AN EXPERIMENTAL STUDY OF COCAINE INTOXICATION AND
ITS TREATMENT

JOHN E. STEINHAUS AND ARTHUR L. TATUM

Department of Pharmacology, University of Wisconsin Medical School, Madison

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The occurrence of serious and fatal toxic reactions due to local anesthetic agents has been recognized and studied for many years; nevertheless, there continue to be reports of fatalities (Himalstein, 1949), indicating that a satisfactory solution of this problem has not yet been attained. One of the early significant studies of these clinical reactions was that made by the Mayer Committee. As a result of the study of reported clinical cases (Mayer, 1924) and a consideration of experimental work which had been done, artificial respiration and cardiac massage were recommended by the committee as the most effective methods of treatment for these intoxications. Tatum et al. (1925) impressed by the convulsions and the rapid irregular respirations observed in experimental cocaine intoxication, were led to use barbital to counteract these effects. They found that the minimal lethal dose of cocaine could be increased severalfold in experimental animals when treated with barbital. Following a clinical study, Leshure (1927) reported that sedative doses of barbital, given prophylactically, were successful in the prevention of reactions to local anesthetics. This latter measure has been recommended widely by textbooks of pharmacology and therapeutics; however, there is no experimental work to substantiate this therapy, and clinical failures (Ahroon, 1946) cast doubt as to its effectiveness.

It is generally recognized that the respiratory system is more susceptible to local anesthetics than the circulatory system (Hirschfelder and Bieter, 1932); however, Knoefel et al. (1930) reported that cardiovascular failure occurred before respiratory arrest when an intravenous injection of cocaine was given rapidly. They also suggested that this experimentally produced reaction corresponded to the less common clinical reaction which is characterized by abrupt onset and cardiovascular collapse, in contrast to the more usual, slower developing, convulsive-respiratory failure reaction (Shumacker, 1941).

There is no agreement as to the effects of epinephrine on local anesthetic intoxication. Eggleston and Hatcher (1919) found that epinephrine was beneficial in local anesthetic intoxication, whereas the Mayer committee cited work to the contrary and cautioned against its use. Eichholtz and Hoppe (1933) found that epinephrine decreased the convulsive and lethal doses of local anesthetics but, on the other hand, Tainter and Thondson (1938) reported that the toxicity of procaine with epinephrine was less than that of procaine alone.

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2 Present address: Department of Pharmacology, Marquette University School of Medicine, Milwaukee, Wisconsin.
The present study has been directed toward the evaluation of present methods of therapy and the development of more effective therapeutic antagonists.

**Methods.** Both rabbits and dogs were employed as experimental animals in this investigation, and in the portion of the study involving the evaluation of the prophylactic use of barbiturates only young rabbits of a New Zealand-white strain were used. Cocaine was the local anesthetic selected for the major portion of this investigation because of its relatively high toxicity and the wealth of available data concerning this drug. The barbiturate chosen was pentobarbital, which is one of the more effective barbiturates in the treatment of local anesthetic intoxication. Of the sympathomimetic drugs employed in the treatment of cocaine intoxication, epinephrine was studied most intensively, however, ephedrine, phenylephrine (Neoepinephrine), and N-isopropylarterenol (Isuprel) were also used.

In the experiments on the prophylactic use of pentobarbital, cocaine was injected subcutaneously to produce the convulsive-respiratory paralysis type of reaction. On account of the marked variation in the rate of absorption with the subcutaneous administration of cocaine, a constant speed intravenous injection of cocaine by means of a mechanical injector was employed in all experiments in which the mode of action was studied. The barbiturates and sympathomimetic agents were administered intravenously.

Cardiovascular and respiratory effects of cocaine intoxication were followed by kymographic recordings of blood pressure and respiration, together with simultaneous electrocardiograms. Blood pressure was recorded by means of a Hürthle-type manometer after carotid or femoral artery cannulation. The recording of respiration was accomplished with the use of either an accordion type pneumograph or a tracheal cannula connected to a Marey tambour. A direct-writing electrocardiograph was used to take electrocardiograms during the course of cocaine intoxication. All operative procedures were carried out under local anesthesia using a maximum of 2 ml. of 1 per cent procaine solution.

