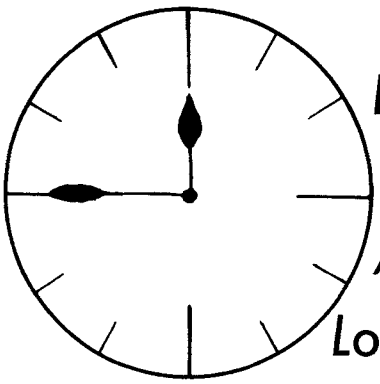

Latency and Duration of Action of Some Local Anesthetic Mixtures

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INTRODUCTION

TETRACAINE is often added to procaine[1, 2] and especially to lidocaine[2-6] to produce blocks of short latency and long duration. Strangely enough, enthusiasm for these combinations has never prompted experimental investigation of their effect. However, proofs of definite advantages seem highly desirable, in view of recent evidence of additive systemic toxicity.[7]

Several interactions are conceivable when 2 local anesthetics are applied to a single myelinated fiber: competition at Ranvier's nodes or membrane surface, with elimination of the slowest or weakest agent; independent diffusion and blocking action; mutual enhancement or antagonism of penetration and action; formation of a mixture with its own physicochemical properties and specific effects. The final action of such mixtures will depend not only upon the chemical nature of its components but also upon the interrelation of their mass, concentration, pH, and other factors. In the intact organism, further complexity is introduced by the perineural and extraneural fibrous tissues and their blood vessels, which control diffusion, penetration, and drug mass equilibrium.

The present investigation was initiated by our occasional disappointment when mixtures of 1 or 1.5 per cent lidocaine and 0.1 per cent tetracaine failed to provide the expected long duration of action. This fact has been noticed elsewhere.[6]

Since practical answers were needed, experimental technics close to clinical ones were selected; however, the necessity to standardize our conditions[4] recommended an animal study.

It is well to remember that duration, although important to the clinician, is only a small part of the total drug effect.

METHODS

Twelve healthy female mongrel dogs, of similar weight (14 to 15 kg.) and size (35 cm., nape to coccyx in standing position) were selected. Pregnancy and extremes of age and obesity were avoided.[8] The dogs' backs were kept closely shaven throughout the experiments.

A veterinary epidural technic[9] was standardized and rigorously followed to inject the various solutions. The animals, prone and with their spread-out extremities attached to a table, were placed in 40-degree Trendelenburg position. Under sterile conditions, the

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epidural space was penetrated through the interarcual ligament with a short-beveled No. 22 spinal needle (bevel cephalad); after identification of the epidural space (aspiration, air injection), 4 ml of the investigated solution were injected from a well-lubricated 5-ml. syringe, equipped with a spring-and-trigger mechanism, allowing a constant injection rate of 2 ml. per second. Containers, syringes, and needles were previously washed with distilled water. Each dog received each of the following solutions:

Procaine hydrochloride, 1 per cent (commercial buffered solution, Cutter Laboratories. Measured pH 6.1 to 6.2)

Procaine hydrochloride, 2 per cent (commercial buffered solution, Cutter Laboratories. Measured pH 6.2 to 6.3)

Lidocaine hydrochloride, 0.5 per cent (commercial buffered solution, Astra Pharmaceutical Products, Inc. Measured pH 6.7 to 6.9)

Lidocaine hydrochloride, 1 per cent (commercial buffered solution, Astra Pharmaceutical Products, Inc. Measured pH 6.7 to 6.9)

Tetracaine hydrochloride, 0.1 per cent (prepared by adding 4 mg. of Niphanoid crystals, Winthrop Laboratories, to 4 ml. of saline solution. Measured pH 6.4 to 6.6)

Tetracaine hydrochloride, 0.2 per cent (prepared by adding 8 mg. of Niphanoid crystals, Winthrop Laboratories, to 4 ml. of saline solution. Measured pH 6.4 to 6.8)

Lidocaine hydrochloride, 1 per cent and procaine hydrochloride, 1 per cent (prepared by adding 40 mg. of procaine crystals, Winthrop Laboratories, to 4 ml. of lidocaine, 1 per cent, Astra Pharmaceutical Products, Inc. Measured pH 6.6 to 6.8).

