

LOCAL ANESTHETIC TOXICITY: A PHARMACOLOGICAL RE-EVALUATION

JOHN E. STEINHAUS, M.D.

THE PROBLEM of toxic reactions to local anesthetic agents is important today because of the widespread use of these agents and the attempts to provide better anesthesia in patients who are extremely poor anesthetic risks. Since these drugs are introduced into limited portions of the body, systemic effects are not expected, and the appearance of toxic manifestations has a marked psychological effect on the administrator of these agents. Unless the physician has a clear knowledge and understanding of the systemic actions of these drugs prior to the event, it is not possible to expect the best treatment of the toxic reaction.

A detailed discussion and classification of reactions to local anesthetic agents is given by Moore (1). As emphasized in this discussion allergy is seldom the mechanism of this intoxication, although the frequent use of the term sensitivity or hypersensitivity suggests allergic responses to be common. A careful examination of the case reports of clinical intoxication strongly support the view that the lethal effect of these drugs is rarely of an allergic or anaphylactoid type (2). This contention is also supported by Vaughan and Black (3) in their discussion of drug allergy. However, the patient with a definite allergic history must always be treated expectantly since these patients may have an allergic response to a wide variety of agents. Since allergy is a minor aspect of this problem, a discussion of the fatal reactions of these drugs can then be considered on the basis of their characteristic pharmacological actions on the cardiovascular and central nervous system.

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

Local anesthetic agents have long been grouped with the stimulant drugs of the central nervous system, although it has been recognized that they are not convulsants in the same manner as pentylene tetrazol and picrotoxin. In experimental studies with these agents it has been observed that cocaine produces more marked convulsions than do the synthetic local anesthetic agents such as tetracaine. The most common explanation of the action of these drugs on the central nervous system (1, 4) proposes that following the initial stimulation, over stimulation results in depression and respiratory arrest. However, clinical ob-

This paper was read before the annual meeting of the American Society of Anesthesiologists in Kansas City, Missouri, October 10, 1956, and was accepted for publication November 19, 1956. Dr. Steinhaus is in the Department of Anesthesiology, University of Wisconsin, Medical School, Madison, Wisconsin.

servations have suggested some of these agents, such as procaine, produce depression without evidence of initial stimulation of the central nervous system (1). Using a technique developed in our laboratory (5), the effect of cocaine on the cortex and higher centers of a rabbit was compared with the effect produced by the administration of this drug to the medulla and lower centers. The effect of cocaine on the higher centers of the brain produced violent convulsions with marked stimulation of respiration as might be expected from the known action in the intact animal. Figure 1 reveals the action of cocaine in similar

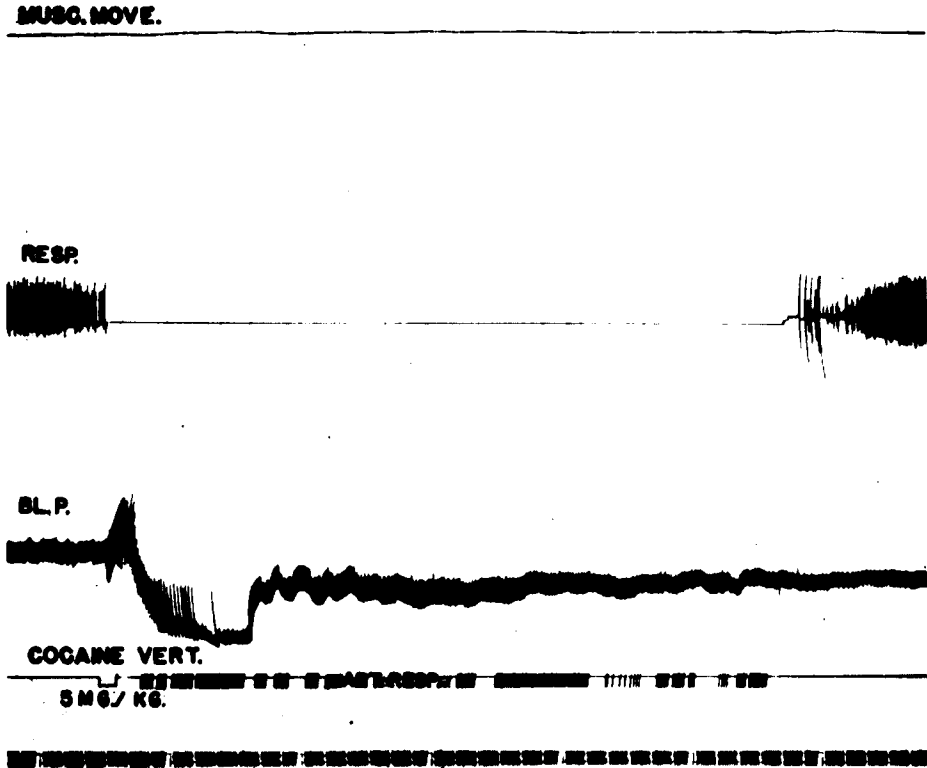


FIG. 1. The effect of cocaine on movement, respiration, and blood pressure of a rabbit when injected into the blood supply of the lower brain stem.