**Experimental.** In order to evaluate the prophylactic effect of pentobarbital against the toxic action of cocaine, selected doses of pentobarbital sodium were injected intravenously into rabbits, followed immediately by lethal doses of cocaine administered subcutaneously. The dosages of pentobarbital selected ranged from 5 to 25 mgm./kgm. A full anesthetic dose of pentobarbital for these rabbits ranged from 25 to 30 mgm./kgm. and it was considered that the 5 mgm./kgm. approximated a "sedative" dose. The selection of the dosage, 100 mgm./kgm. of cocaine subcutaneously, was made because most previous workers had found this to be the LD₃₀. Rabbits fatally intoxicated by this dose of cocaine usually started convulsing between three and five minutes after the injection of cocaine and died within an additional period of five to fifteen minutes. The results of these experiments, listed in table 1, indicate that 15 mgm./kgm. of pentobarbital are required for maximal protection; it was also observed that this dose of pentobarbital prevented convulsions. The 5 mgm./kgm. dose of the barbiturate appeared to have only slight, if any, protective effect and it can be added that convulsions were consistently present in this group although less severe than in the control animals. When larger doses of cocaine were given, the amount of pentobarbital had to be increased to obtain maximal protection. In a second series of experiments in which the time of administration of pentobarbital was varied with respect to that of the injection of cocaine, it was found that maximal protection occurred when the drugs were given at essentially the same time.
The cause of death in cocaine intoxication was studied in experiments in which kymographic recordings of respiration and blood pressure were made during the administration of cocaine intravenously at a constant rate. The initial experi-

**TABLE 1**

*Protective effect of different doses of pentobarbital in cocaine intoxication*

<table>
<thead>
<tr>
<th>COCAINE mgm., kgrm. subc.</th>
<th>PENTOBARBITAL mgm., kgrm. i.v.</th>
<th>NUMBER OF ANIMALS</th>
<th>NUMBER SURVIVING</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>100</td>
<td>5</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
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<td>6</td>
<td>5</td>
</tr>
<tr>
<td>100</td>
<td>15</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>150</td>
<td>5</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>150</td>
<td>15</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>150</td>
<td>25</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

**Fig. 1.** Typical respiratory (upper) and circulatory (lower) changes in rabbits with different rates of cocaine administration, noted at the bottom of the tracing. All animals were premedicated with 5 mgm./kgrm. of pentobarbital. Time intervals, 6 seconds; minutes indicate duration of cocaine injection.

ments were performed to determine the circulatory and respiratory effects at different rates of administration, with the rates varied over a sufficiently wide range so as to produce both the rapid and the slow type of intoxication.

In figure 1 four tracings are shown of experiments on rabbits, in which cocaine
was injected at rates from 2.5 to 15 mgm./kgm./min. after premedication with 5 mgm./kgm. of pentobarbital. The most rapid rate produced death in one minute with approximately simultaneous respiratory and cardiovascular failure, whereas, in the slowest rate, 2.5 mgm./kgm./min., respiration failed after cocaine had been administered for a period of eight to nine minutes, a situation that simulates intoxication produced by subcutaneous administration. The tracing of this latter rate also reveals that at the time of respiratory failure, the cardiovascular system was functioning at an adequate level and did not fail until depression from hypoxia occurred. The institution of artificial respiration would have made possible the resuscitation of the animal provided that the cocaine injection had been discontinued before cardiovascular failure ensued. Still slower rates produced similar tracings except that respiratory failure was delayed; for example, animals receiving 2.0 mgm./kgm./min. of cocaine tolerated up to 40 minutes of the injection before respiratory arrest resulted.

Rates of 4 mgm./kgm./min. produced unexpected results in that circulatory failure occurred distinctly before respiration failed and that the typical terminal respiratory pattern did not develop, indicating that respiratory failure was probably due to the failure of the cardiovascular system. A closely related situation can be seen in the 3 mgm./kgm./min. tracing although a few feeble heart beats do occur after respiration has ceased. It appears that even with intermediate rates of administration the failure of the cardiovascular system may be the primary cause of death in cocaine intoxication. Similar experiments, carried out on rabbits which had not been premedicated with pentobarbital, gave comparable results except that no instance of complete cardiac failure was found before the failure of respiration. Tracings of cardiovascular and respiratory changes produced by subcutaneous injections of cocaine revealed no discernible difference from those produced with intravenous injection provided the rate of absorption was similar, as judged by the time required to produce death.

Changes in the electrocardiograms recorded during cocaine intoxication were essentially those described by previous investigators (Long et al., 1949). Generally there was a slowing of rate, partial to complete sino-auricular block, increase in the duration of the QRS complex, increase in the amplitude of the S and T waves, and a decrease in the amplitude of the R wave. In the electrocardiograms of a certain proportion of the animals, cardiac irregularities appeared as ventricular ectopic beats. As the intoxication progressed ventricular tachycardia often appeared in the unanesthetized animal, whereas intraventricular block with slower rates occurred in the animals receiving sufficient barbiturates to control the convulsions.