Lidocaine hydrochloride, 0.5 per cent and procaine hydrochloride, 2 per cent (prepared by adding 80 mg. of procaine crystals, Winthrop Laboratories, to 4 ml. of lidocaine, 0.5 per cent, Astra Pharmaceutical Products, Inc. Measured pH 6.6 to 6.8)

Procaine hydrochloride, 1 per cent and tetracaine hydrochloride, 0.2 per cent (prepared by adding 8 mg. of tetracaine Niphanoid crystals. Winthrop Laboratories, to 4 ml. of procaine, 1 per cent, Cutter Laboratories. Measured pH 6.1 to 6.3)

Procaine hydrochloride, 2 per cent and tetracaine hydrochloride, 0.1 per cent (prepared by adding 4 mg. of tetracaine Niphanoid crystals, Winthrop Laboratories, to 4 ml. of procaine, 2 per cent, Cutter Laboratories. Measured pH 6.2 to 6.4)

Lidocaine hydrochloride, 1 per cent and tetracaine hydrochloride, 0.1 per cent (prepared by adding 4 mg. of tetracaine Niphanoid crystals, Winthrop Laboratories, to 4 ml. of lidocaine, 1 per cent, Astra Pharmaceutical Products, Inc. Measured pH 6.8 to 7.0)

Lidocaine hydrochloride, 1 per cent and tetracaine hydrochloride, 0.2 per cent (prepared by adding 8 mg. of tetracaine Nipha-

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noid crystals, Winthrop Laboratories, to 4 ml. of lidocaine, 1 per cent, Astra Pharmaceutical Products, Inc. Measured pH 6.8 to 7.0)

Preparations always were mixed immediately prior to injection. Each dog received the 12 solutions in a different, randomly selected[10] order, at 24-hour intervals; each series was completed within 12 to 14 days. Absence of skin-twitch response to pinching with an Allis clamp was considered analgesia. This was tested on both flanks, along a line 2 cm. off the spine. When the 2 sides differed, their average was recorded. To avoid anatomic intricacies and obtain data easier to handle mathematically, the analgesic level was expressed in centimeters above the interarcual ligament. We believe this convention acceptable since the animals were remarkably similar in spinal length and were in an identical position.

Disappearance of contraction of the anal sphincter in response to stroking all quadrants of the anal margin closely correspond to complete analgesia at the level of the interarcual ligament; since it was an easily measurable parameter, disappearance and recurrence of this reflex were chosen as end points of latency and duration of action, respectively. Analgesia was determined every minute for 15 minutes after injection, then every 5 minutes till the analgesic level again reached 4 cm. above the interarcual ligament; 1-minute checks were then resumed until return of the anal reflex. All observations were made by the same investigator. The animals received 250 mg. of Chloromycetin® intramuscularly every other day, and were daily observed for motor and sensory damage (walk and hyperesthesia to pin prick).

A preliminary study in 6 dogs with 6 doses of procaine, 1 per cent, suggested that the method was reliable, confirmed by an analysis of variance of the results ($p = 0.05$)[10] and helped determine the concentrations and injection rate which repeatedly

Table 1

LATENCY AND DURATION OF PROCAINE, LIDOCAINE, AND THEIR COMBINATIONS MEAN OF 12 DOGS (SD BETWEEN PARENTHESES)

Solution	Procaine, 1%	Procaine, 2%	Lidocaine, 0.5%	Lidocaine, 1%	Procaine, 2% Lidocaine, 0.5%	Procaine, 1% Lidocaine, 1%
Latency, minutes	2.17 (0.20)	2.0 (0.17)	2.25 (0.25)	2.02 (0.33)	2.06 (0.13)	2.17 (0.33)
Time, minutes	Height of analgesic level (in cm.)					
5	8.2 (1.2)	10.5 (0.9)	8.6 (0.8)	8.0 (1.4)	10.0 (1.2)	9.5 (1.8)
10	11.1 (0.9)	13.1 (0.9)	13.6 (1.0)	13.2 (1.0)	13.2 (1.1)	13.4 (1.2)
15	11.1 (0.9)	13.1 (0.9)	13.6 (1.0)	13.2 (1.0)	13.2 (1.1)	13.4 (1.2)
20	11.1 (0.9)	13.1 (0.9)	13.6 (1.0)	13.2 (1.0)	13.2 (1.1)	13.4 (1.2)
25	11.1 (0.9)	13.1 (0.9)	13.6 (1.0)	13.2 (1.0)	13.2 (1.1)	13.4 (1.2)
30	10.6 (1.0)	12.4 (1.4)	13.6 (1.0)	13.2 (1.0)	13.2 (1.1)	13.4 (1.2)
35	9.6 (1.9)	11.1 (2.3)	13.6 (1.0)	13.2 (1.0)	12.1 (1.6)	13.4 (1.2)
40	8.3 (2.5)	8.8 (4.3)	13.6 (1.0)	13.2 (1.0)	10.5 (2.6)	13.4 (1.2)
45	7.2 (2.9)	7.4 (3.0)	13.6 (1.0)	13.2 (1.0)	8.8 (2.1)	13.4 (1.2)
50	5.2 (2.6)	5.6 (3.4)	13.6 (1.0)	13.2 (1.0)	6.3 (2.2)	13.4 (1.2)
55	0.7 (1.1)	3.7 (2.4)	13.6 (1.0)	13.2 (1.0)	3.8 (1.7)	13.4 (1.2)
60		1.7 (1.7)	13.6 (1.0)	13.2 (1.0)	1.9 (1.2)	13.4 (1.2)
65		0.5 (0.9)	13.4 (1.0)	13.2 (1.0)	0.6 (1.0)	13.4 (1.2)
70			12.8 (1.4)	13.2 (1.0)		12.9 (1.5)
75			12.2 (2.2)	13.2 (1.0)		11.1 (1.9)
80			10.8 (2.6)	12.2 (1.6)		10.2 (2.1)
85			8.4 (3.5)	11.4 (2.1)		9.6 (2.0)
90			6.5 (3.1)	9.4 (2.0)		7.6 (2.3)
95			4.2 (2.9)	7.7 (2.3)		6.5 (2.2)
100			2.4 (2.3)	5.2 (3.4)		4.8 (2.0)
105			1.5 (2.7)	4.1 (2.1)		3.3 (1.9)
110			1.0 (2.5)	2.1 (1.7)		1.7 (1.4)
115			0.4 (1.6)	0.4 (1.3)		0.9 (4.1)
120						