dosage on the medulla in which there is no evidence of stimulation but only a long period of respiratory arrest. In a series of experiments with various doses of cocaine, no evidence of stimulation of the lower brain stem was produced. The depression of the medulla produced by cocaine in this manner was intensified by thiopental which indicates that in this area of the brain the action of cocaine and thiopental are additive and not antagonistic. These studies substantiate previous opinions (1, 6) that local anesthetic agents stimulate the cortical and higher centers of the brain and depress the medulla and lower pons.

The pattern produced in the intact animal is a summation of these opposite effects and the observed respiratory depression is direct and not the result of overstimulation. Jolly (7) has reported that procaine also depresses the medulla in contrast to its stimulation of the cortex. This evidence of medullary depression also explains previous experimental studies (8) which revealed that barbiturates increased the toxicity of tetracaine. This is contrary to the effect of barbiturates on the toxicity of other local anesthetic agents and it would appear that protection results only in those situations where convulsions are prominent. One can conclude from these studies that, although convulsion is the more dramatic effect of these agents acting on the central nervous system, depression of the medulla with respiratory arrest causes death.

CARDIOVASCULAR EFFECTS

The typical pattern of acute local anesthetic toxicity is one of marked depression of the cardiovascular system, characterized by a decrease in blood pressure, and a direct depression of the myocardium affecting both conduction and contraction (8). Both increases and decreases in heart rate will be noted, the former occurring most commonly in the initial phase of the intoxication and the latter characteristically appearing in the terminal portion. The electrocardiogram reveals intraventricular block in the severely depressed heart as evidenced by a widened QRS complex. Long *et al.* (9) reported that rapid injection of procaine occasionally produced ventricular fibrillation. Our studies (10) with these drugs indicated that although the electrocardiogram appeared to indicate the presence of ventricular fibrillation in this situation, the state of the myocardial conduction system is somewhat different from that found with ventricular fibrillation produced by electrical or mechanical stimuli. There has been general agreement in previous studies of local anesthetic toxicity that the cardiovascular system was more resistant than the central nervous system. This fact emphasizes the importance of adequate oxygenation as the first consideration in the management of these reactions. This contention is further substantiated by an observation noted in earlier studies (11) that rapid and apparently irreversible cardiac failure occurred in these intoxications when marked hypoxia was present.

Although this group of drugs have many similarities in their action on the cardiovascular system, it should be noted (8) that the cardiovascular toxicity does not necessarily parallel the respiratory toxicity. Whereas the cardiovascular depressant dose was more than four times the respiratory depressant dose in the case of procaine, the difference between these two doses for dibucaine was very slight. If further attention is paid to the recovery from these doses the disparity is even greater since 100 per cent recovery was obtained with procaine in contrast to no recoveries with dibucaine.

The fall in blood pressure noted with severe intoxication would appear to be due primarily to the effects of these agents on the cardiovascular system rather than effects mediated by the vasomotor center in the medulla (2). In this study cocaine, injected into the aorta above the level of the coronary arteries, produced typical convulsions and respiratory arrest with little change in blood pressure. In contrast the same dose injected at the level of the coronary arteries produced marked fall in blood pressure and cardiac function without producing respiratory arrest. Obviously in the intact animal there is a summation of the effects on all sites of action, however, the evidence suggests that the direct myocardial effects are the more serious.

