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NARCOSIS WITH PENTOTHAL SODIUM ALONE COMPARED TO NARCOSIS WITH PENTOTHAL SODIUM COMBINED WITH (1) CURARE OR (2) MYANESIN

I. PENTOTHAL SODIUM-CURARE NARCOSIS *

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INTRODUCTION

IN 1938, through the combined efforts of Gill (1, 2), McIntyre and the E. R. Squibb and Sons Laboratories, a pure standardized form of curare, d-tubocurarine chloride, was produced which was considered safe for use in human beings.

Griffith and Johnson (3) reported the first successful use of curare † as an adjunct to cyclopropane anesthesia. It was used to produce additional relaxation of the patient while he was maintained at a relatively shallow plane of anesthesia. As curare became more widely accepted as an adjunct to anesthesia, other commonly used anesthetic agents were employed in combination with it.

Pentothal sodium supplemented with curare became quite widely used by a number of clinicians and, as a result, a variety of opinions as to its efficacy have been expressed. One of those opinions has been that curare used in this manner potentiates anesthetic effects of pentothal sodium, making it possible to accomplish a given depth and duration of anesthesia with less pentothal sodium than would be required if curare had not been administered(4).

The muscle relaxing and paralyzing effects of curare are well recognized and are known to occur under the conditions of our experiments. We were, however, chiefly concerned with the anesthetic effects of pen-

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† The word "curare" is used throughout this paper as a synonym for the pure alkaloid, d-tubocurarine chloride, an extract of Chondodendron tomentosum. Where crude curare is implied, it will be indicated.

tothal sodium as compared to those of the pentothal sodium-curare combination. The experiments described in this paper were designed to test whether there is synergism, and our attention will be concentrated on this question.

The Central Effects of Curare: Review of the Literature

The possibility of central effects of the curares has been recognized by many observers. If curare has a central effect, it would seem logical to assume that its addition to a barbiturate might alter the narcotic and anesthetic effect of the barbiturate in some measurable manner.

Feitelberg and Pick (5) in 1942 and Pick and Unna (6) in 1945 found that d-tubocurarine chloride caused the electropotential of the brain of the frog to disappear and that this effect was entirely independent of the peripheral effect of curare. However, these effects were seen only after the administration of relatively larger doses of curare than were required to produce muscular paralysis. They expressed the belief that the central effects of curare were independent of the peripheral effects because the central effects were of longer duration, lasting several days at times, and they could not be abolished by the use of neostigmine, whereas the peripheral effects were of much shorter duration and were easily and immediately neutralized by the use of neostigmine.

Von Euler and Wahlund (7) reported that intracisternal injections of pot curare, a form of crude curare, and purified curarine in large doses caused first an acceleration of respiration and a rise in blood pressure, followed by a reversal of these effects.

Fegler (8) found that dogs weighing 6 to 10 kg., when anesthetized with morphine and chloralose and given intravenously either a 3.5 per cent solution of "Bambou" curare or a "1 per cent Merck's curare," showed a short period of excitation followed by inhibition of respiration as indicated by a decrease in respiratory frequency and amplitude. The respiratory inhibition was progressive and eventually resulted in cessation of respiratory movements. During the period of respiratory inhibition, stimulation of the phrenic nerve still produced contraction of the diaphragm, suggesting that the inhibition of respiration was a central effect.

Whitacre and Fisher (9) reported their observations in human subjects after the administration of large doses of curare (as much as 405 Squibb units of intocostrin in one hour and forty-five minutes). They observed that when similarly large doses were used soon after respiratory paralysis had occurred, consciousness was lost in spite of the carrying on of efficient artificial respiration; furthermore, such loss of consciousness was not preceded by analgesia. An attempt was made to produce analgesia by administering repeated small doses of intocostrin to the point of respiratory paralysis but not to the point of loss of consciousness. Even though the patients were entirely unable to move,

they showed signs of pain as soon as the operation was started and after a short time it was necessary to perform general anesthesia.

Whitacre and Fisher also reported 2 instances in which local infiltration analgesia was inadequate for abdominal operations. The patients were rendered unconscious by repeated doses of curare and the operations were successfully completed with no further anesthesia. It must be remembered, however, that they were using larger doses of curare to produce the unconscious state than are ordinarily employed clinically.