Further study of the protective effect of pentobarbital in cocaine intoxication was made using a constant intravenous injection of cocaine and recording the course of the intoxication as in the previous experiment. The rate of cocaine administration was 2.5 mgm./kgm./min., producing the slow type of intoxication, and the criterion of protection was the amount of cocaine required to produce respiratory arrest with the various levels of barbiturate premedication. In a series of ten rabbits protected by a dose of 15 mgm./kgm. of pentobarbital,
only four tolerated noticeably greater amounts of cocaine than the controls and there was a much greater variation in the total dosage for the premedicated as compared to the untreated. A possible complicating factor was the low level of blood pressure and weak heart action noted in all of the animals which had received adequate doses of pentobarbital.

This investigation was extended using a group of twenty dogs in a similar experiment. Each of the following doses of pentobarbital, 5, 15, and 30 mgm./kgm., was given to a group of five dogs immediately prior to the start of a continuous injection of cocaine, 2.25 mgm./kgm./min., and the point of respiratory arrest determined. The results obtained were similar to those seen with the experiments on the rabbits, in that no consistent, marked protection was obtained, and that the animals receiving sufficient pentobarbital to control the convulsions (15 and 30 mgm./kgm.) had a very low level of cardiovascular function at the time of respiratory arrest. In figure 2 are represented two tracings, one each from the control and 15 mgm. groups that demonstrate the two general patterns seen in these experiments. In the dogs which had received no pentobarbital, blood pressure and cardiac activity continued at a high level until the occurrence of depression from hypoxia due to the paralysis of the respiratory center. Those receiving pentobarbital revealed a gradually falling blood pressure and decreasing heart action during the course of intoxication, and at the time of respiratory arrest the blood pressure was at shock levels.

![Figure 2: Comparison of the effects of pentobarbital on the “slow type” of cocaine intoxication in dogs. Time intervals, 6 seconds; minutes designate duration of cocaine injection.](image-url)
In table 2 a summation of the results of these experiments is presented which bears out the previously mentioned observation that protection by pentobarbital is uncertain with constant intravenous injection of cocaine, and that an important degree of cardiovascular depression is evident when the doses of pentobarbital used are sufficient to suppress convulsions. The tolerance of dogs to cocaine after receiving 30 mgm./kgm. of pentobarbital appears to be less than that of the untreated animals; however, the number of animals is too small to draw definite conclusions.

The degree of cardiovascular depression which was found with moderate rates of cocaine administration and with the addition of barbiturate therapy led to a search for means to counteract this effect. The lack of cardiovascular depression in non-treated cocaine intoxication suggested that the convulsions, themselves, might be responsible for the liberation of endogenous epinephrine which counteracted the depression. Preliminary experiments on rabbits demonstrated that epinephrine in small doses had marked efficiency in stimulating the cardiovascular system depressed by cocaine, and more extensive experiments revealed this effect to be consistent in both dogs and rabbits. The cardiovascular stimulation produced by epinephrine in cocaine intoxication is illustrated in figure 3 under two conditions, namely, cardiovascular depression with slow cocaine administration and large doses of barbiturate and, secondly, depression with rapid cocaine administration and no barbiturate. The upper tracing is of an experiment in which a dog was given 2.25 mgm./kgm./min. of cocaine after premedication with 30 mgm./kgm. of pentobarbital and the lower is one in which a rabbit received 5.0 mgm./kgm./min. of cocaine with no premedication. Examination of the blood pressure tracing shows that the 2.5 microgm./kgm. of epinephrine produced an increase in heart rate and pulse pressure as well as a general rise in blood pressure.

Electrocardiograms taken during the administration of epinephrine to cocaine-intoxicated animals revealed a ventricular tachycardia with a marked increase

**TABLE 2**

<table>
<thead>
<tr>
<th>PENTOBARBITAL (mgm./kgm. i.v.)</th>
<th>NUMBER OF ANIMALS</th>
<th>COCAINE PRODUCING RESPIRATORY ARREST (mgm./kgm.)</th>
<th>BLOOD PRESSURE AT RESPIRATORY ARREST (AVG.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>25</td>
<td>135/85</td>
</tr>
<tr>
<td>(20-29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>29</td>
<td>190/100</td>
</tr>
<tr>
<td>(23-30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>34</td>
<td>65/35</td>
</tr>
<tr>
<td>(26-54)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>5</td>
<td>22</td>
<td>60/30</td>
</tr>
<tr>
<td>(20-28)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
in the amplitude of the QRS complex. Although many bizarre complexes occurred from time to time, no ventricular fibrillation was found in a series of some 60 injections in fifteen dogs and an equal number of rabbits. In some instances epinephrine appeared to add to the depressant action of cocaine and seemed to cause a failure of the pacemaker.