provided complete analgesia. The femoral mean arterial pressures of these dogs were electronically recorded; no significant pressure changes were detectable with the levels and position adopted here.

RESULTS

Latency, height of analgesia against time and total block duration (as defined above) were recorded for each animal and solution. The results are summarized in table 1 for procaine, lidocaine, and their combinations, and in table 2 for tetracaine and its combinations.

The main parameters: latency, total duration, maximum analgesic level, and time of onset of decline, are shown in table 3. Each figure of the 3 tables is the arithmetic mean of the data of 12 dogs, with its standard deviation (SD). The small SD values suggest a homogenous response of all animals to the same solution, especially for procaine and lidocaine; total duration of tetracaine solutions is somewhat more variable. There are, however, 2 exceptions: lidocaine, 1 per cent and tetracaine, 0.1 per cent; procaine, 2 per cent and tetracaine, 0.1 per cent.

When 2 groups of responses are evident, half the animals show the duration of action expected from lidocaine or procaine alone, while the other half show a tetracaine response. Clearly these results cannot be integrated, and for these 2 mixtures, 2 subgroups have been provided in the 3 tables. An individual idiosyncrasy is improbable since only 2 dogs show the tetracaine response with both mixtures.

Figures 1 and 2 illustrate tables 1 and 2, respectively. The first 10 minutes are enlarged out of scale, thus affording better comparison of latencies. To avoid complex multinomial curves, the scatter plots have been divided into 3 areas: latency, duration of maximum analgesic effect, and span of decline of that level. Linear regression equations were then calculated for each segment.[10] The regression curves are drawn on figures 1 and 2.

Statistical conclusions were drawn from an analysis of variance ($p=0.05$) of the parameters of table 3 and from the 95 per cent confidence intervals of the regression curves.[10] These conclusions are summarized in table 4.

Our findings may thus be outlined:

1. The height of the maximum analgesic level was similar for all solutions: 13 to 14 cm.

2. The latency of procaine, lidocaine, and all the mixtures including them, was identical (about 2 minutes); that of tetracaine alone was about double (4 minutes).

