthetized with an intravenous injection of 20.6 mg. per kilogram bodyweight of sodium pentobarbital, a dose fortified by small repeated injections as necessary. The dog was then strapped on its back on a board and its mouth kept open by a prop. Shallow occlusal cavities were then drilled in two homologous teeth of the upper arch, using either canines or molars. The cavities were filled with a conductive paste and then tested using a weak tetanizing current. The circuit was arranged with a large indifferent electrode applied to the shaved chest and the stimulating electrode to the cavity. The strength of the stimulus was varied so as to elicit a minimal objective response (threshold) by changing the distance of the sliding secondary coil from the fixed primary coil of the Harvard Inductorium. This distance is measured by a scale graduated from 0 to 11 cms. provided on one of the sliding bars of the inductorium, where the greater the distance the secondary coil is set from the primary, the less the intensity of the stimulus.

The response observed with the threshold stimulus was a slight twitching of the skin of the lower jaw as far down as the clavicle. With increase in current, this

response became more marked, with more muscles contracting. The depth of the two cavities was varied until similar minimal responses were elicited on stimulation of either side. The strength of current required, read from the inductorium, was recorded as the control threshold value.

Submucous infiltration was next performed on each side, using 2 per cent procaine with neosynephrine 1:2,500 on one side, and 4 per cent procaine with the same concentration of vasoconstrictor on the opposite side. Two cc. of each strength solution per 100 lbs. bodyweight were used, an amount comparable with that used clinically. Each cavity was then retested, and the strength of stimulus increased, if necessary, until a response was noted on one or both sides. Tests were made at intervals of 5 minutes following injection and continued for one hour. The minimal strength of current required to elicit a threshold response in one or the other tooth was recorded according to the reading on the inductorium and, further, the intensity of the response noted on stimulating either tooth was arbitrarily graded as 1, 2 or 3 plus. Eight such experiments were performed.

RESULTS

Table 1 records the results of a typical experiment. In this dog the cavities in both teeth were prepared to

such a depth as to give an equal minimal (1 plus) response when a very weak tetanizing current was used, found by setting the inductorium coil at 8.5 cms. Following submucous periapical injection of both procaine solutions, a 1 plus response was obtained for both teeth at 6.5 cms. for the first 5 minute period. At 10 minutes after injection a minimal 1 plus response was noted for the 4 per cent solution and a 2 plus response for the 2 per cent strength with a further increase in current intensity to a reading of 4.5 cms. The results obtained for each 5 minute test period show that in every trial except the first after injection, significantly less response was noted from the tooth blocked with 4 per cent procaine.

TABLE I

DOG EXPERIMENT #6, Female Black Mongrel. Wt. 23 lbs. Date: 8/28/47. Given 3½ cc. of Sodium Pentobarbital at 1:42 P.M.

TIME P.M.	PERIOD AFTER INJEC-TION	ESTIMATED RESPONSE FOLLOWING PERIAPICAL INJECTION OF PROCAINE HCl U.R. TOOTH #6 U.L. 4% PROCAINE 2%	INDUCTORIUM READING
	(mins.)		(cms.)
1:54	-	Control Control	8.5
1:59	(INJECTION)	- -	-
2:04	5	1+ 1+	6.5
2:09	10	2+ 1+	4.5
2:14	15	3+ 1+	4.
2:19	20	3+ 1+	4.
2:24	25	3+ 1+	4.
2:29	30	2+ 1+	5.5
2:34	35	2+ 1+	6.5
2:39	40	2+ 1+	7.
2:44	45	2+ 1+	7.5
2:49	50	2+ 1+	7.5
2:54	55	2+ 1+	8.
2:59	60	2+ 1+	8.

Table 2 summarizes the eight experiments. The amounts listed in the column under each concentration of procaine represent the total sum of the arbitrarily graded responses for all of the dog experiments for each five minute period. For example, when each of the eight dogs were tested on the side receiving 4 per cent procaine at 10 minutes after injection, 5 dogs showed a response of 1 plus, another 2 plus and two dogs showed no response thus making an aggregate of plus 7. This sum was compared with the sum of plus marks for the other solutions at the identical time after injection.

