

A COMPARATIVE STUDY OF THE EXPERIMENTAL TOXICITY OF LOCAL ANESTHETIC AGENTS *†

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It is basically difficult to study the clinical problem of toxic reactions to drugs, first, because these reactions are unexpected and, second, because the number of cases which can be observed by any one investigator is comparatively small. An awareness of this problem is probably the best preventative for these reactions and as a consequence the material for observation is reduced. Although limitations must always be considered in the interpretation of animal experiments designed to help solve clinical problems, such animal experimentation undoubtedly furnishes the best basis for the understanding of these toxic effects.

A previous study (1) demonstrated the important role of cardiac depression in acute cocaine poisoning. In this study, the investigation has been extended to a representative group of local anesthetic agents in order to obtain a better understanding of the prevention and control of these serious toxic reactions.

PROCEDURE AND RESULTS

Rabbits were used as the experimental animal during the major portion of this study although dogs were used in certain experiments. The technics employed were similar to those in the previous study (1), including constant intravenous injection, kymographic tracings of respiration and blood pressure, together with electrocardiographic recordings. Artificial respiration was administered with a mechanical respirator, using air; other resuscitative measures employed were cardiac massage through the chest and small intravenous doses of epinephrine, 5 to 10 micrograms per kilogram.

Nature of the Reaction.—Previous studies (2, 3) of local anesthetic agents have demonstrated the experimental toxic reactions as being of two types, which for convenience might be called (1) convulsive-respiratory failure and (2) acute collapse. The essential difference in these two types of intoxication is the more rapid absorption of the drug, in the case of the latter. The cause of the acute collapse is attributed to

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primary cardiac failure, since the drug reaches the heart before the central nervous system.

In our experience with the administration of these drugs, this difference is not clear-cut, and we believe the classification by Sadove *et al.* (4) presents a more satisfactory interpretation of these reactions. With moderately rapid rates of injection in which death occurs in approximately one minute, as illustrated in figure 1, the respiratory system is the most susceptible and the first to fail, although the reaction appears to be of the "collapse" type. Furthermore, artificial respiration alone frequently will effect recovery even though the cardiovascular system appears to have failed. The exception to this general effect, reported by Long and co-workers (5), occurs when procaine is given in large doses at a very rapid rate and ventricular fibrillation results.

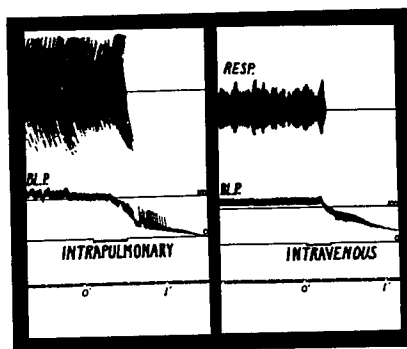


FIG. 1. Respiratory and cardiovascular changes in a rabbit produced by a lethal dose of tetracaine given (1) intrapulmonically, (2) intravenously, during a fifteen-second interval.

This is probably analogous to the effect of the rapid injection of potassium. It should be noted that serious toxic depression of the heart occurs in most of the fatal intoxications even though the cause of death is respiratory paralysis, and in cases of cardiac disability the sensitivity to these drugs may be so increased that cardiac failure is primary.

Although it has been generally considered that all local anesthetic agents produce the same type of toxic reaction, certain differences in the effects on the cardiovascular system should be noted. Figure 2 is a reproduction of typical kymographic tracings of blood pressure and respiratory changes in rabbits, together with simultaneous electrocardiograms, when comparable injections of dibucaine and tetracaine were made. The rate of the intravenous injection of the local anesthetic agents was that which produced respiratory paralysis in seven to eight minutes. The changes in respiration are similar but the

marked slowing of the heart rate seen with dibucaine is in sharp contrast to the effect of tetracaine. Procaine and cocaine usually produce changes in the cardiovascular recordings similar to those produced by tetracaine.

Comparative Toxicity.—There is considerable discrepancy in the toxicity figures reported for local anesthetic agents (6, 7), at least part of which is due to the various routes of administration. Constant intravenous injections give the most consistent results due to the elimination of the variations in absorption. However, in the final evaluation of the toxicity of a drug, the various routes of administration usually employed also should be tested.