3. Doubling the concentration of plain solutions caused no changes in latency or duration.

4. Decline of analgesic level occupied

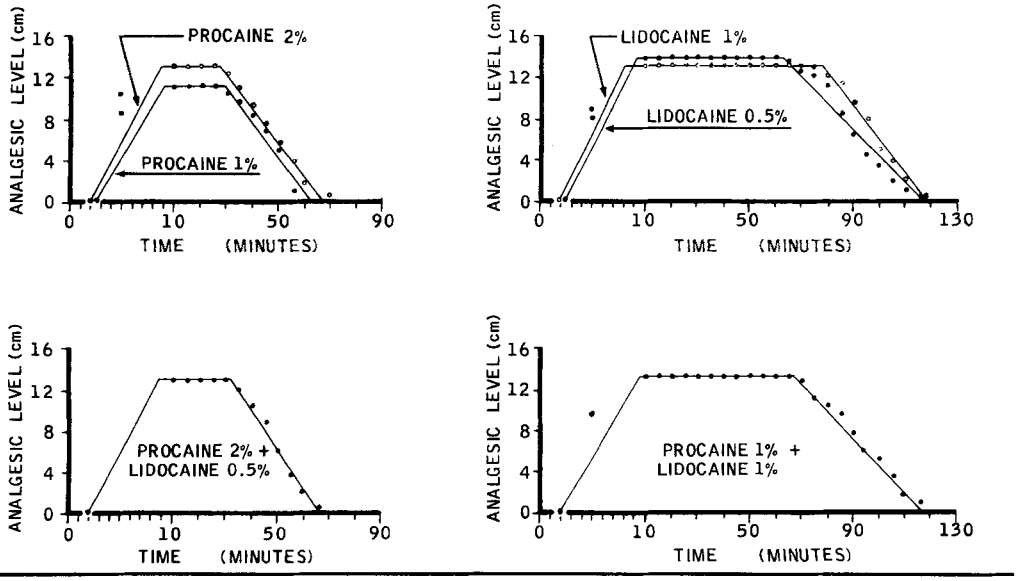

FIG. 1. Latency and duration of procaine, lidocaine, and their combinations (scatter plots and regression lines).

Table 2

LATENCY AND DURATION OF TETRACAINE AND ITS COMBINATIONS MEAN OF 12 DOGS (SD BETWEEN PARENTHESES)

Solution	Tetracaine, 0.1%	Tetracaine, 0.2%	Procaine, 1% Tetracaine, 0.2%	Procaine, 2% 6 dogs +	Tetracaine 0.1% 6 dogs	Lidocaine, 1% Tetracaine, 0.2%	Lidocaine, 1% 7 dogs +	Tetracaine, 0.1% 5 dogs
Latency, minutes	4.13 (0.17)	4.0 (0.66)	2.6 (0.25)	2.33 (0.84)	2.45 (0.84)	2.0 (0.2)	1.95 (0.85)	2.43 (0.6)
Time, minutes	Height of analgesic level (in cm.)							
5	8.6 (4.3)	9.0 (1.5)	7.3 (0.9)	8.1 (2.0)	9.0 (1.6)	9.2 (1.2)	10.3 (1.8)	9.8 (0.9)
10	10.8 (4.3)	11.8 (1.1)	14.0 (0.9)	14.2 (1.0)	14.0 (0.9)	14.0 (1.13)	13.7 (1.2)	13.4 (1.9)
15	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	14.2 (1.0)	14.0 (0.9)	14.0 (1.13)	13.7 (1.2)	13.4 (1.9)
20	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	14.2 (1.0)	14.0 (0.9)	14.0 (1.13)	13.7 (1.2)	13.4 (1.9)
25	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	14.2 (1.0)	14.0 (0.9)	14.0 (1.13)	13.7 (1.2)	13.4 (1.9)
30	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	12.8 (1.9)	14.0 (0.9)	14.0 (1.13)	13.7 (1.2)	13.4 (1.9)
35	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	11.5 (3.1)	14.0 (0.9)	14.0 (1.13)	13.7 (1.2)	13.4 (1.9)
40	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	9.7 (3.1)	14.0 (0.9)	14.0 (1.13)	13.7 (1.2)	13.4 (1.9)
45	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	7.8 (4.3)	14.0 (0.9)	14.0 (1.13)	13.7 (1.2)	13.4 (1.9)
50	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	5.3 (2.8)	14.0 (0.9)	14.0 (1.13)	13.7 (1.2)	13.4 (1.9)
55	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	2.6 (1.2)	14.0 (0.9)	14.0 (1.13)	13.7 (1.2)	13.4 (1.9)
60	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	1.0 (1.1)	14.0 (0.9)	14.0 (1.13)	13.7 (1.2)	13.4 (1.9)
65	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)		14.0 (0.9)	14.0 (1.13)	13.7 (1.2)	13.4 (1.9)
70	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)		14.0 (0.9)	14.0 (1.13)	13.7 (1.2)	13.4 (1.9)
75	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)		14.0 (0.9)	14.0 (1.13)	13.3 (1.2)	13.4 (1.9)
80	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)		14.0 (0.9)	14.0 (1.13)	12.6 (2.1)	13.4 (1.9)
85	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)		14.0 (0.9)	14.0 (1.13)	12.6 (2.1)	13.4 (1.9)
90	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)		14.0 (0.9)	14.0 (1.13)	11.4 (2.9)	13.4 (1.9)
95	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)		14.0 (0.9)	14.0 (1.13)	10.6 (2.8)	13.4 (1.9)
100	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)		14.0 (0.9)	14.0 (1.13)	8.6 (2.8)	13.4 (1.9)
105	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)		14.0 (0.9)	14.0 (1.13)	5.4 (2.1)	13.4 (1.9)

