# A NEW LETHAL DOSE OF CURARE, WITH SOME OBSERVATIONS ON THE PATHOLOGY PRODUCED BY LARGE DOSES * †

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LETHAL doses of curare have apparently been determined by the severity and duration of the anoxia attending its administration. During the three years in which curare has been used in anesthesia, it has been administered both in small doses in conjunction with other agents, particularly cyclopropane, and recently in larger doses to produce actual anesthesia (1, 2); the view has been expressed (3) that, in the frog, curare inhibits central synaptic transmission. In neither case, however, is the anesthetist willing to tolerate the presence of anoxia. It is his purpose and practice to perform continuous artificial respiration whenever curarization is followed by apnea or by inadequate respiratory excursions. In view of the widespread use of curare today in anesthesia and in neurology, it seemed advisable to determine, in the laboratory animal, whether or not very large single doses of this drug could be harmful in the presense of adequate pulmonary ventilation, what these harmful effects and possibly a new lethal dose of curare might be when not associated with a preventable anoxia. The possibility of a fatal effect of continuous deep curarization (4) has been demonstrated. This study seemed, after it had been started, to be especially important, in view of the newer tendency to use large doses of curare. In connection with curare anesthesia, it should be noted that the deliberate combination of complete curarization and artificial respiration in the laboratory animal was practiced by earlier investigators (5).

Intocostrin,* a Squibb preparation of curare, was used throughout. Tubocurarine was not employed. The microliter pound unit or microliters per pound (M/P) referred to in the following tables and discussion is one thousandth of a cubic centimeter (0.001 cc.) of intocostrin per pound of body weight. It is a relative amount and must not be confused with the biological unit of curare equivalent to one-twentieth of a cubic centimeter (0.05 cc.) of intocostrin. The curare was always injected intravenously, quickly, and in one dose.

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Blood pressures were not taken, as accurate determinations could not be made without cannulizing an artery; they were not considered necessary for the purposes of this study.

The purpose of the first series of experiments was to determine the anoxic lethal dose; the results are given in table 1.

TABLE 1

| Dog Number | Weight in lbs. | Dose in cc. | Dose in microliters per lb. (M/P) | Time in minutes from curare injection to: | |
|---|---|---|---|---|---|
| | | | | Recovery | Death |
| 1 | 55 | 1.0 | 18 | 10 | |
| 2 | 46 | 1.4 | 30 | 12 | |
| 3 | 40 | 1.6 | 40 | 34 | |
| 1 | 55 | 2.5 | 45 | | 13 |
| 3 | 43 | 1.95 | 45 | 42 | |
| 6 | 20 | 1.0 | 50 | 80 | |
| 2 | 45 | 2.7 | 60 | | 18 |
| 4 | 39 | 2.4 | 62 | hrs. | |
| 3 | 40 | 2.6 | 65 | | 12 |
| 5 | 21 | 1.4 | 67 | | 20 |
| 7 | 20 | 1.3 | 65 | | 13 |

The lethal dose, death being apparently due to simple anoxia, was thus established at 65 M/P or 0.065 cc. (1/15 cc.) per pound. One death followed the administration of 45 M/P; this dog (number 1) had been curarized on the preceding day, however. Repeated curarization on succeeding days was avoided in all subsequent experiments.

TABLE 2

| Dog Number | Weight in lbs. | Dose in cc. | Dose in microliters per pound (M/P) |
|---|---|---|---|
| 4 | 37.5 | 1.9 | 51 |
| 4 | 36 | 2.5 | 69 |
| 8 | 36.75 | 2.5 | 68 |
| 9 | 28.5 | 2.3 | 81 |
| 9 | 28.5 | 2.9 | 101 |

The next series of experiments was directed at determining the anoxic lethal dose under endotracheal cyclopropane-oxygen anesthesia. Five dogs received pentothal induction, tracheal intubation, cyclopropane-oxygen anesthesia; the curare was administered through the rubber-tube side arm of an intravenous-Y arrangement, its administration being both preceded and followed by the injection of saline solution through the same needle. Although previously established lethal doses were given in four of the five cases, no death was encountered in this series. The diaphragm continued to function in all five cases, and cyanosis was never seen. The number of cubic centimeters of 2.5 per cent pentothal sodium injected intravenously was in each case

two-sevenths of the weight in pounds. Results of these five experiments are given in table 2.