In table 1 the comparative toxicity of four representative local anesthetics is listed, as determined by their constant intravenous injection

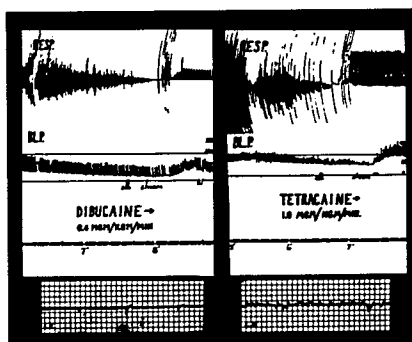


FIG. 2. Differences in the effect of the intravenous administration of tetracaine and dibucaine on the cardiovascular system of rabbits and the subsequent stimulation of 10 micrograms per kilogram of epinephrine (intravenously).

into rabbits at a rate which produces respiratory arrest in seven to eight minutes. The figures in this table are the averages of the results for groups of 5 rabbits. The rates shown give a toxicity ratio of procaine 1, cocaine 3, tetracaine 8, and dibucaine 20, which approximate those previously reported (7) for intravenous administration. When respiratory arrest occurred, artificial respiration was instituted and the injection continued until cardiac arrest resulted or, in the case of tetracaine and cocaine, for a period of twenty minutes (two and a half times that required for respiratory paralysis).

As can be seen from the table, there is a marked difference between the comparative respiratory and cardiovascular toxicities of these agents. The last column gives the percentage recovery of these animals when the injection was continued until cardiac arrest occurred or

for a period of twenty or more minutes. Because there were no recoveries in the group of animals which received dibucaine, the administration of dibucaine was discontinued at respiratory arrest in an additional 3 rabbits. Despite the use of artificial respiration and other resuscitative measures, cardiovascular failure occurred after several minutes in these rabbits in spite of the reduced dosage of dibucaine. To prevent cardiovascular failure small doses of epinephrine (5 to 10 micrograms per kilogram) were injected intravenously when indicated by dangerously low levels of cardiac function. At the time of cardiac arrest when the injection of the local anesthetic agent was discontinued, cardiac massage was employed for periods of three to four minutes to facilitate cardiac recovery.

The results with piperocaine at a rate of 4 mg. per kilogram per minute (toxicity ratio 2.0) have not been included in the table because

TABLE 1
COMPARATIVE RESPIRATORY AND CARDIOVASCULAR TOXICITY
OF REPRESENTATIVE LOCAL ANESTHETICS

Drug Rate, Mg./Kg./Min.	Resp. Arrest, Minutes	Card. Arrest, Minutes	Recovery
Procaine 8.0	7.7 ± 2.1*	>37	100%
Cocaine 2.75	7.8 ± .2	12.8 (10-14)	60%
Tetracaine 1.0	7.4 ± .3	>20 (9-30)	40%
Dibucaine 0.35	8.4 ± .4	11.2 (10-13)	0%

* Mean ± S.E. for five rabbits.

of the unusual variation in the amount of drug required to produce respiratory paralysis. With this drug, 3 of 6 animals had respiratory arrest in six minutes, whereas respiratory failure did not develop in the other 3 in twenty-four minutes. This suggests marked differences in the amount or activity of a specific detoxifying enzyme for this agent similar to the situation causing the marked variation in the toxicity of atropine for rabbits.

Rates of Absorption.—As has been emphasized by previous authors, the rate of absorption is an important factor in the production of these toxic reactions, in addition to the inherent toxicity of a given concentration of the local anesthetic agent. From recent clinical reports of local anesthetic intoxications (8, 9), it would appear that topical administration is most frequently involved in toxic reactions, especially when used for bronchoscopy. In fact, the study of Weisel and Tella (9) revealed the rather unexpected total of seven serious reactions in 1000 topical

administrations of tetracaine despite the limitation of the tetracaine administered to relatively small doses (2 cc. of 2 per cent solution).