110	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	14.0 (0.9)	14.0 (1.13)	3.8 (2.0)	13.4 (1.9)
115	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	14.0 (0.9)	14.0 (1.13)	1.7 (2.7)	13.4 (1.9)
120	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	14.0 (0.9)	14.0 (1.13)	1.3 (2.6)	13.4 (1.9)
125	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	14.0 (0.9)	14.0 (1.13)		13.4 (1.9)
130	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	14.0 (0.9)	14.0 (1.13)		13.4 (1.9)
165	12.4 (1.3)	12.9 (1.2)	14.0 (0.9)	14.0 (0.9)	14.0 (1.13)		13.4 (1.9)
170	12.2 (1.2)	12.9 (1.2)	14.0 (0.9)	14.0 (0.9)	14.0 (1.13)		13.4 (1.9)
175	12.2 (1.2)	12.9 (1.2)	14.0 (0.9)	14.0 (0.9)	14.0 (1.13)		13.4 (1.9)
180	12.2 (1.3)	12.9 (1.2)	14.0 (0.9)	14.0 (0.9)	14.0 (1.13)		13.4 (1.9)
185	12.2 (1.3)	12.9 (1.2)	13.6 (1.5)	14.0 (0.9)	14.0 (1.13)		13.4 (1.9)
190	11.9 (1.6)	12.9 (1.2)	13.6 (1.5)	14.0 (0.9)	14.0 (1.13)		13.4 (1.9)
195	11.3 (1.5)	12.5 (1.6)	13.6 (1.5)	14.0 (0.9)	13.7 (1.5)		13.4 (1.9)
200	11.1 (1.8)	12.5 (1.6)	13.6 (1.5)	14.0 (0.9)	13.7 (1.5)		13.4 (1.9)
205	9.4 (2.1)	11.9 (1.7)	13.0 (2.0)	14.0 (0.9)	13.7 (1.5)		13.4 (1.9)
210	8.3 (4.1)	10.5 (2.3)	12.2 (2.5)	13.7 (1.0)	12.9 (2.5)		13.4 (1.9)
215	7.7 (3.9)	10.2 (2.3)	11.0 (3.9)	13.2 (1.0)	12.5 (2.6)		13.2 (2.0)
220	6.7 (4.2)	9.0 (2.9)	9.2 (3.8)	12.2 (1.8)	11.5 (2.8)		11.6 (2.0)
225	5.2 (4.1)	8.1 (3.1)	8.2 (3.5)	11.2 (2.9)	10.2 (3.3)		11.6 (2.0)
230	4.1 (4.2)	6.8 (3.0)	6.5 (3.7)	9.2 (3.1)	9.0 (2.6)		10.8 (3.1)
235	2.9 (3.3)	5.7 (2.8)	5.9 (4.0)	8.2 (3.2)	8.0 (2.8)		10.4 (3.6)
240	2.0 (3.2)	4.2 (2.9)	4.4 (3.1)	6.5 (2.5)	6.8 (2.6)		9.6 (3.38)
245	1.3 (3.1)	3.3 (2.5)	3.0 (2.1)	4.7 (2.7)	5.3 (3.2)		9.2 (3.3)
250	1.0 (2.5)	2.2 (2.6)	1.6 (1.8)	4.2 (2.2)	4.0 (3.6)		8.4 (4.1)
255	0.9 (2.4)	1.7 (2.9)	0.9 (1.2)	3.3 (2.4)	3.5 (3.2)		6.6 (5.2)
260	0.6 (1.4)	1.5 (2.1)	0.4 (0.8)	3.2 (1.8)	2.3 (3.5)		6.2 (5.0)
265	0.4 (1.0)	1.1 (1.5)		1.8 (2.0)	1.9 (3.3)		5.2 (4.8)
270		0.7 (1.1)		1.2 (1.3)	0.8 (0.4)		4.6 (4.9)
275		0.3 (1.0)		0.5 (0.8)	0.6 (0.4)		4.2 (5.2)
280					0.6 (0.4)		3.4 (5.0)
285							2.4 (0.9)