Other sympathomimetic drugs, ephedrine, Neosymphrine and Isuprel, were investigated to determine their effect on the cardiovascular depression caused by cocaine. It was found that moderate doses of ephedrine and Neosymphrine produced very slight stimulation of the cardiovascular system, whereas Isuprel caused a marked increase in cardiac activity. The comparative effects of the

![Graph showing the effects of different drugs on the cardiovascular system.](image-url)

**Fig. 3.** Stimulating effect of epinephrine on the cardiovascular system during "slow" cocaine intoxication in dog (upper) and "rapid" intoxication in rabbit (lower). Time intervals, 6 seconds; minutes designate duration of cocaine injection.

three drugs are evident in the tracing shown in figure 4. This was obtained from an experiment in which a dog was anesthetized with 30 mgm./kgm. of pentobarbital and then injected with cocaine at the rate of 2.25 mgm./kgm./min. until marked cardiovascular depression was produced. Doses of 5 mgm./kgm. of ephedrine, 50 microgm./kgm. of Neosymphrine, and 1 microgm./kgm. of Isuprel were injected at the points indicated on the tracing. In a series of twelve injections on five dogs, similar results were obtained with a few minor variations, irrespective of the order in which the sympathomimetic drugs were given. Neosymphrine produced a slight, transient elevation in blood pressure in some of the experiments and also appeared to depress cardiac automaticity and pulse pressure. Isuprel was found to be as effective a cardiac stimulant as epineph-
raine; however, there was a noticeably smaller elevation of the mean blood pressure than after the administration of epinephrine.

Discussion. The cause of toxic reactions arising from the use of local anesthetics in clinical medicine can be ascribed to several factors. One of these is overdosage, another is hypersusceptibility of some individuals, and a third is an unpredictable increase in the rate of absorption. Added care in the use of these drugs has reduced the hazard of the first factor but present techniques do not adequately control the latter two. Treatment is directed toward the maintenance of the effective function of the respiratory and cardiovascular systems until natural detoxication and elimination of the drug can take place. One of the therapeutic measures concerned with the maintenance of respiration, which was investigated, was the prophylactic use of a barbiturate for the control of excessive stimulation and respiratory failure. From our studies on rabbits it appeared that approximately one-half of the anesthetic dose of pentobarbital was required for adequate protection against cocaine intoxication. The protective effect of a barbiturate is apparently correlated with the ability of the drug to prevent convulsions, as indicated by the lack of convulsions when 15 mgm./kgm. of pentobarbital were employed. A direct comparison of drug dosage in man and animal cannot be made; however, a comparison of the depressant effects of the protective dose of pentobarbital in the rabbit and so-called prophylactic dose of barbiturate in man reveals that the latter is of a much lower order and more nearly compares with the 5 mgm./kgm. dose used in rabbits, which afforded no protection. This comparison taken with the clinical failures, mentioned previously, suggests that the sedative doses used for prophylaxis clinically are far below those necessary for adequate protection.

Studies on the nature of the toxic action of cocaine with various rates of administration support the accepted concept that the respiratory system is generally more susceptible than the cardiovascular system. At rates of absorption from moderate to fast, the time-concentration factor is such as to make the apparent susceptibility of the two systems nearly equal, and under some condi-
tions the failure of the cardiovascular system may actually be the cause of death. The presence of barbiturates, and possible preexisting cardiac pathology (Long et al., 1949), seem to increase the susceptibility of the cardiovascular system to local anesthetic agents.

The most obvious effect of cocaine on respiration is one of stimulation, especially in rabbits. An examination of the respiratory tracings reveals that respiratory exchange gradually declines because of the very rapid rate, the increasing irregularities, and the decreasing amplitude of respiration. The tracing obtained during the recovery from cocaine intoxication is practically a mirror image of the failing respiration, suggesting that recovery involves a decrease in stimulatory effects rather than recovery from depression. If this view is correct, the effectiveness of barbiturates in the treatment of cocaine intoxication appears to be limited to the control of the stimulatory properties of cocaine. Any barbiturate over that amount necessary to control stimulation adds to the apparent depressant factor of the action of cocaine and decreases the tolerance of an animal to this local anesthetic. This is borne out by the findings on the animals listed in table 2 which had received 30 mgm./kgm. of pentobarbital.

