Local Anesthetic Toxicity Modified by Oxygen and by Combination of Agents

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CONSIDERATION of current use of local anesthetic drugs provided a stimulus for investigation of two situations which might affect the safety of patients. The first concerns the use of oxygen to offset toxicity of local anesthetic agents. Moore and Bridenbaugh [1] have stressed the value of using succinylcholine and administering oxygen to offset damage from convulsions. The other situation relates to combinations of short and longer acting anesthetic agents. For example, when rapid onset of analgesia is desired with the use of procaine, chloroprocaine or lidocaine, tetracaine is frequently added to prolong the period of analgesia. Does this addition increase the toxicity of the material injected? It was deemed better to employ animals than man for studies on toxicity, consequently rats were chosen for these experiments.

Method

White female rats, weighing 200 ± 10 g., of the Charles-River strain were used except for instances noted later in which this strain was unavailable. They were anesthetized with pentobarbital, 60 mg./kg. intraperitoneally. A tracheostomy was performed and a metal cannula inserted to insure a free airway. A jugular vein was cannulated and a polyethylene catheter was inserted to within 1 cm. of the heart. The volume of this catheter was noted and taken into account during injection of drugs. Another catheter was inserted into the carotid artery for registration of blood pressure which was recorded on a kymograph.

Local anesthetic agents were given to rats intravenously at constant rates. Each group contained ten rats. To learn whether this method produced results comparable to standard findings, two series of injections were made in which the concentration of the agent was the variable. One-half, 1, 2, and 3 per cent procaine was utilized in each of four groups, and 1, 2, and 3 per cent chloroprocaine was used in each group of the other series. Carworth-Farm rats were utilized for the experiments with chloroprocaine. Another series of experiments was done in which the rate of administration was the variable. One group received 2 per cent solutions of procaine, another 2 per cent chloroprocaine, and 2 per cent mepivacaine was used with the third group. Rockland-Farm rats were employed in the experiments with mepivacaine. Two end points were noted. First was the time which elapsed prior to respiratory arrest determined by observation and the other was the time before cardiac standstill ensued, indicated by zero blood pressure. Rates of injection were 0.1, 0.2, and 0.4 ml. per minute. An additional group was given procaine at 0.05 ml. per minute.

To test the effect of oxygen given in combination with local anesthetic drugs, the rats were placed, when cannulation was complete, into a chamber through which 100 per cent oxygen flowed. Five minutes was allowed for equilibration. Administrations were made of 2 per cent procaine at rates of 0.05, 0.1, 0.2, and 0.4 ml./minute. Two per cent procaine with 0.1 per cent tetracaine was also tested, injecting at 0.1 ml./minute. Two per cent chloroprocaine, with and without tetracaine, 1.5 per cent lidocaine with and without tetracaine, and 2 per cent mepivacaine with and without tetracaine were employed at injection rates of 0.1 ml./minute. After establishing values for these eleven groups, the experiments were repeated with eleven additional groups of animals that were breathing air.

For investigation of combinations of agents,

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TABLE 1. Effect of Concentration

Agent	Rate of Injection (ml. minute)	Time to Respiratory Arrest (seconds)	P	Time to Circulatory Arrest (seconds)	P	Drugs (mg.)	P	Rat Strain
Procaine 0.5%	0.4	401.2±40.3		560.2±49.9		18.7±1.7		C.R.
			<0.001		<0.001		N.S.	
Procaine 1%	0.4	214.2±19.5		341.2±38.5		22.8±1.9		C.R.
			<0.001		<0.001		N.S.	
Procaine 2%	0.4	89.2± 8.8		187.0± 7.9		24.4±1.0		C.R.
			N.S.		<0.025		N.S.	
Procaine 3%	0.4	72.5±15.1		149.0±15.2		29.9±3.0		C.R.
Chloroprocaine 1%	0.4	118.2±13.1		213.0±21.7		14.2±1.4		C.F.
			<0.001		<0.001		N.S.	
Chloroprocaine 2%	0.4	56.0± 5.7		121.5±16.0		16.2±2.1		C.F.
			<0.001		<0.001		N.S.	
Chloroprocaine 3%	0.4	32.2± 3.5		66.0± 2.3		13.2±0.5		C.F.