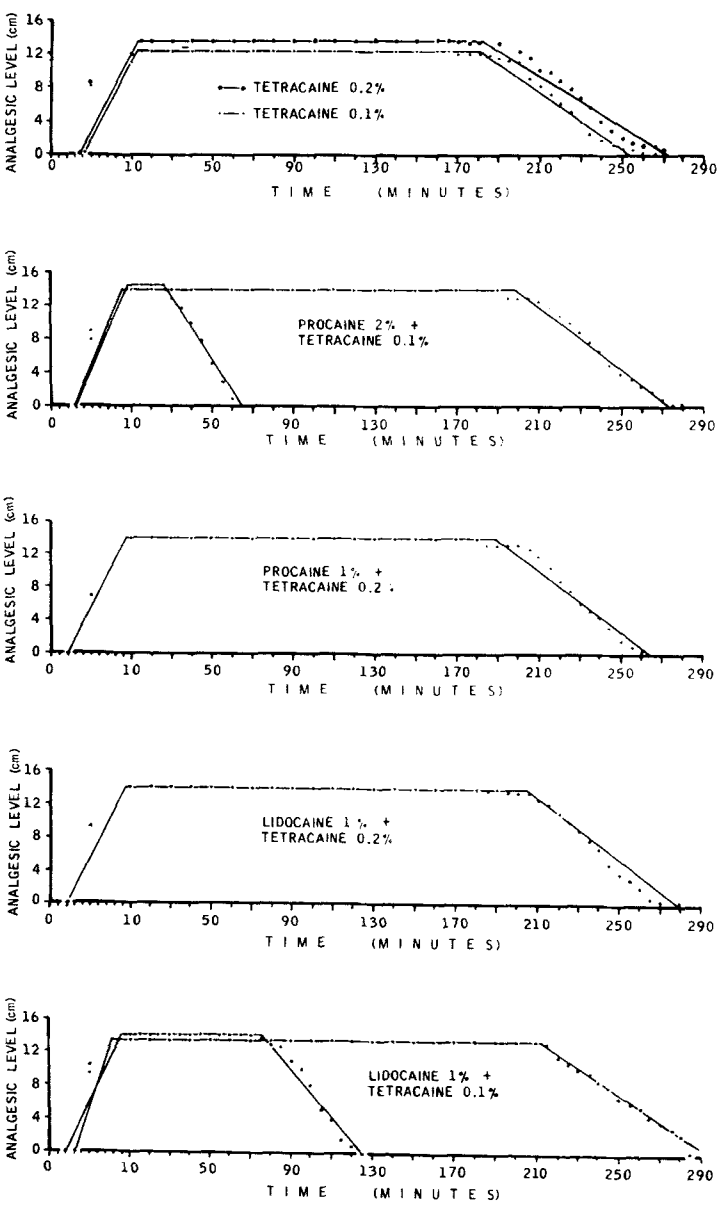

FIG. 2. Latency and duration of tetracaine and its combinations (scatter plots and regression lines).

about ½ of the total duration time for procaine and lidocaine alone and 1/3 of it for tetracaine alone. For the mixtures, the same relation to total duration occurred, depending on the drug-type of duration-response: procaine, lidocaine, or tetracaine.

5. Total duration of combinations:

Procaine, 1 per cent	Lidocaine, 1 per cent: duration expected from lidocaine alone.
	Tetracaine, 0.2 pepr cent: duration expected from tetracaine alone.
Procaine, 2 per cent	Lidocaine, 0.5 per cent: duration expected from procaine alone.
	Tetracaine, 0.1 per cent: half of animals (50 per cent) show duration expected from procaine alone; half of animals (50 per cent) show that expected from tetracaine alone.
Lidocaine, 1 per cent	Tetracaine, 2 per cent: duration expected from tetracaine alone.
	Tetracaine, 0.1 per cent: 58 per cent of animals show duration expected from lidocaine alone; 42 per cent that of tetracaine alone.

Table 3

SUMMARY OF MAIN PARAMETERS FOR EACH SOLUTION
MEAN OF 12 DOGS (SD BETWEEN PARENTHESES)

Parameter	Procaine, 1%	Procaine, 2%	Lidocaine, 0.5%	Lidocaine, 1%	Procaine, 2% Lidocaine, 0.5%	Procaine, 1% Lidocaine, 1%	Tetracaine, 0.1%	Tetracaine, 0.2%	Procaine, 1% Tetracaine, 0.2%	Procaine, 2% Tetracaine, 0.1%		Lidocaine, 1% Tetracaine, 0.2%	Lidocaine, 1% Tetracaine, 0.1%	
										6 dogs	6 dogs		7 dogs	5 dogs
Latency, minutes	2.17 (0.2)	2.0 (0.17)	2.25 (0.25)	2.02 (0.33)	2.06 (0.13)	2.17 (0.33)	4.13 (0.17)	4.0 (0.66)	2.60 (0.25)	2.33 (0.84)	2.45 (0.84)	2.0 (0.2)	1.95 (10.85)	2.43 (0.6)
Maximal analgesic level (cm.)	11.1 (0.9)	13.1 (0.9)	13.6 (1.0)	13.2 (1.0)	13.2 (1.1)	13.4 (1.2)	12.4 (1.3)	13.2 (1.7)	14.0 (0.9)	14.2 (1.0)	14.0 (0.9)	14.0 (1.13)	13.7 (1.2)	13.4 (1.9)
Time of onset of fall of maximal analgesic level (in minutes)	20.0 (4.3)	28.0 (3.9)	62.1 (4.1)	77.1 (5.0)	31.5 (4.8)	65.6 (3.9)	178.1 (8.7)	179.3 (7.4)	190.8 (9.1)	25.6 (4.7)	198.0 (9.3)	204.4 (7.9)	76.4 (5.0)	212.1 (9.5)
Total duration, minutes	62.1 (6.1)	65.4 (6.0)	122.2 (6.6)	123.8 (6.8)	64.4 (6.4)	114.9 (6.7)	255.4 (20.4)	272.4 (27.4)	284.7 (24.3)	64.1 (7.1)	277.1 (26.4)	282.7 (23.1)	125.8 (8.4)	292.0 (27.1)

