2-CHLOROPROCAINE: A NEW LOCAL ANESTHETIC AGENT * †

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Since the discovery of procaine in 1905 by Einhorn, a number of ester type local anesthetic agents were synthetized and introduced into clinical practice. Most of these agents are more potent, but also more toxic, than procaine, and their therapeutic index on intravenous administration is usually lower than that of procaine (1). Recently, two new procaine derivatives, procaine ascorbate (2) and metahydroxy-procaine (3), have undergone pharmacologic investigation. The experimental findings indicate that, with regard to toxicity and potency, both drugs compare favorably with procaine. Data on the clinical application of these two new procaine derivatives have not yet been reported.

The newest addition to the procaine-type local anesthetic agents is 2-chloroprocaine.‡ 2-Chloroprocaine hydrochloride is a white, amorphous powder; its molecular weight is 307.21, and its melting point is 174.0 C. Its solubility in water is good but less than that of procaine; 5 per cent solutions can be made without any difficulty. Heating and alkalinization increase solubility. The pH of the 1 per cent solution is 4.90 and that of the 2 per cent solution 4.80. The watery solution at room temperature is stable for several months.

In vitro studies reported elsewhere (4) indicate that 2-chloroprocaine is hydrolyzed about four times as fast as procaine by plasma procaine esterase. The hydrolysis of 2-chloroprocaine in alkaline solutions similarly is much faster than that of procaine (4). It was also found that certain neostigmine-type enzyme inhibitors can prevent this hydrolysis in concentrations as low as 1:5,000,000 to 1:20,000,000 (5).

Preliminary pharmacologic studies § on the mouse and guinea pig indicated that the LD_{50} of 2-chloroprocaine in male mice was 1,000 ± 76 ‖ mg. per kilogram as compared to the LD_{50} of procaine which was 515 ± 18 ‖ mg. per kilogram. The LD_{50} of 2-chloroprocaine in guinea

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§ Unpublished data of Dr. Walter Loewe.

‖ Standard error.

pigs was 380 ± 36 ‖ mg. per kilogram. The latent period before convulsions and the interval between administration of the drug and death were shorter with 2-chloroprocaine than with procaine. A 1 per cent solution instilled into the eye of the rabbit gave complete anesthesia for a minimum of 20 minutes. The pseudohernia test in guinea pigs revealed that whereas the threshold level for procaine was 0.25 per cent, the same value for 2-chloroprocaine was 0.025 per cent.

Bacteriologic studies ¶ with the nephelometer method of McFarland (6) showed that, compared to procaine, 2-chloroprocaine in concentrations of 1.0 to 0.2 mg. per cubic centimeter possessed a marked bacteriostatic effect on cultures of Aerobacter aerogenes. The effect was even more marked with cultures of *E. coli.* With cultures of *Staphylococcus aureus* and *albus,* only the concentration of 1.0 mg. per cubic centimeter of 2-chloroprocaine proved to be more effective than the corresponding concentrations of procaine.

EXPERIMENTAL DATA

The local anesthetic potency of 2-chloroprocaine was investigated by skin wheal tests on human volunteers and by the production of regional nerve blocks and spinal anesthesia in patients.

The skin wheal tests were carried out as follows: 0.16 per cent, 0.40 per cent and 1.00 per cent procaine and 2-chloroprocaine solutions were prepared with and without the addition of 1 : 100,000 epinephrine, using 0.9 per cent sodium chloride solution as solvent. Only one concentration was investigated at a time. Four intracutaneous wheals were made on the flexor surface of the forearm of human volunteers with 0.2 cc. of procaine, 2-chloroprocaine, procaine with epinephrine, and 2-chloroprocaine with epinephrine solutions, respectively. The visible borders of the skin wheals were encircled with ink. The volunteers were tested for the presence or absence of analgesia at five minute intervals following the injection by allowing the weight of a tuberculin syringe attached to a number 25G, one-half inch hypodermic needle to press against the skin surface of the injected areas. The effect of the local anesthetic agent was assumed to be worn off when, on testing in the described manner, pain was perceived by the volunteers. The analgesic solutions to be tested were marked by numbers 1, 2, 3 and 4. Neither the volunteers nor the person who made the skin wheals and did the testing knew the composition of the various solutions used until the testing was concluded and the data obtained were analyzed. The results of our findings are presented in table 1.