C.R. = Charles-River rats.
C.F. = Carworth-Farm rats.

0.1 per cent tetracaine was added to other drugs. Concentrations of procaine used were 1 and 2 per cent, chloroprocaine 2 and 3 per cent, and mepivacaine 1 and 2 per cent, all injected at 0.4 ml./minute. Lidocaine 1 per cent, lidocaine 1.5 per cent with and without oxygen, procaine 2 per cent, chloroprocaine 2 per cent, and mepivacaine 2 per cent were injected at 0.1 ml. minute. After establishing control values for each drug, 0.1 per cent solid tetracaine was added to the solutions, and twelve further sets of experiments were performed. Where Charles-River animals were not available, additional control values were obtained with the strain of rats employed for comparison with the experimental values.

TABLE 2. Rate of Injection

Agent	Rate of Injection (ml. minute)	Time before Respiratory Arrest (seconds)	P	Time before Circulatory Arrest (seconds)	P	Drugs (mg.)	P	Rat Strain
Procaine 2%	0.4	89.2± 8.8		187.0± 8.0		24.4±1.0		C.R.
			<0.001		N.S.		<0.001	
Procaine 2%	0.2	159.0± 4.2		209.5± 13.6		14.7±0.9		C.R.
			<0.001		<0.001		N.S.	
Procaine 2%	0.1	369.0± 52.4		412.5± 49.6		14.2±1.7		C.R.
			<0.001		<0.001		<0.01	
Procaine 2%	0.05	138.4±258.9		143.9±260.8		24.4±4.4		C.R.
Chloroprocaine 2%	0.4	56.0± 4.2		130.5± 14.1		17.4±1.9		C.R.
			<0.001		N.S.		<0.001	
Chloroprocaine 2%	0.2	83.8± 5.1		118.5± 7.9		8.2±1.8		C.R.
			<0.001		<0.001		N.S.	
Chloroprocaine 2%	0.1	151.5± 13.0		200.0± 10.8		7.1±0.6		C.R.
Mepivacaine 2%	0.1	68.8± 1.8		149.2 ± 11.9		19.9±1.6		R.F.
			<0.001		N.S.		<0.001	
Mepivacaine 2%	0.2	102.5± 8.2		131.8± 10.7		9.2±0.8		R.F.
			<0.001		<0.001		N.S.	
Mepivacaine 2%	0.1	218.8± 14.9		255.8± 13.2		8.7±0.4		R.F.

C.R. = Charles-River rats.
R.F. = Rockland-Farm rats.