DISCUSSION

The present findings should not be extrapolated to clinical situations without serious reservations:

1. Evidence in the literature of species variations suggests extreme caution in applying, to humans, observations made in dogs.[11]

2. In all probability, differences of diffusion processes exist between epidural and peripheral nerve blocks: the selective passage through dural root sleeves, the action upon the root fibers and even spinal tracts, the importance of concentration for the spread of analgesia, the epidural space content (notably its sympathectomized vessels) are kinetic factors which set apart epidural from other regional blocks.[8]

3. The pH of our solutions were similar and the epidural tissues were most likely able to buffer the small amounts injected. Damage and infection of these tissues were avoided and we have no reason to believe that the experiments modified their pH.

4. Present conclusions may only hold true for the concentrations here selected; a wider range of concentrations ought certainly to be investigated in the future.

5. Testing analgesia with a clamp has obvious pitfalls; while too coarse to detect small differences of effect, the technic is a poor measure of the anesthesia required for a surgical procedure. Latencies, durations, and analgesic levels, therefore, may be different in clinical practice.

To clinicians and investigators, the term "potency" usually implies a comparison of Minimum Effective Concentration (Cm), ideally performed in identical conditions, especially fiber diameter, pH, local tissues, and length of application.[12] Because such concept ignores important parameters of the effect (for example, latency, duration), "activity" rather than "potency" will be used in the following discussion.

Thus defined, drug activity is a measure of its capability of producing an effect, independent of the magnitude of the effect. Obviously the activity of a solution of local anesthetic is the product (Q) of 2 factors:

(a) The mass or concentration (C) — ideally, molar concentration of free base.

(b) An intrinsic and specific property of the drug; its relative activity (A_r), a constant obtained by comparing the Minimum Effective Concentration with that of a standard (usually procaine).

Table 4

STATISTICAL DIFFERENCES BETWEEN PARAMETERS FOR EACH SOLUTION

Existence of statistically significant difference ($p = 0.05$)	Latency	Maximum analgesic level	Time of onset of decline of maximum analgesic level	Total block duration
No difference	(1) Between procaine, 1 to 2% and lidocaine, 0.5 to 1% and lidocaine-tetracaine mixtures and procaine-tetracaine mixtures (2) Between tetracaine, 0.1% and tetracaine, 0.2%	Between all solutions	(1) Between procaine, 1 or 2% and procaine, 2%-lidocaine, 0.5% and 50% of procaine, 2%-tetracaine, 0.1%	(1) Between procaine, 1 or 2% and procaine, 2%-lidocaine, 0.5% and 50% of procaine, 2%-tetracaine, 0.1%
			(2) Between lidocaine, 0.5 or 1% and procaine, 1%-lidocaine, 1% and 50% of lidocaine, 1%-tetracaine, 0.1%	(2) Between lidocaine, 0.5 or 1% and procaine, 1%-lidocaine, 1% and 50% of lidocaine, 1%-tetracaine, 0.1%
			(3) Between tetracaine, 0.1 or 0.2% and lidocaine, 1%-tetracaine, 0.2% and procaine, 1%-tetracaine, 0.2% and 50% of procaine, 2%-tetracaine, 0.1%	(3) Between tetracaine, 0.1 or 0.2% and lidocaine, 1%-tetracaine, 0.2% and procaine, 1%-tetracaine, 0.2% and 50% of procaine, 2%-tetracaine, 0.1%
Difference	Between above group 1 and above group 2		Between above groups 1 and 2 above groups 1 and 3 above groups 2 and 3	Between above groups 1 and 2 above groups 1 and 3 above groups 2 and 3

It is encouraging to find that, notwithstanding the wide variety of methods utilized, there is good agreement among the estimates of the relative activities of procaine, lidocaine, and tetracaine.

Procaine, 1
Lidocaine, 2 to 2.5
Tetracaine, 10 to 15

If these values are accepted, the following hypothesis may be proposed to explain our results:

Let C and A_r be, respectively, the concentration and relative activity of a local anesthetic solution, and Q be the product C x A_r. When 2 anesthetics of different duration and latency are combined to produce a regional block:

(a) the fastest-acting drug will determine the latency, even if its Q is the smallest; (b) the component with the largest Q directs the duration of the block and the time of decline of maximum analgesic area; (c) if both Q's are equal, the duration will either be that of the shortest or that of the longest-acting drug; the type of response appears randomly distributed.