As a possible explanation of these reactions, the relative rates of absorption from various areas involved in the topical application of these agents for bronchoscopy were investigated. Groups of 10 rabbits were given doses of 18 mg. per kilogram of cocaine or 6 mg. per kilogram of tetracaine, which correspond to the reported intravenous M.L.D. (7) and which approximate our own figures for the average amount required to produce respiratory arrest when these drugs are injected intravenously at a rate that produces cessation of respiration in approximately four minutes. The drugs were administered topically to young adult albino rabbits by means of a small plastic catheter to the following sites: lungs (by way of tracheal cannula), posterior nasal cavity, and esophagus. The amount of solution administered was 0.1 ml. per

TABLE 2
TOXICITY OF TOPICALLY APPLIED COCAINE AND TETRACAINE

Drug and Route of Administration	Animals		Time in Minutes to	
	No.	Mortality, Per Cent	1st Convulsion	Respiratory Arrest
6% Tetracaine Intrapulmonically	10	80*	0.8	2.0
18% Cocaine Intrapulmonically	10	10**	7.0	4.0
6% Tetracaine + Epinephrine† Intrapulmonically	10	60	0.6	1.0
6% Tetracaine Intranasally	10	20**	5.6	5.5
6% Tetracaine Intra-esophageally	10	0**	0	0

* Statistically significant difference from**.

† Epinephrine 1:25,000, 5 animals; 1:50,000, 5 animals.

kilogram and the concentrations of the solution were 18 per cent cocaine and 6 per cent tetracaine.

The results of these experiments (table 2) indicate that the administration of these drugs into the lung is essentially equivalent to an intravenous injection, especially for tetracaine. Comparison of the mortality from tetracaine administered intrapulmonically with that of tetracaine given by the intranasal or esophageal route, and cocaine by intrapulmonary instillation, reveals statistically significant differences (10). The rapid onset of convulsions and high mortality with tetracaine injected intrapulmonically indicate rapid absorption from this area. In contrast, tetracaine intranasally and cocaine intrapulmonically reveal a much slower onset of convulsions while the esophageal administrations of the above dose of tetracaine do not even produce convulsions. The addition of epinephrine, 1:25,000 or 1:50,000, to the

tetracaine (5 animals with each concentration) produces very little reduction in the absorption of tetracaine instilled into the lung.

A comparison of the lethal effects of tetracaine when administered into the lung or given intravenously is shown in figure 1. The respiratory and blood pressure tracings illustrate the effects of 6 mg. per kilogram of tetracaine when administered by each of the two routes. The tracings indicate a marked similarity of effects produced by both means of administration.

Treatment of Reactions.—The effectiveness of barbiturates in the treatment of cocaine intoxication when the drug is administered subcutaneously was demonstrated by Tatum and co-workers (11) and is the basis for the clinical use of barbiturates in the treatment of these toxic reactions. Our experience in cocaine intoxication produced by constant intravenous injections (1) revealed the antagonism of the barbiturates to be somewhat less effective than previous workers had reported. We have extended the study to other local anesthetic agents.

TABLE 3
PROTECTIVE EFFECT OF PENTOBARBITAL IN LOCAL ANESTHETIC INTOXICATION

Drug Rate, Mg./Kg./Min.	Minutes to Respiratory Arrest (\pm S.E.)	
	No Barbiturate	Pentobarbital (20 mg./kg.)
Procaine 8.0	7.7 \pm 2.1	11.5 \pm 4.5
Cocaine 2.75	7.8 \pm 0.2	9.7 \pm 0.8
Tetracaine 1.0	7.4 \pm 0.31*	4.9 \pm 0.27*

* Statistically significant $P < .01$.

In table 3 are listed the results of an experiment in which groups of 5 rabbits were given procaine, cocaine and tetracaine intravenously at the previously described rates with and without treatment with pentobarbital. The results suggest that procaine and cocaine intoxication are benefited by pentobarbital, whereas pentobarbital appears to increase the potency of tetracaine in causing respiratory arrest. Statistically, the difference between the two groups receiving tetracaine is significant at the 1 per cent level using the "t" test (12). Even though counteraction of respiratory paralysis in tetracaine intoxication is not obtained, the convulsive manifestations are controlled, as is the case with the other local anesthetic agents.

The effect of small doses of epinephrine (10 micrograms per kilogram intravenously) in stimulating the depressed cardiovascular system is illustrated in figure 2. It will be seen that the cardiovascular depression occurring with tetracaine intoxication responds well. Similar results are obtained with cocaine and procaine; however, in the case of dibucaine, relatively little effect is produced. It should be noted that

larger doses, 50 micrograms per kilogram of epinephrine, were deleterious in local anesthetic intoxication and sudden cessation of cardiac activity was noted in several instances. Phenylephrine, 50 micrograms per kilogram, previously found to be much less effective in the stimulation of hearts depressed by cocaine, gave results comparable to those with epinephrine in cardiovascular depression produced by the other local anesthetic agents.