TABLE 3. Survival With and Without Oxygen

Agents	Rate of Injection (ml./minute)	Respiratory Arrest (seconds)	P	Circulatory Arrest (seconds)	P	Milligrams of Drugs				Strain of Rats
						Short Acting	P	Tetracaine	P	
Procaine 2%	0.4	89.2± 8.8	N.S.	187.0± 7.9	<0.01	24.4±1.0	<0.025			Charles River
Procaine 2% with oxygen	0.4	68.5± 4.8		235.5± 18.3		30.6±2.4				
Procaine 2%	0.2	159.0± 4.2	N.S.	209.5± 13.6	<0.001	14.7±0.9	<0.001			Charles River
Procaine 2% with oxygen	0.2	158.5± 18.5		710.0± 85.5		49.8±6.0				
Procaine 2%	0.1	369.0± 52.4	N.S.	412.5± 49.6	<0.001	14.2±1.7	<0.001			Charles River
Procaine 2% with oxygen	0.1	470.0± 59.0		1,188.0±165.8		40.9±5.7				
Procaine 2%	0.05	1,384.0±258.9	N.S.	1,439.0±260.8	<0.01	24.4±4.4	<0.01			Charles River
Procaine 2% with oxygen	0.05	1,589.0±222.4		2,307.0±163.4		39.2±2.8				
Procaine 2% + Tetracaine 0.1%	0.1	198.7± 14.0	N.S.	245.2± 15.1	<0.001	8.4±0.5	<0.001	0.42±0.02	<0.001	Charles River
Procaine 2% + Tetracaine 0.1% with oxygen	0.1	237.0± 18.6		606.0± 73.4		20.8±2.5		1.04±0.12		
Chloroprocaine 2%	0.1	151.5± 13.0	N.S.	200.0± 10.8	<0.001	7.1±0.6	<0.001			Charles River
Chloroprocaine 2% with oxygen	0.1	147.5± 11.0		357.5± 32.1		12.3±1.1				
Chloroprocaine 2% + Tetracaine 0.1%	0.1	113.5± 12.1	N.S.	154.5± 12.0	<0.001	5.3±0.4	<0.001	0.27±0.02	<0.001	Charles River
Chloroprocaine 2% + Tetracaine 0.1% with oxygen	0.1	103.5± 7.6		309.0± 28.3		10.6±1.0		0.53±0.05		
Lidocaine 1.5%	0.1	204.0± 16.7	N.S.	265.5± 12.5	<0.001	6.1±0.3	<0.001			Charles River
Lidocaine 1.5% with oxygen	0.1	207.0± 21.3		613.0± 95.0		14.1±2.2				

TABLE 3. (Continued)

Agent	Rate of Injection (ml./minute)	Respiratory Arrest (seconds)	P	Circulatory Arrest (seconds)	P	Milligrams of Drugs			Strain of Rats
						Short Acting	P	Tetracaine	P	
Lidocaine 1.5% + Tetracaine 0.1%	0.1	165.0± 18.0		238.0± 19.0		5.5±0.4		0.41±0.03		Charles River
			N.S.		<0.001		<0.001		<0.001	
Lidocaine 1.5% + Tetracaine 0.1% with oxygen	0.1	160.5± 13.9		477.0± 47.0		10.9±1.1		0.82±0.08		
Mepivacaine 2%	0.1	291.0± 18.4		330.0± 15.2		11.5±0.5				Charles River
			N.S.		<0.001		<0.001			
Mepivacaine 2% with oxygen	0.1	275.0± 22.4		672.0± 63.8		23.1±2.2				
Mepivacaine 2% + Tetracaine 0.1%	0.1	155.3± 11.1		196.0± 11.0		6.7±0.4		0.34±0.02		Charles River
			N.S.		<0.001		<0.001		<0.001	
Mepivacaine 2% + Tetracaine 0.1% with oxygen	0.1	174.0± 13.2		381.0± 29.8		13.1±1.0		0.66±0.02		

Results

Table 1 reveals that the toxicity of the anesthetic agents used became progressively greater as the concentration was increased. The time elapsed prior to respiratory and circulatory arrest was shortened with increasing concentrations of the drug, whether procaine or chloroprocaine, and whether Charles-River or Carworth-Farm rats were used. The total amounts of the drug used were not significantly different with changing rates of injection, however.

It will be seen in table 2 that the rate of injection of local anesthetic drugs was diminished, the survival time lengthened. This was true of both respiration and circulation. The total amount of drug used did not have a direct relationship to rate of injection. These facts were borne out with Charles-River and Rockland-Farm animals, and with procaine, chloroprocaine, and mepivicaine, each at the 2 per cent concentration.

Oxygen lengthened the time elapsing before circulatory arrest and consequently significantly increased the quantity of drug that could be tolerated in all the circumstances, summarized in table 3. Although the total elapsed time for the 110 rats receiving oxygen was greater than that for those breathing air before respiratory arrest, the individual series differences were not significant.

Four different strains of animals were used in the experiments with added tetracaine, as indicated in table 4. Two rates of injection were utilized, 0.4 and 0.1 ml./minute. In all comparisons, the average time before either respiratory arrest and before circulatory arrest was less with added tetracaine than without. Most of these differences were statistically significant. Even in those cases in which the differences were not of statistical significance, the average survival times were always less when tetracaine was employed.