It can be seen from table 1 that when epinephrine was not used, the duration of action of the various 2-chloroprocaine solutions was always significantly greater than that of the corresponding procaine solu-

¶ Carried out by Dr. M. M. Bracken of the Department of Pathology, the Mercy Hospital, Pittsburgh, Pa.

tions. The lower the concentration used, the greater was the difference between the duration of the action of 2-chloroprocaine and procaine. Thus, the increase in the duration of analgesia of the 0.16 per cent, 0.40 per cent and 1.00 per cent solutions of 2-chloroprocaine as compared to solutions of procaine of the same concentrations was about 100 per cent, 50 per cent and 30 per cent, respectively. The addition of 1:100,000 epinephrine to both the procaine and 2-chloroprocaine solutions markedly increased the duration of their effect. Under the circumstances, however, there was no statistically significant difference between the duration of the identical 2-chloroprocaine and procaine concentrations. The significance of these findings will be discussed later.

Contrary to our expectations, the addition of a potent enzyme inhibitor, RO2-683,# in 1:100,000 concentration, did not increase the dura-

TABLE 1

SUMMARY OF THE INTRACUTANEOUS SKIN WHEAL TESTS

Agent Used	Concentration					
	0.16 Per Cent		0.40 Per Cent		1.00 Per Cent	
	No. of Cases	Duration in Minutes*	No. of Cases	Duration in Minutes*	No. of Cases	Duration in Minutes*
Procaine	10	7.9±0.7	10	10.5± 0.5	16	23.5± 1.4
2-Chloroprocaine	10	16.9±0.1	10	15.5± 1.4	16	30.5± 1.4
Procaine with epinephrine	10	66.9±2.3	9	122.2±27.5	10	166.5±13.9
2-Chloroprocaine with epinephrine	10	56.7±2.5	10	121.9±19.8	17	144.5± 9.9

* Mean and standard error (standard deviation of the mean).

tion of the effect of 2-chloroprocaine or procaine solutions with or without 1:100,000 epinephrine.

A total of 176 skin wheals was made on 27 volunteers. With the exception of moderate erythema and itching which developed after both procaine and 2-chloroprocaine in one volunteer, no irritating effects or allergic phenomena were observed in this series.

Regional Nerve Blocks.—2-Chloroprocaine alone or with the addition of 1:200,000 epinephrine or 1:200,000 RO2-683, or both, was used for the production of regional nerve blocks in 130 cases.** Whenever possible, the duration of the effect of the block was carefully observed. The results obtained with the different blocks are summarized in tables 2, 3 and 4.

RO2-683 was supplied by the courtesy of Dr. R. J. Floody of Hoffman LaRoche, Inc., Nutley, N. J.

** Seven of the regional nerve blocks were performed by Dr. R. L. Patterson of the Allegheny General Hospital, Pittsburgh, Pa., and 2 by Dr. L. G. David of the Montefiore Hospital, Pittsburgh, Pa.

TABLE 2

SUMMARY OF REGIONAL NERVE BLOCKS WITH 2-CHLOROPROCAINE

Type of Block	No. of Blocks	Solution		Successful		Duration	
		Cc.	Per Cent	No. of Cases	Per Cent	Range, Minutes	Average, Minutes
Infra-orbital	3	3	2.0	3	100	75–90	80
Brachial plexus	3	40	2.0	3	100	90–150	110
Finger and metacarpal	6	15	2.0	5	83	50–90	70
Paravertebral	5	4	2.0	5	100	45–95	70
Toe	1	20	2.0	1	100	120	120
Stellate ganglion	7	10	1.5	7	100	70–130	80
Lumbar sympathetic	13	25	1.5	13	100	65–130	100

TABLE 3

SUMMARY OF THE REGIONAL NERVE BLOCKS WITH 2-CHLOROPROCAINE AND 1:200,000 EPINEPHRINE

Type of Block	No. of Blocks	Solution		Successful		Duration	
		Cc.	Per Cent	No.	Per Cent	Range, Minutes	Average, Minutes
Maxillary	6	4	2.0	6	100	60–120	80
Cervical	1	4	2.0	1	100	115	115
Brachial plexus	32	40	2.0	29	90	75–200	120
Stellate ganglion	1	10	1.5	1	100	130	130
Lumbar sympathetic	7	25	1.5	7	100	70–240	160