An attempt has been made in the last column of Table 2 to present quantitatively a one figure ratio of the depth of anesthesia produced by the two procaine solutions. This ratio has been obtained by using the formula $D = \frac{B}{A}$ where B = sum of graded response for 8 dogs with 4 per cent procaine and A = sum of graded response of 8 dogs with 2 per cent procaine and D = the relative superiority of depth of anesthesia obtained with the stronger solution. Judged by this evaluation, the ratio was always higher than 1.33 in favor of the 4 per cent solution and at 20 and 25 minutes after injection it was greater than three.

While we do not have positive knowledge that the dogs actually suffered pain through stimulation from the active electrode their responses, when positive, permitted the conclusion that conduction through the "blocked" nerve

was occurring, and would have produced pain in a conscious animal. We were aware also that there exists a question as to whether conclusions based solely upon the reactions of animals to a particular stimulus constitute a sufficient index for the degree of anesthesia[24]. To determine whether our findings could be corroborated in human patients the following clinical tests were performed.

TABLE 2

SUMMARY OF RESULTS COMPARING DEPTH OF PULPAL ANESTHESIA OBTAINED WITH 2 AND 4 PER CENT PROCAINE HYDROCHLORIDE IN EIGHT DOGS.

PERIOD TESTED AFTER INJECTION (MINS.)	SUM OF ARBITRARY RESPONSE UNITS AFTER INJECTION OF 4% PROCAINE HCl	SUM OF ARBITRARY RESPONSE UNITS AFTER INJECTION OF 2% PROCAINE HCl	RATIO OF DEPTH OF ANESTHESIA
5	6	8	1.33
10	7	14	2.00
15	7	13	1.85
20	5	16	3.20
25	5	16	3.20
30	7	19	2.71
35	6	16	2.66
40	6	18	3.00
45	6	15	2.50
50	6	17	2.83
55	8	16	2.00
60	8	17	2.12

CLINICAL TESTS IN HUMAN PATIENTS

Volunteers were selected that had in their upper arch homologous vital teeth that were to be extracted in the course of prosthetic restoration. Cuspids or teeth posterior to cuspids were used to avoid overlap of the field of anesthesia. The teeth were radiographed and then prepared for a test in a manner similar to that described in the animal experiments with some minor points of difference in the arrangement.

(1) No barbiturates were used preliminarily.

(2) The indifferent electrode was connected with the palm of the patient's hand.

(3) Volume of solution used was 1 cc. for each 100 lbs. of patient's bodyweight.

(4) We tested preliminarily and after injection every 5 minutes for bare perception of stimulation and then, immediately afterwards, for slight but definite pain.

Nine such experiments have been run. Solutions used were the same as in the animal experiments, that is, procaine hydrochloride 2 per cent and 4 per cent, both with neo-synephrine 1:2,500. The solutions for these tests as well as for the animal experiments were freshly prepared; their pH was approximately 4.8. The higher and the lower concentration have been used on either side in these cases. When in these tests we raised the intensity of the stimulus

above that required for eliciting a slight but definite pain, progressively more marked flinching and twitching of the muscles of the face could be observed.

The results show significantly deeper anesthesia on the side anesthetized with the stronger solution. These clinical tests have also shown the correctness of our interpretation of the animal experiments, namely that the flinching and twitching seen were responses to stimulation of an intensity experienced as pain. Table 3 records the results of a typical test.

DISCUSSION

Previously, experimental data comparing the potency of anesthetic agents have been derived from the routine testing of the rabbit cornea, the frog or guinea pig sciatic nerve, the human dermal wheal and by other procedures(15),(19),(25),(26),(27),(28),(29). Transfer of data obtained from these experiments directly to clinical dentistry or medicine involves two assumptions: (a) that onset and duration of anesthesia indicate depth, and (b) that different tissues respond similarly to subcutaneous or submucous injection with procaine solutions of identical concentrations. The first of these assumptions arose because of the obvious difficulty of quantitatively measuring pain. Recently, however, Wolff and Hardy(30) and others have devised methods of comparing analgesics without