COMMENT

The nature of the toxic reaction to local anesthetic agents derives its importance from the necessity of selecting the best possible treatment of this situation without delay. Since failure of respiration occurs more readily in local anesthetic intoxication than does failure of cardiovascular function, the maintenance of adequate ventilation is of primary importance even though the reaction may appear to be the result of acute cardiovascular collapse. With the establishment of adequate ventilation the next concern must be the cardiovascular system, in which case cardiovascular depression is more likely to occur than ventricular fibrillation.

Many experimental studies have been made to determine the relative toxicity of the different local anesthetics which, when considered with the relative potency, gives the therapeutic ratio as a means of comparison. Although toxicities must always be determined on experimental animals, the final evaluation of relative potency should be in the clinic under the actual conditions of use. The local anesthetic agents employed in this study have been used in the clinic for years and the amounts of various agents required to give adequate local anesthesia have been determined from experience. It is interesting to note that in a survey made by Himalstein (8) of the procedure used by the members of the American Broncho-Esophagologic Association, the average amounts of tetracaine and cocaine used for intralaryngeal instillation in topical anesthesia for bronchoscopy were 70 and 240 mg., respectively. This ratio is similar to the 1:3 ratio of the lethal intravenous doses of these agents determined experimentally and used as a basis of comparison in this study.

The comparative toxicity of local anesthetic agents, using respiratory paralysis as an end point, gives a ratio of toxicity similar to previously published results (7). With the use of artificial respiration, the comparative cardiovascular toxicity was determined and our results indicate that relative cardiovascular toxicity does not parallel that for the respiratory system. This is important from a clinical viewpoint since death due to respiratory paralysis can be prevented by artificial respiration. The toxicity ratio of procaine to dibucaine is 1:80, using cardiovascular failure as an end point, compared to the 1:20 figure obtained by ordinary toxicity determinations, in which death is due to respiratory failure. Results of even greater importance are suggested

by the differences in recovery from intoxication with these agents and undoubtedly reflect differences in rates of detoxification. Complete recovery after the administration of large amounts of procaine and no recoveries from dibucaine intoxication indicate that even the 1:80 ratio of toxicity is not a true expression of relative toxicity. On the basis of limited numbers, it appears that cocaine is relatively more toxic to the cardiovascular system than is tetracaine when doses which paralyze respiration are used as a basis for comparison. However, our records suggest that in cocaine intoxication, recovery occurs more readily after severe depression of the heart than after a similar depression due to tetracaine.

Results obtained with piperocaine show a marked variability in toxicity for the rabbit, which may well be caused by the variable presence of an esterase capable of splitting piperocaine. It is not impossible that the relatively rare clinical intoxications with procaine may be the result of the occasional lack or deficiency of this specific enzyme which is normally present in man, although the widespread use of intravenous procaine suggests that man possesses a procaine esterase enzyme with great regularity.

A more practical finding in our study is the possible explanation of the clinical reactions encountered in topical application of agents such as tetracaine. The results of intrapulmonary instillation of tetracaine indicate that absorption is approximately as rapid as with intravenous injection. The addition of epinephrine, 1:25,000 or 1:50,000, does not appear to retard the absorption, although the stimulation of the heart by epinephrine appears to be beneficial for survival of the severe hypoxia caused by the intoxication. The use of comparable doses of cocaine results in much lower mortality rate and gives evidence that there is a much slower absorption of the drug. This suggests that vasoconstriction is produced by cocaine in the pulmonary bed which is not produced by the concentrations of epinephrine added to the tetracaine solution. Application of this local anesthetic agent to the various areas involved in bronchoscopic anesthesia indicates that the rate of absorption from the pulmonary bed is far greater than that encountered in other areas.

When one considers that a commonly accepted method of topical anesthesia (8, 9) includes intralaryngeal instillation of 1 to 4 cc. of a 2 per cent solution of tetracaine during inhalation, it would not be surprising if a large part of the administered drug would sometimes reach the lung alveolae and give rise to reactions. Absorption from the esophagus and stomach does not seem to be the likely cause of reactions, as judged by our results, which conclusion is substantiated by the comparatively low blood levels attained with oral administration of cocaine (13).

Little can be added to the treatment of these reactions except to mention the limitation of usefulness of intravenous barbiturate, espe-

cially with agents such as tetracaine, where it would appear to be valuable only as an anticonvulsant. Obviously, the control of convulsions is important both for the purpose of managing the patient for administration of artificial respiration and for the reduction of oxygen demand associated with the convulsion. The rate of absorption may also be reduced if the violent motions of convulsions are prevented (14).