TABLE 4

SUMMARY OF THE REGIONAL NERVE BLOCKS WITH 2-CHLOROPROCAINE, 1:200,000 EPINEPHRINE AND 1:200,000 RO2-683

Type of Block	No. of Blocks	Solution		Successful		Duration	
		Cc.	Per Cent	No.	Per Cent	Range, Minutes	Average, Minutes
Mandibular	1	5	2.0	0	0	0	0
Cervical	3	4	2.0	3	100	95–100	95
Brachial plexus	9	40	2.0	9	100	80–165	110
Paravertebral	1	4	2.0	1	100	75	75
Stellate ganglion	27	10	1.5	27	100	75–155	105
Lumbar sympathetic	3	25	1.5	3	100	110–135	125

The regional nerve blocks done with 2-chloroprocaine were characterized by: (1) a higher percentage of success than with other agents even when paresthesias were not obtained, (2) a rapid onset of action and (3) the absence of any systemic absorption reactions. The apparently greater penetrating power of 2-chloroprocaine, resulting in an immediate onset of anesthesia, and a higher incidence of successful blocks make this drug eminently suitable for the production of regional

nerve blocks. The addition of 1:200,000 epinephrine markedly increased the duration of the various nerve blocks, but the addition of 1:200,000 RO2–683 had no appreciable effect.

Dental Anesthesia.—2-Chloroprocaine alone or with 1:100,000 RO2–683 or 1:100,000 epinephrine, or 1:100,000 RO2–683 and 1:100,000 epinephrine was used for the production of regional nerve blocks in dental anesthesia in 90 cases.†† Sixty-seven of these were mandibular blocks, 15 were infra-orbital blocks and 8 were tuberosity blocks. Two cubic centimeters of 2 per cent solution were used for all the injections. The onset of anesthesia was almost instantaneous and was complete within three minutes. The results of the dental blocks are summarized in table 5. The blocks done with 2-chloroprocaine alone wore off completely in about twenty minutes. No toxic reactions were observed in any of these cases with the exception of slight nervousness in 10 patients and sweating in 1 patient. The addition of RO2–683

TABLE 5

SUMMARY OF THE DENTAL NERVE BLOCKS WITH 2-CHLOROPROCAINE

Agent	No. of Blocks	Successful		Duration, Minutes*
		No.	Pre Cent	
2-Chloroprocaine	19	19	100	19.5±0.89
2-Chloroprocaine with epinephrine	36	35	97	59.0±1.10
2-Chloroprocaine with RO2–683	16	15	94	25.0±1.76
2-Chloroprocaine with epinephrine and RO2–683	19	19	100	58.0±1.88

* Mean and standard error (standard deviation of mean).

to 2-chloroprocaine had no effect on the duration of the dental nerve blocks.

Spinal Anesthesia.—2-Chloroprocaine alone or with epinephrine or RO2–683 was used for the production of spinal anesthesia in 214 patients. One hundred milligrams of 2-chloroprocaine was dissolved in 3 cc. of 10 per cent dextrose, or 2.4 cc. of 10 per cent dextrose and 0.6 cc. of 1:1,000 epinephrine, or 2.4 cc. 10 per cent dextrose and 0.6 cc. 1:2,000 RO2–683, resulting in a 3.3 per cent hyperbaric solution of 2-chloroprocaine. When the duration of the contemplated surgical procedure was expected to be sixty minutes or less, 2-chloroprocaine alone or with RO2–683 was used. For surgical procedures of longer duration 2-chloroprocaine with epinephrine was employed. If the desired level of anesthesia was below the twelfth thoracic segment, 2.5 cc. of the 3.3 per cent solution of 2-chloroprocaine was used and for higher levels, 3 cc. was employed. Within these dosage limits the desired height of anesthesia was obtained by varying the site of puncture between the

†† All the dental blocks were done under the supervision of Dr. L. M. Monheim by the students in the School of Dentistry of the University of Pittsburgh.

second and fourth lumbar interspace and changing the plane of the operating table. The 100 mg. dose (3 cc. of 3.3 per cent solution) was not exceeded in any of our cases. Excellent anesthesia for any upper abdominal surgical procedure was provided by 100 mg. Whenever possible, the duration of sensory and motor anesthesia was observed. Motor anesthesia was considered terminated when the patient was able to flex either knee voluntarily. Perception of pinprick sensation in the inguinal fold was taken as the end point of sensory anesthesia.