The frequent occurrence of cardiovascular depression and its attendant danger in all cases of local anesthetic intoxication, except those with very slow absorption, is emphasized by our investigations. Previous experimental work has demonstrated both favorable and unfavorable effects of epinephrine on local anesthetic intoxication; however, a common clinical belief, as indicated in the Technical Bulletin 10-A-106 of the Veterans Administration (Himalstein, 1949), is that epinephrine should not be administered during cocaine intoxication because of the danger of inducing ventricular fibrillation. In our experience, small doses of epinephrine have consistently produced a beneficial stimulation of the depressed cardiovascular system during cocaine intoxication with no evidence of ventricular fibrillation in approximately 60 administrations to 30 different animals. Long and coworkers, 1949, found that three out of twenty dogs developed ventricular fibrillation when concentrated solutions of procaine were injected rapidly. It is doubtful that such rapid rates of administration and high concentrations of a drug are ever duplicated in cases of clinical intoxication and makes it questionable whether or not ventricular fibrillation is ever the cause of death in these accidental toxic reactions. This dual action of local anesthetics is probably analogous to potassium which produces ventricular fibrillation with rapid injections, whereas moderate rates of administration produce the commonly expected effect, namely, cardiac slowing, depression, and finally arrest. Epinephrine may cause respiratory failure in acute cocaine intoxications (Steinhaus, 1950), and this possibility should be kept in mind if epinephrine is used in the treatment of clinical reactions to local anesthetics. The explanation of this effect of epinephrine may be due to an increase in the reflex apnea produced by epinephrine or an actual increase in the susceptibility of the respiratory center to cocaine because of the presence of epinephrine, as indicated by some workers (Eichholtz and Hoppe, 1933).

When cocaine was given intravenously at a slow rate it was found that pento-
barbital afforded less marked protection than was the case when subcutaneous injections of cocaine were employed. This difference may be explained in two ways: first, the control of the convulsions may have a marked effect on the rate of absorption with subcutaneous administration, whereas the occurrence of convulsions would not affect the rate of a constant intravenous administration; and secondly, the blood concentration curves of subcutaneous and constant intravenous administrations of a drug change in a different manner with an increase in the dosage, as indicated by the work of Burgen and Keele (1948) in which they determined the concentration of procaine in the blood following its intravenous administration at a constant rate.

A secondary beneficial effect of pentobarbital in cocaine intoxication was the reduced sensitivity of the cardiovascular system to hypoxia, observed when resuscitation of the animals having had no premedication was compared to those receiving a barbiturate. The tracing in figure 2 illustrates this point since it is shown that despite a very short delay in starting artificial respiration, irreversible depression of the cardiovascular system had occurred. In contrast, the dog receiving barbiturate tolerated a longer delay before artificial respiration was begun and yet it was resuscitated without difficulty. This marked susceptibility to oxygen-lack was a constant finding with those animals which had received insufficient barbiturate to control their convulsions. These results are consistent with the findings of previous workers (Robbins et al., 1939) that barbiturates reduced the sensitivity of the heart to hypoxia.

Although no extensive studies were done with other sympathomimetic agents, our investigations indicated that there are marked differences in the ability of the different members to counteract the depression of the cardiovascular system produced by cocaine. A comparison of Isuprel with epinephrine revealed that they are equally good cardiac stimulants; however, Isuprel does not produce as great a rise of blood pressure, especially that of diastole. This conforms to the present knowledge of Isuprel, in that its vasomotor properties are more likely to cause vasodilatation than constriction. The failure of ephedrine and Neosynephrine to counteract the depression of cocaine intoxication in view of their good vasoconstrictor activity and their lesser cardiac stimulatory effects, supports the idea that direct myocardial depression is the primary consideration in the treatment of cocaine intoxication.

CONCLUSIONS

1. The dose of pentobarbital required to give adequate prophylactic protection against cocaine intoxication was found to be approximately one-half the anesthetic dose. Doses of pentobarbital which produced depression equivalent to a sedative dose (approximately one-sixth of the anesthetic dose) afforded relatively little protection against cocaine intoxication.

2. From these studies it was concluded that the use of barbiturates in the treatment of cocaine intoxication is limited to the control of the central stimulating effects of the toxic process and doses above that necessary to control the convulsions increase the possibility of respiratory failure.
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3. Serious cardiovascular depression was found to occur during cocaine intoxication with moderate to rapid rates of administration and with slower rates if barbiturates were present in quantities sufficient to control convulsions.

4. The depression of the heart by cocaine, under the circumstances described above, can be counteracted by certain of the sympathomimetic agents, such as epinephrine and Isuprel.

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REFERENCES