TABLE 3

TIME 3/13/48 EXP. #3	RIGHT SIDE 2% INDUCTORIUM READING		LEFT SIDE 4% INDUCTORIUM READING	
8:40	10.5	perceptible	10.5	control
	10.	painful	10.	control
8:43	injections			
8:48	6.5	perceptible	2.	
	5.	painful	-*)	
8:53	6.	perceptible	1.	
	5.	painful	-*)	
8:58	6.	perceptible	1.	
	5.	painful	-*)	
9:03	6.	perceptible	-*)	
	5.2	painful	-*)	
9:08	7.	perceptible	1.	
	6.	painful	-*)	
9:13	8.	perceptible	5.	
	7.5	painful	4.	
9:18	9.3	perceptible	7.	
	8.8	painful	6.2	
9:23	10.3	perceptible	8.3	
	10.1	painful	7.9	
9:28	10.4	perceptible	8.5	
	10.2	painful	8.1	
9:33	11.	perceptible	9.2	
	10.5	painful	8.8	
9:38	11.	perceptible	9.5	
	10.5	painful	9.	
9:43	10.8	perceptible	10.	
	10.4	painful	9.5	
9:48	11.	perceptible	10.2	
	10.5	painful	9.8	

making this assumption, and the need for similar comparisons in the field of local anesthesia is apparent. It is a common clinical observation that local anesthesia may be inadequate for the contemplated procedure yet last for long periods. Moreover, with the use of vasoconstrictors, duration of local anesthesia becomes less dependent upon the factor of concentration of the anesthetic agent.

The second assumption is similarly not tenable. There is no reason to assume that simply because a ½ per cent solution of procaine will suffice for subcutaneous infiltration anesthesia and block pain receptors, that the same concentration will also effectively block the sensory fibers of a nerve trunk some distance from the site of injection. In the former case it is only necessary for the agent to act upon scattered single receptors, while with submucous administration for pulpal anesthesia the solution must first penetrate the outer compact layer of the alveolar process; during this comparatively slow passage considerable dilution probably occurs. This weakened solution then has to act not on scattered pain receptors as in the mucosa but on the sensory fibers and their sheaths of the moderately large pulpal nerve trunk and may prove ineffective, unless a solution of higher concentration has been administered. In other words, in submucous infiltration for cavity preparation, we are actually attempting block anesthesia of the pulpal nerve

trunk but are injecting the solution in an area separated from that trunk by compact bone; it is probably this physical obstacle that necessitates the increase of concentration in conjunction with the further fact that a nerve block is attempted requiring stronger solution than that essential for terminal anesthesia. Furthermore, the nervous structures of the dental pulp probably have a pain and anesthetic threshold quite different from that of the periodontal membrane, that of bone, mucous membrane or the skin. It would seem therefore, that the determination of comparative anesthetic potencies by methods employed in the past have but little significance when applied to dental pulp anesthesia by submucous infiltration.

Goetzl, Burrill and Ivy[23] have used the dental pulp as a test organ to measure effectiveness of analgesic and hynotic drugs such as morphine and acetylsalicylic acid. They state that "the tooth pulp possesses specific pain receptors and there is good evidence that receptors of other afferent systems are absent." Histological studies reported by Noyes, Schour and Noyes[31] and Orban[32] support this concept. With the technic devised in this study, it is felt that testing of the dental pulp provides a quantitative procedure for comparing the effectiveness of various concentrations of different anesthetic agents also. Although the data summarized in Table 2 permit only a relative estimation of the

anesthetic depth obtained with the two procaine solutions, they suggest that superior depth of pulpal anesthesia is obtained with the 4 per cent solution of procaine hydrochloride.

PART II

COMPARISON OF TOXICITY OF 2 AND 4 PER CENT PROCAINE HYDROCHLORIDE SOLUTIONS.

INTRODUCTION

In 1924 Mayer[1] undertook a review of the question of toxicity of various local anesthetic agents. His recommendation, not to exceed a strength of 1 per cent of procaine hydrochloride for purposes of infiltration were based on a thorough study of fatalities that had been caused by a number of local anesthetic agents. Out of the 43 fatalities reported only 2 could be ascribed by him to procaine. One of these two cases, a tonsillectomy patient, received infiltration anesthesia with 10 minims of ½ per cent procaine solution with epinephrine 1:10,000. He died on the operating table. On autopsy status lymphaticus was demonstrated. The second case mentioned received ½ per cent procaine solution subcutaneously in a case of extensive burns; no amounts of procaine were mentioned nor presence or absence of vasoconstrictors. The patient died within 30 seconds after injection. Hatcher and Eggleston[33] mention 2 procaine fatalities. Both their cases were spinal anesthesias, in neither case was concentration mentioned and in one of the 2 cases no total dose of procaine was given. The fatality reported by Hansen[34] was a patient with severe asthma whose stellate ganglion

was blocked with from 20 to 80 cc. of 1% procaine hydrochloride 5 times within 20 days. She died at the sixth injection of respiratory failure (epidural injection?).