Discussion

Moore and Bridenbaugh's [1] observation that oxygen is necessary in cases of severe toxic reactions to local anesthetic agents is borne out by these studies. Although the time before respiratory arrest was not significantly greater when the animals breathed oxygen, the crucial

TABLE 4. Effect of Added Tetracaine

Agent	Rate of Injection (ml./minute)	Respiratory Arrest (seconds)	*P*	Circulatory Arrest	*P*	Milligrams of Drugs				Strain of Rats
						Short Acting	*P*	Tetracaine	*P*	
Tetracaine 0.1%	0.4	211.5±21.3		304.5±15.4		2.0±0.001				
Procaine 1%	0.4	214.3±19.5	<0.001	341.3± 8.5	<0.001	22.8±3.6	<0.001			Charles River
Procaine 1% + Tetracaine 0.1%	0.4	106.5± 5.9		171.0± 6.8		11.4±0.45		1.1 ±0.04		
Procaine 2%	0.4	89.2± 8.8	N.S.	187.0± 7.9	<0.001	24.4±1.0	<0.001			Charles River
Procaine 2% + Tetracaine 0.1%	0.4	73.5± 5.6		141.0± 7.8		18.7±1.0		0.94±0.003		
Chloroprocaine 3%	0.4	32.2± 2.4	N.S.	117.8±17.6	<0.01	23.6±5.0	<0.01		<0.001	Charles River
Chloroprocaine 3% + Tetracaine 0.1%	0.4	28.0± 2.4		67.5± 9.4		12.9±1.4		0.43±0.03		
Tetracaine 0.1%	0.4	174.8± 3.2		270.8±20.1				1.8 ±0.01		Carworth Farms
Chloroprocaine 2%	0.4	56.0± 5.7	N.S.	121.5±16.0	N.S.	16.2±2.1	N.S.		<0.001	Carworth Farms
Chloroprocaine 2% + Tetracaine 0.1%	0.4	49.2± 5.2		90.0±10.7		12.0±1.1		0.6 ±0.07		
Tetracaine 0.1%	0.4	212.2±22.9		306.0±25.1				2.0 ±0.03		Rockland Farms
Mepivacaine 1%	0.4	131.0±16.2	<0.001	231.0±18.4	<0.001	15.4±1.2	<0.001		<0.001	Rockland Farms
Mepivacaine 1% + Tetracaine 0.1%	0.4	71.0± 9.2		144.0±11.8		9.6±0.8		0.96±0.08		
Mepivacaine 2%	0.4	68.8± 4.8	N.S.	149.2±11.9	<0.001	19.9±1.6	<0.001		<0.001	Rockland Farms
Mepivacaine 2% + Tetracaine 0.1%	0.4	56.5± 6.9		101.2± 6.3		13.5±0.8		0.68±0.03		

TABLE 4. (Continued)

Agent	Rate of Injection (ml./minute)	Respiratory Arrest (seconds)	P	Circulatory Arrest	P	Milligrams of Drugs				Strain of Rats
						Short Acting	P	Tetracaine	P	
Procaine 2%	0.1	369.0±52.4	<0.001	412.5±49.6	<0.001	14.2±1.7	<0.001			Charles River
Procaine 2% + Tetracaine 0.1%	0.1	198.7±14.0		245.2±15.1		8.4±0.5		0.42±0.02		
Mepivacaine 2%	0.1	218.8±14.9	<0.001	255.8±13.2	<0.001	8.7±0.45	<0.001			Charles River
Mepivacaine 2% + Tetracaine 0.1%	0.1	155.3±11.1		198.0±11.0		6.7±0.38		0.31±0.02		
Chloroprocaine 2%	0.1	151.5±13.0	<0.025	200.0±10.8	<0.001	7.1±0.55	<0.025			Charles River
Chloroprocaine 2% + Tetracaine 0.1%	0.1	113.5±12.1		154.5±12.0		5.3±0.41		0.27±0.02		
Lidocaine 1.5%	0.1	204.0±16.7	N.S.	265.5±12.5	N.S.	6.1±0.27	N.S.			Charles River
Lidocaine 1.5% + Tetracaine 0.1%	0.1	165.0±18.0		238.0±19.0		5.5±0.43		0.41±0.03		
Lidocaine 1.5% with oxygen	0.1	207.0±21.3	N.S.	613.0±95.0	N.S.	14.1±0.03	N.S.			Charles River
Lidocaine 1.5% + Tetracaine 0.1% with oxygen	0.1	160.1±13.9		477.0±47.0		10.9±0.08		0.82±0.08		
Tetracaine 0.1%	0.1	404.4±47.7		530.5±70.3				1.20±0.16		University of Denver
Lidocaine 1%	0.1	178.3±18.6	N.S.	263.3±18.4	<0.025	6.0±0.4	<0.01		<0.001	University of Denver
Lidocaine 1% + Tetracaine 0.1%	0.1	143.0± 9.2		212.5±11.0		4.8±0.24		0.48±0.02		