This offers an interesting method of comparing anesthetic activities, independent of Minimum Effective Concentration (often difficult to determine),[11, 12] and applicable for all concentrations, while drugs are necessarily studied in the same conditions. To compare the activity of a drug B to that of a standard A, different concentrations of B are combined to a fixed concentration of A, and the duration of these mixtures is determined. Our hypothesis suggests that within a narrow concentration interval $\triangle C$, the duration of action in 100 per cent of the animals will shift from that of drug A to that of B. Three or more concentrations may then be chosen within $\triangle C$, and the percentage of animals giving either type of response esti-

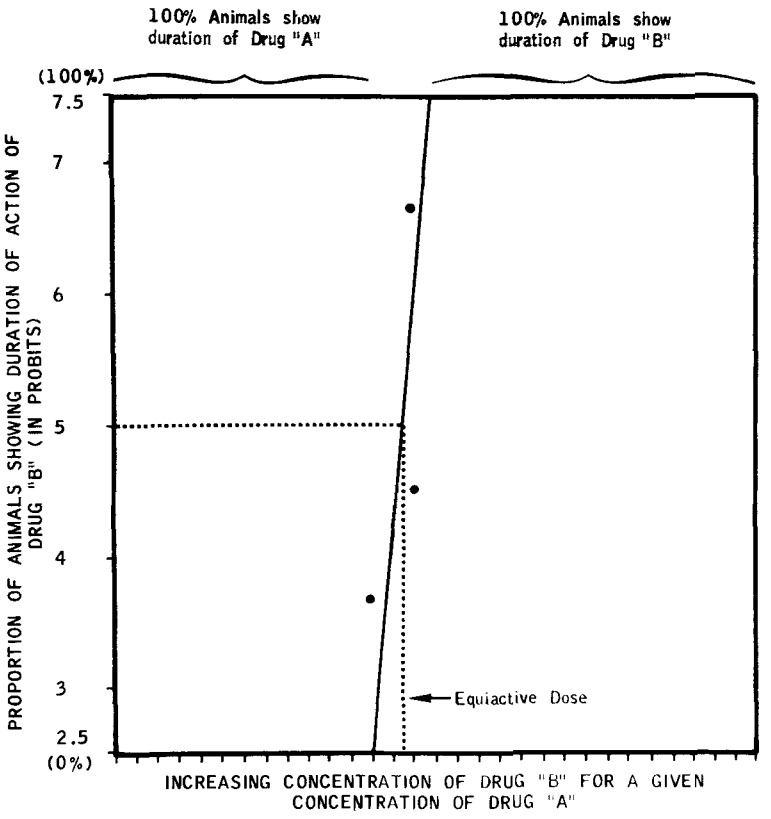

FIG. 3. Graphic method of determining equiactive concentrations of 2 drugs, A and B.

mated. Through probit transformation,[13] a straight regression line can be obtained (figure 3). Probit 5 will then provide the equiactive concentrations.

Let us repeat that our results cannot be extrapolated to clinical practice without extreme caution. The present investigation leaves many questions unanswered. It does not pretend to be more than a mere introduction — and we hope a stimulus — to the fascinating study of local anesthetic combinations.

SUMMARY

Clinical concentrations of procaine, lidocaine, and tetracaine were mixed in paired combinations and the latency and duration of analgesia of these mixtures were experimentally determined in 12 dogs. This investigation was carried out with a standardized uniform epidural technic, the sensory blockade being estimated by Allis clamp. Statistical evidence proves the method both accurate and reliable. The results suggest an attractive hypothesis: When 2 drugs of different blocking time are combined, latency and duration of the mixture depends upon the activity of both components, that is, the quotient of concentration x drug relative activity. The period of latency is determined by the fastest-acting component, whatever its activity. If the drugs differ in activity, the total duration will be that of the more active solution. With equiactive components, the duration will be that of the shortest or that of the longest-acting drug. The response appears randomly distributed. An advantageous method of comparing relative anesthetic activities, based on these findings, is proposed.

Generic and Trade Names of Drugs

Procaine—Novocain
Lidocaine—Xylocaine
Tetracaine—Pantocaine
Chloramphenicol—Chloromycetine

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SHORT TAKES

A teacher asked her class the difference between a primitive man and a modern man. Johnny answered, "When his wife talks too much a modern man goes to his club. A primitive man just reaches for it."

— *Woodmen of the World Mag.*

* * *

The lady was shaking hands with the preacher as she left the church, and congratulating him, with glowing eyes, on the service.

"And what a marvelous sermon," she said. "Everything you said applies to someone or other I know."

—*Variety*, London.