Spinal anesthesia with 2-chloroprocaine was characterized by an immediate onset and a rapid rate of climb that made constant observation necessary during the first few minutes until the desired height

TABLE 6

OPERATIONS DONE UNDER 2-CHLOROPROCAINE ANESTHESIA

Type of Operation	Number of Procedures Done Under		
	2-Chloroproc.	2-Chloroproc. + Epinephrine	2-Chloroproc. + RO2-683
Intra-abdominal: gastrectomy, cholecystectomy, umbilical-, ventral-, incisional-herniorrhaphy, hysterectomy, appendectomy, colostomy	21	34	12
Urologic: nephrectomy, pyelolithotomy, retropubic prostatectomy, cystotomy, bladder resection, transurethral prostatectomy, hydrocelectomy	5	16	4
Inguinal herniorrhaphy	11	13	6
Lower extremity: vein ligation, open reduction, amputation, arthrotomy, skin graft, manipulation	29	20	9
Miscellaneous: coccygectomy, hemorrhoidectomy, pilonidal cyst, circumcision, dilatation and curettage	24	1	9
Total	90	84	40

of anesthesia was obtained. However, even in the cases in which the level of sensory anesthesia accidentally ascended to the cervical segments there was no sign of respiratory embarrassment, and artificial or assisted respiration was not necessary in any of our cases.

The operative procedures done with 2-chloroprocaine spinal anesthesia are summarized in table 6. It can be seen from this table that not only surgical procedures requiring low spinal anesthesia, but also major intraperitoneal procedures (cholecystectomy, hysterectomy, etc.) can be carried out satisfactorily with a single subarachnoidal injection of 100 mg. 2-chloroprocaine.

The duration of sensory and motor anesthesia obtained with the subarachnoidal injection of 2-chloroprocaine is summarized in table 7. These figures indicate that the duration of sensory anesthesia is

TABLE 7

The Duration of Motor and Sensory Anesthesia Following Subarachnoidal Block with 2-Chloroprocaine

Agent	No.	Duration of Motor Anesthesia, Minutes*	Duration of Sensory Anesthesia, Minutes*
2-Chloroprocaine	83	70±2.2	82±2.8
2-Chloroprocaine with RO2-683	40	73±1.9	84±2.7
2-Chloroprocaine with epinephrine	84	110±2.8	121±3.0

* Mean and standard error (standard deviation of mean).

moderately greater than that of motor anesthesia. It can also be seen that the addition of epinephrine markedly increased the duration of both sensory and motor anesthesia, but the addition of RO2-683 had no appreciable effect.

The incidence of postoperative complications was about the same as observed after other spinal anesthetic agents. Postoperative headache was present in 11 of 214 patients, an incidence of 5 per cent; of these, only 3 patients (1.5 per cent) were not relieved by aspirin and the headache lasted more than forty-eight hours. No neurologic complications developed in any of these patients during their hospital stay or after their discharge.

Comment

The toxicity of any local anesthetic agent depends on the presence of a certain concentration in the blood stream. This concentration is not necessarily the same in different species. The concentration of local anesthetic agent in the circulating blood depends on at least four factors: (1) the rate with which the agent reaches the intravascular fluid, (2) the total volume of the intravascular fluid, (3) the rate with which the agent penetrates into the interstitial and intracellular fluids and (4) the rate with which the agent is hydrolyzed or otherwise detoxified within the blood stream.

On intravenous administration, the concentration in the blood depends on milligrams per kilogram per minute of the drug injected. However, if the agent in question is administrated by the intraperitoneal, intramuscular or subcutaneous route, in addition to the size of the dose given, the penetrating capacity of the agent in question is also of great importance.

It is evident that the faster the hydrolysis of an agent within the blood stream, the larger the quantity that has to reach the blood stream to maintain a toxic concentration. Conversely, if an agent is hydrolyzed or detoxified slowly, relatively small quantities will produce a toxic blood level.

It was shown in *in vitro* studies that 2-chloroprocaine is hydrolyzed

by the plasma procaine esterase about four times as fast as procaine. This finding explains the fact that on subcutaneous administration in male mice, the LD_{50} of 2-chloroprocaine was found to be almost twice as high as that of procaine. That the LD_{50} of 2-chloroprocaine on subcutaneous administration was not found to be even more favorable was probably because of the fact that the penetrating capacity, and thereby the rate of absorption, of 2-chloroprocaine is greater than that of procaine. This was demonstrated by the finding that when convulsions did develop after the subcutaneous administration of 2-chloroprocaine to mice, the latent period was shorter than following the administration of procaine. Similarly, in the fatal cases the time between administration of the drug and death was shorter with 2-chloroprocaine than with procaine.