As this second series of experiments seemed to suggest that the dose previously established as lethal might not be so, the technic used in the first series of cases was repeated in four experiments. Doses ranging from 74 to 101 M/P were injected directly into the vein, without recourse to pentothal, cyclopropane-oxygen anesthesia, intubation, administration of saline solution, or rubber tubing. These cases are tabulated in table 3.

TABLE 3

| Dog Number | Weight in lbs. | Dose in cc. | Dose in microliters per pound (M/P) | Died in .... minutes |
|---|---|---|---|---|
| 8 | 37.5 | 3.4 | 91 | 8 |
| 9 | 28.8 | 2.9 | 101 | 9 |
| 10 | 23.5 | 1.75 | 74 | 12 |
| 12 | 37.5 | 2.65 | 71 | 8 |

Employing this same technic, dog Number 11, weighing 23.5 pounds, received 1.6 cc. of intocostrin (68 M/P) and appeared to recover completely in about fifty minutes. He was found dead in his cage two days later, however; no autopsy was done.

This third series of cases confirmed our earlier results. Several attempts were now made to discover why no deaths occurred in series 2. In series 4 (see table 4), our technic included the administration of pentothal, endotracheal intubation, and cyclopropane-oxygen anesthesia; the curare was injected directly into the vein, eliminating the rubber tubing and saline solution. Whenever pentothal was used for induction, its depressing effect on the respirations was always allowed to disappear before the curare was administered; the curare was not given unless spontaneous breathing was present, with positive chest movement.

TABLE 4

| Dog Number | Weight in lbs. | Dose in cc. | Dose in microliters per pound (M/P) | Died in .... minutes |
|---|---|---|---|---|
| 16 | 29 | 1.9 | 66 | 15 |
| 17 | 24.5 | 1.7 | 69 | 52 |

Injecting the curare in the simplest manner, directly into the vein, the anoxic lethal dose was thus shown to be unaffected by the cyclopropane-oxygen anesthesia in conjunction with which curare is commonly administered in man.

It seemed at this point that whatever anticurare effect was present might be due to its dilution with saline solution. It is interesting to recall, in this connection, that the natives of South America who made

and used curare believed salt to be an antidote for the paralysis it produced (6).

Two dogs were then given curare with saline solution, through the same rubber tube arrangement, but without anesthesia or the high oxygen concentrations that accompany it; these experiments are listed in table 5.

TABLE 5

| Dog Number | Weight in lbs. | Dose in cc. | Dose in microliters per lb. (M/P) | Died in .... minutes |
|---|---|---|---|---|
| 15 | 26.3 | 2.4 | 91 | 8.5 |
| 14 | 29.3 | 2.0 | 68 | 8 |

The fallacy of the aforementioned hypothesis was thus demonstrated and, returning to the technic used in the second series (table 2), dog number 19, weighing 37 pounds, received 70 M/P of curare (2.6 cc.) between saline injections, during cyclopropane-oxygen anesthesia with pentothal induction and endotracheal intubation; the animal recovered in fifty-five minutes.

It now seemed advisable to by-pass this problem for the following reasons:

1. The figures seemed too large to be explained by individual variations. It was believed that some extraneous anticurare factor had been introduced, which, without being identified, was removed in all subsequent experiments. Failure to produce death with an apparently lethal dose of curare occurred only when there was a combination of endotracheal cyclopropane-oxygen anesthesia, pentothal induction, and the rubber tube-saline arrangement. Whenever one of these factors was omitted, the previously determined lethal dose was confirmed. From this point on, all curare administrations were made directly into the vein, without tubing or saline solution. It was thus felt that results obtained in subsequent experiments could be honestly used for comparison, and the anoxic lethal dose had been correctly established.

2. The lethal dose established in series 1 was confirmed in series 3 and was shown to be unaltered by anesthesia in series 4.

3. Attempts to solve this side problem were proving time-consuming.

4. It seemed that, while a solution to this phenomenon was desirable (it might explain variations in curare effects in man; it might be a clue to an anticurare mechanism which could be useful in terminating the effects of an overdose of curare), it was not, for the purposes of these experiments, essential. It appeared certain that their results would not be invalidated.