TREATMENT

Prophylactic.—The most effective prophylactic measure which can be employed to prevent toxic reactions to these agents is intelligent use which avoids rapid absorption and overdosage. Careful attention to the vascularity of anatomical region together with the use of dilute vasoconstrictor drugs such as epinephrine does much to control rapid absorption following infiltration anesthesia. In recent years the reported reactions to these agents have followed topical application more frequently than other methods of administration. Previous work (8) indicates that the practice of instilling 2 ml. or more into the trachea to produce anesthesia below the vocal cords may be the explanation of these reactions. It is not hard to conceive that occasionally a large fraction of the injected material may be inhaled into the alveolar portion of the lung rather than being spread evenly on the surface of the trachea and bronchi. The experimental work mentioned above demonstrated that tetracaine was absorbed from the lung fields at a rate equivalent to intravenous injection. Recommended maximum doses such as listed by Moore (1) are good guides in the prevention of overdosage, especially where the technique of spraying or pledget application lend themselves to the use of large amounts of these drugs. The use of sedative doses of barbiturates has no demonstrated value as a prophylactic measure for the prevention of these reactions except for the desirability of sedation in these patients (11). Doses of barbiturate which are required to prevent convulsions and give some evidence of protection in animal intoxication are almost equivalent to anesthetic doses. When one considers the more serious nature of the cardiovascular depression which may occur with these reactions it might be well to consider the comparative cardiovascular toxicity of these agents in the selection of a local anesthetic agent. The study previously referred to (8) demonstrated that the difference between the cardiovascular toxicity of the less potent agents, such as procaine, and the more potent agents, such as dibucaine, was much greater than the difference in toxicity normally given, which is based on respiratory de-

pression. These experiments confirm the often repeated advice to use the least potent agent which will accomplish the anesthetic procedure.

Central Nervous System.—When it is necessary to treat a serious toxic reaction to local anesthetic agents, the most important measure is the maintenance of adequate oxygenation. The more marked sensitivity of the central nervous system and the comparative simplicity of this therapeutic procedure make maintenance of respiration the matter of first consideration. As indicated in the discussion of the effects of these agents on the central nervous system, the most serious result is the depression of respiration. The presence of convulsions which are frequently very mild often obscures the need for assisted or artificial respiration. Although short acting barbiturates have long been recommended as a treatment for these reactions, there is considerable evidence to suggest that their only value is the control of the convulsions (8). With some local anesthetic agents, such as tetracaine, the animal experiments demonstrated that barbiturates increase the toxicity. Furthermore, no evidence can be found that the cardiovascular system is benefited by the use of barbiturates, and the depressant effect of these drugs on cardiovascular function is well documented. With these findings in mind it would seem advisable to limit the use of barbiturates to the control of the convulsions and that this would be secondary to the institution and maintenance of artificial respiration.

Cardiovascular.—After adequate oxygenation is established, the status of the cardiovascular system should be determined and specific treatment instituted as indicated. It should be emphasized that cardiovascular depression owing to the toxic effects of these drugs is more serious and may be irreversible if hypoxia is also present (2). In our earlier studies (11) on the cardiovascular effect of cocaine, we reported that epinephrine resulted in marked and beneficial stimulation of seriously depressed cardiovascular systems. This experience has been borne out in further studies on cardiac resuscitation in our laboratories (10) in that epinephrine and levarterenol are excellent stimulants for cardiovascular systems depressed by these drugs. The onset of ventricular fibrillation as the result of the administration of sympathomimetic drugs in a toxic reaction to local anesthetic agent has never been observed in our studies. The dosage of epinephrine or levarterenol used for these purposes has always been comparatively low being in the range of .002–.005 mg./kg.

If cardiac arrest has occurred, cardiac massage should be instituted immediately as would be the case in any other case of acute heart stoppage. Recent studies in our laboratory resulted in the development of a method for cardiac resuscitation from ventricular fibrillation using lidocaine (10). In this procedure, the local anesthetic agent is injected into the left ventricle to interrupt the ventricular fibrillation after which levarterenol is used to support myocardial contraction and to

sustain blood pressure. This technique has been successful in a wide range of experimental conditions and it demonstrates the reversibility of the cardiac depression produced by these agents. Although lidocaine appears to be the most suitable agent for this type of resuscitation, procaine and tetracaine have also been used successfully. Figure 2 reveals a cardiac arrest produced by rapid injection of procaine, 100 mg./kg. in a dog. Resuscitation was performed using cardiac massage until a coordinated heart beat returned followed by levarterenol, .004 mg./kg., as needed to support the cardiovascular system. On several occasions in our study when long periods of massage were required following cardiac arrest with procaine or tetracaine, ventricular fibrilla-