As pointed out by Hertzler(35), none of these cases is conclusively due to the toxicity of procaine alone and they certainly do not afford an adequate basis for comparing the toxicity of procaine in any specific concentrations. Drug sensitivity and shock probably account for the majority of fatalities mentioned above.

It might be well in this connection to consider briefly the following figures. There are about 120,000 physicians in this country and 70,000 dentists. Let us surmise that each physician gives 1 procaine injection daily, that each dentist gives 5 procaine injections daily and that a work year has 300 days. A total number of 1,710,000,000 procaine injections are then given in this country each year. Even allowing for the use of substitutes well over one billion procaine injections are probably given in the U.S. alone annually. That includes concentrations of ½ per cent up to spinal injections of 10 per cent. In the light of this information the list of procaine fatalities does not appear impressive.

The New and Nonofficial Remedies advise that "the total amount injected should not exceed 200 mg. of the drug". For dental purposes usually 2 cc. of anesthetic solution are used; occasionally 3 or 4 cc. may be injected.

The drug amounts administered therefore are well below the maximum dosage recommended, even when a 4 per cent solution is used.

When any material is injected subcutaneously or submucously certain histological changes may occur. Whether the stronger solution will cause tissue damage has been answered by Braun[15] and Farr[36]. They state that even a 10 per cent solution of procaine hydrochloride is absorbed after injection without leaving any trace of tissue irritation.

It might be well to point out here that procaine was synthetized by Einhorn in 1905 and that Braun had recommended the addition of epinephrine to local anesthetic agents in 1903. Procaine therefore from the date of its discovery on has almost always been used in combination with vasoconstrictor. It is most probable that the majority of the toxic symptoms seen after the administration of local anesthetics are due to the vasoconstrictor rather than the anesthetic agent.

Dramatic changes in bloodpressure occur when epinephrine is injected intravenously even in minute amounts; they account undoubtedly for the occasional case of perspiration, clammy skin or fainting seen in the dental chair.

Dentists, in their overwhelming majority, use cartridge syringes which, while convenient otherwise, do not permit aspiration to test for accidental intravenous injection.

Recently Nevin[37] has described a cartridge syringe permitting aspiration; however in the hands of the writer the syringe permits aspiration only by using undue pull, thereby making it difficult to maintain the position of the needle point.

That we probably have been wrongly indicting the toxicity of the comparatively innocent component, namely that of procaine, instead of that of the vasoconstrictor has been demonstrated in recent years in the clinical use of procaine hydrochloride, of course without vasoconstrictor, for intravenous analgesia and anesthesia. Allen, Bigelow and others[10],[11],[12] have reported the use of as much as 425 cc. of a 1% solution intravenously for general anesthesia over a period of one and 3/4 hours. The first 8 cc. of the solution are administered over a period of just one minute. At the University of Oregon up to 10 grams in 1% solution given intravenously have been used within one hour[38]. If one considers now that animal experiments have established that intravenous administration is approximately 10 times as toxic as subcutaneous administration, one cannot help wonder about the arbitrary maximal dose of 200 mg. for subcutaneous use prescribed in the N.N.R.

New research in recent years is also forcing changes in our concept of the fate and ultimate disposal of procaine in the body, a question very important for the understanding

of the toxicity of this substance[39],[40].

As for data in the literature pertaining to the toxicity of procaine when used for local anesthesia in different concentrations, we find repeated references to the "geometric ratio of increase in toxicity of procaine hydrochloride solutions"[41],[42]. By this formula the authors refer to a progression according to which 1 cc. of a 2 per cent solution of procaine hydrochloride is not twice but 4 times as toxic as 1 cc. of a 1 per cent solution. An inquiry on this subject at the Council of Pharmacy and Chemistry of the American Medical Association brought a telegram from Walton Van Winkle Jr.[43] with a list of references.