In addition to the remote possibility of delayed death in the case of dog number 11, the two following experiments are significant. Dog number 13, weighing 30¼ pounds, was given pentothal, intubated, anesthetized with cyclopropane-oxygen, and finally received 2 cc. of into-

costrin (65 M/P). He seemed to make a complete recovery in twenty-eight minutes, breathed well and had good color two minutes after extubation, but suddenly died two minutes later. Dog number 20, weighing 47¼ pounds, received pentothal, was intubated and anesthetized with cyclopropane-oxygen. He was given 7.1 cc. of intocostrin (150 M/P), and artificial respiration was performed. He, too, appeared to make a complete recovery in eighty-eight minutes; the tube was removed (thirty-three minutes after the return of voluntary breathing) and he was returned to his cage where he was found dead ten minutes later. These experiments suggest that the animal is in a precarious state on emergence from deep curarization.

Curare anesthesia, the use of large doses of curare without the administration of any other anesthetic drug, was employed in the last series of experiments. The technic in these cases included the intravenous administration of curare, intubation of the trachea, and continuous artificial respiration with pure oxygen (using the carbon dioxide absorption technic). Prostigmine was administered to one of the dogs (number 21) in an attempt to neutralize the effects of a large dose of curare. Two hundred M/P (three times the anoxic lethal dose, or 3 a.l.d.) was injected, after which 6 cc. of prostigmine (1: 2000) and a total of 2 mg. (gr. 3/100) of atropine were administered. Diaphragmatic respiration returned quickly, but intercostal function could not be brought back. The animal's respiratory efforts were ineffectual; prompt tracheal intubation and artificial respiration were now unavailing; consciousness never returned and death occurred twenty minutes after curarization. The effect of curare on the brain potential of the frog is said to be unaffected by prostigmine (3).

Experiments involving large doses of curare are listed in table 6. Dog number 23 made an uneventful and complete recovery after five and a half hours of continuous artificial respiration following the injection of 200 M/P (three times the anoxic lethal dose, or 3 a.l.d.) of curare. Dog number 24 recovered completely from the effects of 335 M/P or 5 a.l.d. of curare, after six hours of artificial respiration. Dog number 25 received 670 M/P or 10 a.l.d. The trachea was intubated and artificial respiration was started immediately, but cyanosis appeared and persisted for twelve minutes. This dog recovered after thirteen and a half hours of artificial respiration, but showed signs of permanent brain damage. When taken from his cage and put on the floor, he always walked incessantly in small counterclockwise circles, holding his head down; all four legs were spastic. Bloody diarrhea appeared in this case six and a half hours after curarization and persisted until recovery. Dog number 22 was given 1000 M/P, or 15 a.l.d.; cyanosis appeared immediately and persisted until death, despite prompt intubation of the trachea and institution of artificial respiration. The same dose was administered to dog number 26 (who seemed unusually alert); this animal made a complete recovery after eighteen

hours of artificial respiration. The apparently complete recovery in this case suggests that the brain damage in dog number 25, who received a smaller dose of curare and underwent a shorter period of deep curarization but suffered a greater period of anoxia, as shown by the twelve minutes of cyanosis, was the result not of direct curare poisoning of the brain but of anoxia.

Dogs number 27 and number 28 received 1340 M/P or twenty times the anoxic lethal dose; a bloody diarrhea was present in the latter case. An autopsy on dog number 27 revealed the presense of numerous punctate hemorrhages throughout the intestinal tract. The stomach of dog number 28 showed a similar tendency, but the entire intestinal tract, from the duodenum to the rectum, was covered with a thick, jelly-like, bloody coat, the result of severe mucosal hemorrhages of the entire small and large intestine. The stomach and duodenum are shown in figure 1. The diarrhea in the two cases with recovery, dogs number 25 and number 26, disappeared within a day or two.

FIGURE 1.

Before curarization, dog number 28 appeared to be far more alert than dog number 27; this may have accounted for his longer survival time.

Difficulty in raising the chest wall was encountered in the series in which large doses were used. This resistance was present immediately after intubation (following curarization), but disappeared in about five minutes. In two cases, the trachea was reintubated, to confirm the correct position and length of the tube. The possibility of intercostal or bronchiolar spasm immediately following curarization is suggested. Laryngospasm was never encountered. Respiratory spasm during the administration of curare has been described (1, 2). During the first minute after the injection of curare, convulsive movements of the entire body, including particularly the throat and jaw muscles, were always seen. It will be recalled that the topical application of curare to the spinal cord is followed by convulsions (7). Defecation occurred commonly after the injection of curare, even under anesthesia.