factor, the period before circulatory arrest, was definitely greater when oxygen was available. The manner of action of oxygen is not absolutely defined, but the result of adding oxygen undoubtedly prolonged the time before death supervened in these acute experiments. Hypoxia alone cannot explain the death of the rats, for observations on animals whose circulation has been entirely cut off and consequently who had absolutely no supply of oxygenated blood have shown that the heart will beat for much longer periods than those observed in these experiments. The drugs must, therefore, exert a direct toxic action on the heart. Concerning the point of view of diminishing morbidity rather than mortality, it would seem logical that patients having administration of local anesthetic agents might well breathe oxygen rather than air to offset the possibility of toxicity to the myocardium.

There are a few reports concerning mixtures of anesthetic agents. Issekutz,[2] in 1912, reported that antipyrene potentiated cocaine as a local anesthetic agent, and that beta-eucaine synergized novocaine. These were based on the concentrations of mixtures of these agents necessary to produce a twitch of a frog's leg when immersed in $N/10$ HCl. The observation was made that lesser concentrations of these substances were necessary when mixed than when half the amounts were used separately. Control studies were of doubtful validity, for it was reported that exactly 5.0 per cent of novocaine and 6.0 per cent of antipyrene were required in the "standard" studies.

Schmidt,[3] the following year, observed that combinations of local anesthetics did not show synergism. Sollmann,[4] a few years later, not only found that mixtures of agents showed no potentiation, but that "on the contrary, summation appears to be imperfect." He found no anesthesia from mixtures of equal volumes of quinine urea 2 per cent and cocaine ½ per cent, after each of these separately had given complete anesthesia to a rabbit's cornea.

One report of synergism of local anesthetic agents appeared in 1930 when Rider[5] found that butyn appeared to synergize cocaine, but this was explained on the basis of water-solubility of the salts used. These earlier observations on use of combined agents were made in attempts to determine whether synergism might be obtained by employing two substances together.

In the present study, toxicity, rather than anesthetic potency, of combinations of presently used agents was determined. The factor of potency was not in question, because it is well known that mixtures of the agents used have been quite successful in producing adequate clinical analgesia. The question at hand is whether the patient is more likely to have convulsions or other toxic reactions when mixtures of agents are employed. If our results may be transferred to human subjects they indicate that this indeed is the case. One may prolong the analgesia induced with a short acting agent by adding such material as tetracaine, but this is done at the expense of added toxicity and if performed should be done with this in mind. It might be safer to lower the concentration of the faster-acting agents if such combinations are used. The observed effects of tetracaine were additive, but no suggestion was found here that tetracaine was syngeristic with the other agents.

Summary

White, female rats were given intravenous injections of procaine, chloroprocaine or mepivacaine at a constant rate until respiration and circulation ceased. Elapsed time before these phenomena occurred was noted.

More rapid rates of injection resulted in earlier death. Death occurred earlier as the concentration of the agent was increased.

Inhalation of oxygen delayed the death of the animals receiving procaine, chloroprocaine, mepivacaine or lidocaine. Addition of tetracaine to the agents employed resulted in additional toxicity.

References

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