The first article mentioned in this telegram is by Eggleston and Hatcher[44]; in their toxicity studies concentrations of between 5 and 20 per cent of procaine hydrochloride were used, but no attempt was made to elaborate any difference in toxicity between any of these concentrations. Meeker and Fraser[45], mentioned next, used one concentration only, namely 0.5 per cent. Schmitz and Lovenhart[25], reference number three, gives drug amounts only, but no concentrations at all. The fourth reference, Dunlop[46], deals with the fate of procaine rather than its toxicity. Schamp[13], mentioned next, used 2 per cent solutions only. Issekutz and Kovari[47] dealt not with

toxicity but with metabolism of procaine. Epstein and Silver's[48] article, the last reference, contains a table comparing the toxicity on subcutaneous administration of several commercial 2 and 4 per cent procaine solutions containing different vasoconstrictors and preservatives; these additions diminish the usefulness of their findings for our study of the toxicity of procaine hydrochloride alone in different concentrations. It is interesting enough though, that in this table the 4 per cent solutions appear less than doubly toxic on the average, when compared cc. by cc. with the 2 per cent solutions containing a comparable amount of vasoconstrictor. For their determination of toxicity of procaine hydrochloride without vasoconstrictor these authors used 2 per cent solution only.

No experimental or clinical proof for the theory of the geometric progression in toxicity of procaine had been found. Dr. Waters in a personal communication[49] suggested revision and re-examination of this problem. We have felt therefore the necessity of a comparison of the toxicity of 2 per cent and 4 per cent procaine hydrochloride in order to establish the influence, if any, of concentration of this drug on its toxicity.

EXPERIMENTAL

Rapid intravenous injection into the ear vein of male white rabbits was used for the establishment of the intravenous LD_{50} for 2 and 4 per cent isotonic procaine hydrochloride solutions. Animals of 1.3 kg. to 2.8 kg. weight were used, the majority of them around 2 kg. body-weight. The drug was administered within periods of from 18 to 25 seconds to simulate clinical conditions where the drug may be administered at that rate intravenously inadvertently. This mode of administration is considered the best yardstick for establishment of the toxicity of procaine hydrochloride[45],[50]. Table 4 shows the results.

Rapid subcutaneous injection in Swiss male white mice has been used for the establishment of the LD_{50} in the 2 concentrations for this usual mode of administration [26]. Animals of 13 grams to 32 grams weight were used, the majority of them around 20 to 25 grams weight. Results are shown on Table 5.

In all toxicity studies we used animals only once notwithstanding reports by Schamp, Schamp and Tainter[51], who reinjected the survivors after 10 days and found no significant difference in the percentage mortality between fresh animals and those used for a second time. To

TABLE 4

MORTALITY RATE IN RABBITS GIVEN RAPID INTRAVENOUS INJECTIONS OF 2 AND 4 PER CENT SOLUTIONS OF PROCAINE HYDROCHLORIDE.

DOSE	2% PROCAINE HCl	4% PROCAINE HCl
mg./kg.	No. dying/No. used	No. dying/No. used
40	0/4	0/4
45	1/4 (25% died)	0/4
50	5/10 (50% died)	5/9 (55% died)
55	7/8 (87% died)	4/6 (66% died)
60	4/4 (100%died)	4/4 (100% died)

TABLE 5

MORTALITY RATE IN SWISS MALE WHITE MICE GIVEN SUBCUTANEOUS INJECTIONS OF 2 AND 4 PER CENT SOLUTIONS OF PROCAINE HYDROCHLORIDE.

DOSE	2% PROCAINE HCl	4% PROCAINE HCl
mg./kg.	No. dying/No. used	No. dying/No. used
800	2/20 (10% died)	3/20 (15% died)
900	14/28 (50% died)	15/28 (54% died)
1000	14/20 (70% died)	16/20 (80% died)

minimize any effect on our results from slight variations in the different batches of animals we injected approximately the same number of each batch with 2 as with 4 per cent solution.

RESULTS OF TOXICITY STUDIES

The LD_{50} for rapid intravenous injection (administration time 18-25 seconds) into the ear vein of the rabbit was found to be 50 mg./kg. for the 2 per cent solution and only very slightly less than 50 mg./kg., but definitely more than 45 mg./kg. for the 4 per cent solution.