The unavoidable cyanosis occurring immediately after the injection

of large doses of curare, despite the prompt institution of adequate artificial respiration, may be due to this respiratory spasm or to a profound effect of the drug on the circulation. Large doses of curare produce, in the frog, the effect of blocking all the veins entering the heart; a marked hypotension occurs even when the vagi and spinal cord are cut and atropine is given (8).

Lowering of the pulse rate occurred commonly when artificial respiration was stopped for a few seconds at any time during the deep curarization.

TABLE 6

| Dog No. | Wt. in pounds | Dose in cc. | Dose in microliters per pound (M/P) | Dose in a.l.d. | Cyanosis in min. | Time from curare injection (hours) to: | | Remarks |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Recovery | Death | |
| 23 | 28.5 | 5.7 | 200 | 3 | 0 | 5.5 | | |
| 21 | 31.5 | 6.3 | 200 | 3 | 20 | | 0.33 | Prostigmine |
| 24 | 29.8 | 10.0 | 335 | 5 | 0 | 6.0 | | |
| 25 | 28.0 | 18.7 | 670 | 10 | 12 | 13.5 | | Bloody diarrhea |
| 22 | 14.0 | 14.0 | 1000 | 15 | 30 | | 0.5 | No autopsy |
| 26 | 21.0 | 21.0 | 1000 | 15 | 5 to 10 | 18.0 | | Bloody diarrhea |
| 27 | 23.0 | 31.0 | 1340 | 20 | ca 5 | | 0.42 | Punctate hemorrhages |
| 28 | 35.0 | 47.0 | 1340 | 20 | 5 to 15 | | 4.0 | Bloody diarrhea, mucosal hemorrhages |

In ten experiments not listed, the end of the needle was not properly within the lumen of the vein during the entire administration of curare, as shown by an obvious swelling during the injection. The injections were always stopped in such cases; no deaths occurred in these experiments.

## CONCLUSIONS

1. The anoxic lethal dose of intocostrin in the dog is 0.065 cc. (1/15 cc.) per pound of body weight.

2. The anoxic lethal dose is unaffected by cyclopropane-oxygen anesthesia.

3. The possibility of a cumulative effect of curare is indicated by the death of one dog following the administration of what appeared later to be a sublethal dose. The suggestion is offered that the use of curare on succeeding days may be associated with a heightened effect of the drug.

4. An unidentified anticurare effect was encountered with a technic including tracheal intubation, cyclopropane-oxygen anesthesia, pentothal induction, and the administration of the curare with saline solution through rubber tubing.

5. As evidenced by the deaths of two dogs (number 13 and number 20), the animal is in a dangerous condition on emergence from deep curarization.

6. There is a nonanoxic lethal dose of curare. Dogs can make complete recoveries, with artificial respiration, after receiving five times the anoxic lethal dose of curare or 0.33 cc. of intocostrin per pound of body weight. The lethal dose of intocostrin in dogs, in the presence of continuous artificial respiration, is about twenty times the anoxic lethal dose, or 1 1/3 cc. per pound. Complete recovery was made in one case following the administration of 1.0 cc. of intocostrin per pound (fifteen times the anoxic lethal dose); artificial respiration was maintained for eighteen hours.

7. The cardiovascular system appears to be affected by large doses of curare. A temporary unavoidable cyanosis was present following the administration of large doses of curare in the presence of proper artificial respiration. Marked slowing of the pulse rate occurred whenever artificial respiration was stopped.

8. Bronchiolar or intercostal spasm is suggested immediately following the injection of large doses of curare by the greater amount of force required to raise the chest wall during artificial respiration.

9. No clinical evidence of brain damage could be found (other than that due to anoxia) attributable to large doses of curare.

10. Bloody diarrhea was a constant finding in the later experiments. Postmortem examination in two cases revealed the presence of severe mucosal hemorrhages involving the entire intestinal tract. There may be at least a relative contraindication for the use of large doses of this drug when there is disease of the intestinal tract.

11. The forelegs always recover function before the hind legs. Weakness of all legs persists for a period of minutes to several hours after recovery.

12. Prostigmine does not appear to be a perfect neutralizing agent for large doses of curare.

13. The safest and proper method of terminating the effects of a very large dose of curare is continuous artificial respiration until the animal has recovered completely.

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