Our experience indicates that small doses, 5 to 10 micrograms per kilogram, of epinephrine are beneficial in the stimulation of the cardiovascular system depressed by local anesthetic agents. This stimulant action of epinephrine is much less effective against dibucaine in contrast to the other agents studied. When one considers the potency of 0.05 mg. of epinephrine in man when given by rapid intravenous injection (15), it is probable that 0.5 to 1.0 mg. of epinephrine by intracardiac or intravenous administration is excessive in clinical intoxication by a local anesthetic agent. Resuscitative doses of epinephrine for local anesthetic intoxication in the range of 0.02 to 0.05 mg. given intravenously should be less hazardous.

SUMMARY

Although respiratory failure is the usual cause of death in untreated cases of local anesthetic intoxication, the use of artificial respiration makes the cardiovascular depression in these intoxications very important. The relative respiratory and cardiovascular toxicity of representative agents is not parallel and this difference may be important in selecting the least dangerous agent.

The absorption of the local anesthetic agent, tetracaine, from the lungs is very rapid and approximates intravenous injection.

Barbiturates do not increase the tolerance of the respiratory center to paralysis by the action of some of these agents.

REFERENCES

1. Steinhaus, J. E., and Tatum, A. L.: Experimental Study of Cocaine Intoxication and Its Treatment, *J. Pharmacol. & Exper. Therap.* 100: 351-361 (Nov.) 1950.
2. Shumacker, H. B., Jr.: Reactions to Local Anesthetic Agents; Experimental Studies with Procaine, *Surgery* 10: 119-133 (July) 1941.
3. Knoefel, P. K.; Herwick, R. P., and Loevenhart, A. S.: Prevention of Acute Intoxication from Local Anesthetics, *J. Pharmacol. & Exper. Therap.* 39: 397-411 (Aug.) 1930.
4. Sadove, M. S.; Wyant, G. M.; Gittelson, L. A., and Kretschmer, H. E.: Classification and Management of Reactions to Local Anesthetic Agents, *J.A.M.A.* 148: 17-22 (Jan. 5) 1952.
5. Long, J. H.; Oppenheimer, M. J.; Webster, M. R., and Durant, T. M.: Effect of Intravenous Procaine on Heart, *Anesthesiology* 10: 406-415 (July) 1949.
6. Bonica, J. J.: Regional Anesthesia with Tetracaine, *Anesthesiology* 11: 606-622 (Sept.) 1950.
7. Hirschfelder, A. D., and Bieter, R. N.: Local Anesthetics, *Physiol. Rev.* 12: 190-282 (April) 1932.
8. Himalstein, M. R.: Topical Anesthesia in Endoscopy, Critical Evaluation with Case Reports and Survey of Current Opinion, *Laryngoscope* 59: 1102-1132 (Oct.) 1949.
9. Weisel, W., and Teila, R. A.: Reaction to Tetracaine (Pontocaine) Used as Topical Anesthetic in Bronchoscopy, *J.A.M.A.* 147: 218-222 (Sept. 15) 1951.

10. Mainland, D.: Statistical Methods in Medical Research; Qualitative Statistics (Enumeration Data), *Canad. J. Research Sect. E* **26**: 1-166 (Feb.) 1948.
11. Tatum, A. L.; Atkinson, A. J., and Collins, K. H.: Acute Cocaine Poisoning, Its Prophylaxis and Treatment in Laboratory Animals, *J. Pharmacol. & Exper. Therap.* **28**: 325-335 (Dec.) 1925.
12. Snedecor, George W.: Statistical Methods Applied to Experiments in Agriculture and Biology, ed. 4, Ames, Iowa, The Collegiate Press, Inc.
13. Woods, L. A.; McMahon, F. G., and Seever, M. H.: Distribution and Metabolism of Cocaine in Dog and Rabbit, *J. Pharmacol. & Exper. Therap.* **101**: 200-204 (Feb.) 1951.
14. Steinhaus, J. E.: Thesis, Ph.D., University of Wisconsin, unpublished, 1950.
15. Nathanson, M. H., and Miller, H.: Action of Nor-Epinephrine and of Epinephrine on Ventricular Rate of Heart Block, *Am. Heart J.* **40**: 374-381 (Sept.) 1950.