The LD_{50} for rapid subcutaneous injection near the tail in Swiss male white mice was found to be 900 mg./kg. for 2 per cent solution, and slightly less than 900 mg./kg. but definitely more than 800 mg./kg. for 4 per cent solution.

Our findings both in the rapid intravenous and in the subcutaneous tests with procaine hydrochloride rather definitely show that there is no, or only a very insignificant increase in toxicity as expressed in LD_{50} when the solution administered is increased in concentration from 2 to 4 per cent as long as the drug amount is kept constant.

DISCUSSION OF TOXICITY STUDIES

A very great number of findings on the toxicity of procaine hydrochloride, when administered subcutaneously or intravenously in laboratory animals, have been published in the past 43 years. Insufficient or no regard has been given in these investigations to dependence of toxicity on concentration. For convenience of administration studies in the past have used generally a very high concentration,

as 10 per cent, for the rapid intravenous administration; neither do these studies as a rule specify exactly the period of time in seconds, within which this rapid administration took place. Both the factors of concentration and that of the exact period of administration time are most important in the determination of toxicity of a drug as rapidly disposed of as procaine. That probably explains the wide divergence in toxicity figures (LD_{50}) quoted in standard monographs[28], particularly in regard to intravenous administration. We have not been able to find in the literature any references to a comparison of toxicity in procaine solutions of various strength, 2 and 4 per cent in particular, when identical drug amounts were used.

Instead we have encountered arbitrary standards as that of the "geometric ratio of increase in toxicity of procaine", a theory taught even today in many schools. Our findings show that this theory can not be substantiated by LD_{50}'s in laboratory animals.

Toxicity might however express itself in untoward symptoms in man only.

Lovestedt[8] has administered 4 per cent procaine in a series of 500 cases of heart disease, treated for dental conditions at Mayo, and shown the absence of any untoward symptoms with these poor risk patients.

In view of the experimental findings on toxicity presented in this paper and the clinical studies of

Lundy[6], Stafne[7], Farquhar[9] and especially those of Lovestedt[8] it is felt that the use of 4 per cent solution in dentistry is safe.

CONCLUSIONS

The necessity for more profound anesthesia than that obtained by administration of 2 per cent solutions of procaine hydrochloride is frequently felt by dental clinicians. Tainter[4] has shown in one of his studies that an average of 5.5 cc. of 2 per cent solution containing epinephrine 1:50,000 was required to obtain adequate clinical dental anesthesia. Out of the 344 cases examined in this study 21 per cent showed inadequate depth of anesthesia even with this rather large drug amount and volume. In another paper Winter and Tainter[5] report a clinical comparison of 2 and 3 per cent procaine solutions, both containing epinephrine 1:50,000. In this study they state that an average of 2.8 cc. of the 3 per cent solution and an average of 3.4 per cent of the 2 per cent solution was required to obtain adequate anesthesia. The amount of 3.4.cc. of the 2 per cent solution needed in this study varies considerably from the amount of 5.5 cc. of the same solution needed for identical purposes by the same author in his previous work. Winter and Tainter state that an average of 2.8 of the 3 per cent solution causes a smaller incidence of nervous perspiration and of respiratory changes

than an average of 3.4 cc. of the weaker solution but that it doubled the frequency of tremors and greatly increased the incidence of nervousness. These symptoms are of course very much of a subjective nature and hard to measure. The authors also claim a shorter duration of anesthesia for the stronger solution, supposedly caused by the vasodilator effect of the procaine that offset the vasoconstrictor effect of the epinephrine more potently when a stronger solution of procaine was used. These findings contradict Sollman[19] and Braun's[15],[18] reports, who found an increase in duration of anesthesia when the concentration of procaine hydrochloride was increased and that of epinephrine was kept constant. The durations given by Winter and Tainter are 136 minutes for the 3 per cent solution and 190 minutes for the 2 per cent solution. They state however that with the 3 per cent solution there was a significantly higher incidence of complete anesthesia and only a small number of reinjections. In their paper these authors consider anesthesia as adequate when it permitted the completion of the operation. However they do not specify the type of operative or surgical procedures performed for which these anesthesias were administered beyond saying that their observations were made on patients subjected to the ordinary operations in oral surgery, mostly extractions[4]. In their other paper[5] it can be deduced that their cases were also cases of oral surgery only.