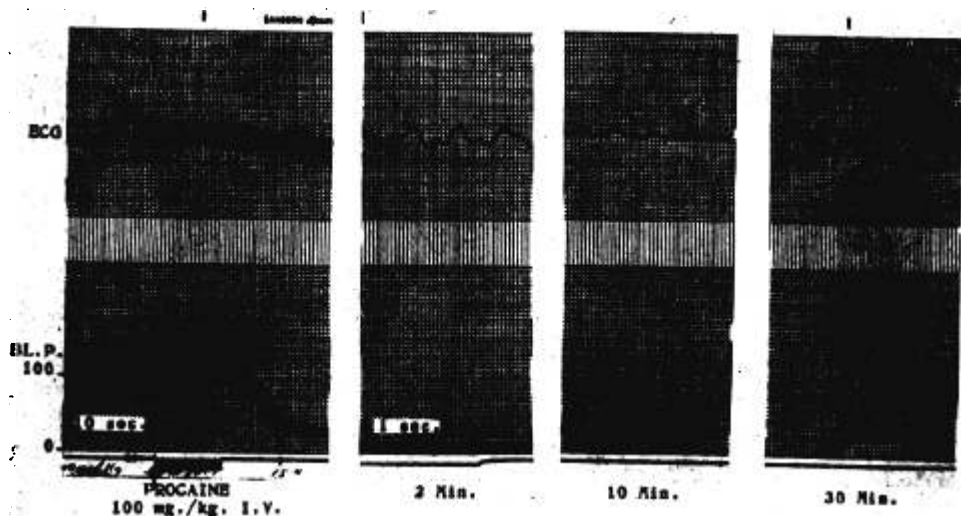


Fig. 2. Blood pressure and electrocardiographic tracings of a dog following the injection of 100 mg./kg. of procaine, intravenous, and the subsequent resuscitation.

tion developed and was treated successfully with our standard lidocaine technique. The probability of successful resuscitation following cardiac arrest depends upon the agent involved and the dosage administered. The more potent, longer acting, local anesthetics such as cocaine, tetracaine, or dibucaine will always present a more difficult problem of resuscitation than easily detoxified local anesthetics such as procaine and lidocaine.

SUMMARY

Serious toxic effects of local anesthetic agents are due to an action upon either the cardiovascular or central nervous systems or both. Although they are generally thought of as convulsant drugs, experimental evidence indicates that only the cortical areas are stimulated and their effect on the medulla is primarily depression. Their action on the cardiovascular system is chiefly depressant, although this system

is much more resistant than the brain, especially in the presence of adequate oxygenation. Recent use of some of these agents in cardiac resuscitation indicates that even complete cardiovascular depression is reversible. The treatment of the effects on the central nervous system is primarily one of maintaining respiration. Control of convulsions can be accomplished with a thiobarbiturate, but great care must be taken that additional depression is not superimposed on that already present. There is little evidence that barbiturates counteract the depressant action which these agents have on the respiratory center. Depression of the cardiovascular system can be treated with small doses of epinephrine or arterenol. If complete arrest is produced, cardiac massage should be instituted.

REFERENCES

1. Moore, Daniel C.: *Complications of Regional Anesthesia*. Springfield, Illinois, Charles C Thomas, 1955, pp. 6-31.
2. Steinhaus, J. E.: Thesis, Ph.D., University of Wisconsin, 1950, Unpublished.
3. Vaughn, W. T., and Black, J. H.: *Practice of Allergy*, ed. 3. St. Louis, Missouri, C. V. Mosby Company, 1954, p. 849.
4. Goodman, Louis S., and Gilman, Alfred.: *The Pharmacological Basis of Therapeutics*. New York, The Macmillan Company, 1955, p. 358.
5. Jolly, E. R., and Steinhaus, J. E.: Effects of Drugs Injected into Limited Portions of Cerebral Circulation, *J. Pharmacol. & Exper. Therap.* **116**: 273 (March) 1956.
6. Sadove, M. S., Wyant, G. M., and Gittelson, L. A.: Classification and Management of Reactions to Local Anesthetic Agents, *J. A. M. A.* **148**: 17 (Jan. 5) 1952.
7. Jolly, E. R.: Actions of Procaine on Lower Brain Stem, *J. Pharmacol. & Exper. Therap.* **116**: 33 (Jan.) 1956 (Abstract).
8. Steinhaus, J. E.: Comparative Study of Experimental Toxicity of Local Anesthetic Agents, *ANESTHESIOLOGY* **13**: 577 (Nov.) 1952.
9. Long, J. H., Oppenheimer, M. J., Wester, M. R., and Durant, T. H.: Effect of Intravenous Procaine on Heart, *ANESTHESIOLOGY* **10**: 406 (July) 1949.
10. Carden, N. L., and Steinhaus, J. E.: Lidocaine in Cardiac Resuscitation from Ventricular Fibrillation, *Circulation Res.*, In press.
11. Steinhaus, J. E., and Tatum, A. L.: Experimental Study of Cocaine Intoxication and Its Treatment, *J. Pharmacol. & Exper. Therap.* **100**: 351 (Nov.) 1950.