Our clinical findings corroborated the results of the *in vitro* studies and the pharmacologic experiments. The fact that no systemic absorption reaction was observed even when as much as 40 cc. of a 2 per cent solution was administered within two minutes, in the course of brachial plexus blocks, to old and debilitated patients, can only be explained by the rapid intravascular hydrolysis of 2-chloroprocaine. This rapid hydrolysis is a definite advantage when infiltration or regional anesthesia has to be used in poor risk patients, because the systemic reactions occasionally observed after the use of procaine can thus be prevented. For the same reason 2-chloroprocaine is the logical choice of a local anesthetic agent in the seriously injured or wounded patient.

The almost instantaneous onset of anesthesia following regional nerve blocks with 2-chloroprocaine is caused by the increased penetrating capacity, also observed in the pharmacologic studies. The rapid onset of anesthesia with 2-chloroprocaine is a great advantage in a busy operating room and is especially helpful in dental anesthesia.

The dentists using 2-chloroprocaine for dental blocks were favorably impressed with the short duration of the blocks and the absence of residual numbness after the blocks. They believe that this property of 2-chloroprocaine makes it eminently suitable for dental use in cases in which analgesias of only short duration are required. The reason for the relatively short duration of the dental nerve blocks is that in these types of blocks the 2-chloroprocaine is infiltrated into very vascular areas with a high procaine esterase content; therefore, the 2-chloroprocaine at these sites is decomposed rapidly and completely.

That 2-chloroprocaine is definitely more potent than procaine is evident from both the pharmacologic and the clinical studies. In the pseudohernia test on the guinea pig, 2-chloroprocaine was found to be ten times as potent as procaine. In the clinical studies the increased potency was manifested in the intradermal skin wheal tests in which 2-chloroprocaine was found to be more potent than procaine.

The increased potency of 2-chloroprocaine could also be seen in spinal anesthesia when 100 mg. produced satisfactory relaxation and

analgesia for upper abdominal operations on the average adult patient. To obtain similar results with procaine, about 150 mg. is necessary. Since the molecular weight of 2-chloroprocaine is about 20 per cent higher than that of procaine, the increased potency of 2-chloroprocaine is even more outstanding if the two agents are compared on a molar basis.

The fact that on intracutaneous administration the duration of action of 2-chloroprocaine with 1:100,000 epinephrine was not greater than that of procaine with epinephrine needs some explanation. It has been shown (7) that not only the blood, but also almost every animal tissue contains procaine esterase. Epinephrine prolongs the duration of action of local anesthetic agents by preventing their absorption from the site of injection. However, the presence of epinephrine will not prevent the *in situ* hydrolysis of the local anesthetic agents. Since 2-chloroprocaine is hydrolyzed more rapidly than procaine, its advantage over procaine gained by its greater potency will be counteracted when, by the addition of epinephrine, it is subjected to a more prolonged action of the tissue procaine esterase. The end result of the effect of these two divergent factors (potency and stability) is that on subcutaneous administration the duration of the effect of 2-chloroprocaine and procaine with epinephrine was about the same.

Our clinical experience with 2-chloroprocaine seems to indicate that in this drug we possess a highly useful local anesthetic agent which is not only more potent but also considerably less toxic than procaine. The findings presented encourage extensive clinical trials with this promising new local anesthetic agent. We believe that it will prove to be useful primarily for infiltration anesthesia, field block, dental anesthesia and regional nerve blocks.

SUMMARY

2-Chloroprocaine with or without the addition of epinephrine and RO2-683, or both, was used in intradermal skin wheal tests on 27 human volunteers, for the production of regional nerve blocks in 130 patients, dental nerve blocks in 90 patients and for spinal anesthesia in 214 patients.

No local or systemic toxicity was observed in any of these 461 individuals, with the exception of slight local urticaria in one of the volunteers.

The duration of the local analgesic effect of 2-chloroprocaine in the skin wheal tests was significantly greater than that of procaine.

As a spinal anesthetic agent, 2-chloroprocaine was more potent than procaine.

Because of the rapid onset of its action, very low incidence of failure and the lack of systemic absorption reactions, combined with a satisfactory duration of action, 2-chloroprocaine is an excellent agent for the production of regional nerve blocks.

Owing to its relatively high potency and low systemic toxicity, 2-chloroprocaine has a higher therapeutic index than any of the currently used local anesthetic agents.

Extensive clinical trials with 2-chloroprocaine are recommended.

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