Tainter and his co-workers were probably attempting to determine the best single all round anesthetic solution for oral surgery. His findings therefore have but small significance for the determination of depth or duration of pulpal anesthesia. It has been the contention of this writer that not one but at least 2 concentrations ought to be used routinely for all the various operative and surgical procedures of a dental practice, namely a 2 per cent and a 4 per cent solution of procaine hydrochloride.

In our own findings we have found not a decrease but rather an increase in the length of pulpal anesthesia with 4 per cent procaine as compared with 2 per cent solution containing identical amounts of vasoconstrictor. The explanation for this divergence possibly lies in the difference of the end points taken and tissues tested by those authors and this writer. Winter and Tainter judged duration by recurrence of sensation as determined by the use of an explorer on the mucous membrane. In pulpal anesthesia for cavity preparation, one of the indications for the stronger solution advocated by this author, obviously the anesthesia or lack of anesthesia of the mucous membrane is immaterial.

Our own observations extended over one hour only, that is the length of a fairly long dental appointment. Anesthesia of good depth and a duration of one hour is desirable. It is of questionable practical advantage to have protracted

anesthesia after completion of the operation and is rarely welcomed by the patient.

A duration of 2 hours as produced by 3 per cent solution in Winter and Tainter's study would be actually preferable to one of 3 hours as produced by 2 per cent solution by these authors.

Thus Winter and Tainter have found in comparing 2 and 3 per cent procaine solutions, that for a dental appointment of ordinary length the more concentrated solution gives a deeper, hence more satisfactory anesthesia. This agrees fully with our findings in comparing 2 and 4 per cent solutions of procaine.

The use of repeated injections as advocated by Winter and Tainter for the purpose of obtaining sufficient anesthesia also introduces an element of chance as far as the determination of toxicity and duration are concerned. It has been shown that the toxicity of procaine increases after injection of an unchanged total drug amount in several places, instead of into one depot(52). On the other hand, toxicity is bound to decrease when repeated smaller dosages are administered until sufficient depth of anesthesia is obtained, even when only as little as 5 or 10 minutes elapse between the original injection and the second supplementary dose because of the rather rapid elimination of the drug from the system. As far as duration of anesthesia is concerned it can not very well be measured

accurately if repeated injections at arbitrary intervals are given.

In the first part of our study then we have shown that experimentally and clinically 1 cc. of a 4 per cent solution of procaine hydrochloride gives a more profound anesthesia of the dental pulp than 1 cc. of a 2 per cent solution when administered submucously in the upper jaw.

In the second part of this paper we have shown that a 4 per cent solution of procaine hydrochloride is approximately as toxic as a 2 per cent solution in laboratory animals, when drug amounts are kept constant. 4 per cent solution is therefore just about twice as toxic as 2 per cent solution when equal volumes are used. A "geometric ratio of increase in toxicity of procaine hydrochloride" could not be shown to exist. Drug amounts used in either concentration in dentistry, let us say up to 4 cc., are well within the strictest permissible limits of 200 mg.

We wish to emphasize however that we do not recommend universal use of 4 per cent solution in dentistry but rather the establishment of indications for the use of the stronger solution, which may be then used by the profession with confidence.

The 4 per cent solution should be used mainly in maxillary infiltration anesthesia for cavity preparation and also in any local anesthesia, block or terminal, for

the extraction of a tooth with involvment of the apex, the periodontal membrane, or the curreting of granulomatous apical foci[53]. The 2 per cent solution should be used in all other operations.

SUMMARY

1. An objective experimental laboratory procedure for comparing depth of anesthesia after administration of different local anesthetic agents is described.

2. Experimental and clinical tests are reported corroborating the applicability of such a method in comparing intensity of anesthesia for different concentrations of procaine hydrochloride.

3. The results of this study indicate a greater depth of anesthesia of the dental pulp following the submucous administration of 4 per cent procaine hydrochloride solution as compared with the 2 per cent solution.

4. Toxicity of Procaine Hydrochloride is not materially dependent upon concentration in laboratory animals when 2 and 4 per cent concentrations are used and drug amounts are kept constant.

5. The theory of the "geometric ratio of increase in toxicity of procaine" is untenable in laboratory animals when death is used as an endpoint.

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