McIntyre and his associates, working with dogs, pointed out that subparalytic doses of d-tubocurarine chloride caused a variety of changes in the electroencephalogram suggestive of central depression (10). Smith and co-workers (11) suggested the possibility that this depression was caused by the barbiturate administered, or perhaps it may have been due to hypoxia that possibly was present during the study.

Harvey and Masland (12) could detect no significant central effects in man after subparalytic doses of curare extract had been given.

Harris, Pacella, and Horwitz (13) observing the effects of metrazol-induced convulsions on curarized mental patients, found no therapeutic or electroencephalographic effects attributable to the curare.

Smith (11) allowed himself to be given, in thirty-three minutes, two and one-half times the amount of d-tubocurarine chloride necessary to produce complete respiratory and muscular paralysis. Careful observations were made upon him and no changes occurred in the electroencephalogram, consciousness or sensorium. He concluded that d-tubocurarine chloride has no significant central stimulant, depressant or analgesic action.

PROCEDURE

In the present study the barbiturate used was pentothal sodium (sodium ethyl (1-methylbutyl) thiobarbiturate) Abbott, with anhydrous sodium carbonate as a buffer. The curare used was Abbott's solution of d-tubocurarine chloride, each cubic centimeter of which contained 3 mg. of d-tubocurarine chloride pentahydrate, 1 mg. of sodium metabisulfite and, as a preservative, sufficient benzyl alcohol to make a content of 0.9 per cent in a buffered aqueous solution made isotonic with sodium chloride.

It was necessary in each species of animal to determine, separately, effective but well-tolerated doses of pentothal sodium and d-tubocurarine chloride so that the pentothal sodium-d-tubocurarine chloride solution might be prepared for use in the experimental series. The dose, per kilogram of body weight, of pentothal sodium that would cause all animals to lose their righting reflex and the dose, per kilogram, of d-tubocurarine chloride that would cause generalized paresis in all animals without respiratory paralysis were determined. These doses were found by trial and error.

All injections in the guinea pig, rabbit and dog were intravenous, while those in the rat were intraperitoneal.

Doses of pentothal sodium, per kilogram of body weight, which caused all animals to lose their righting reflex were 4.0 mg. for the guinea pig, 12.5 mg. for the rabbit, 20 mg. for the dog and 40 mg. for the white rat. Doses of d-tubocurarine chloride per kilogram which caused all animals to become generally paralyzed but did not cause respiratory paralysis were found to be 0.04 mg. for the guinea pig, 0.14 mg. for the rabbit, 0.20 mg. for the dog and 0.20 mg. for the white rat.

Because of the possibility of tolerance for the barbiturate as shown by Green and Koppanyi (14) and Gruber and Keyser (15) or cumulative action as suggested by Veal and Reynolds (16), the animals were used no oftener than once each seven days.

As often as possible, the same animal was used in the control (pentothal sodium) series and the experimental (pentothal sodium-curare) series so that a comparison in the same animal could be made between the two series.

In these experiments, the pentothal sodium was used in 2 per cent solution in distilled water, and when curare was used it was contained in a 2 per cent solution of pentothal sodium. This permitted the same volume of fluid to be injected in the control series as in the experimental series.

In the guinea pig, rabbit and dog, in which the injections were intravenous, all injections were done in one minute. In the white rat, in which the injections were intraperitoneal, no attempt was made to control the rate of injection; it was always done as rapidly as possible.

After the injection was made and the drug had caused the righting reflex to disappear, the time was noted and the animal was placed upon its back and left undisturbed until it recovered. The end point of the action of the drugs was considered to be the time of the return of the righting reflex, that is, when the animal assumed its normal position. This end point in most instances was very definite and often appeared suddenly. The time between the loss of the righting reflex and the return of the righting reflex has been referred to as the narcosis time.

RESULTS

White Rats.—One hundred and twenty-six experiments were done on 36 mature rats. In 51 experiments the animals received 4 mg. of pentothal sodium per 100 Gm. of body weight; in 75 experiments the animals received 4 mg. of pentothal sodium plus 0.020 mg. of d-tubocurarine chloride per 100 Gm. In 24 experiments of the latter group the rats died from the effects of the drugs, leaving only 51 experiments in which the time of narcosis could be recorded.

In those rats receiving pentothal sodium alone, the narcosis time ranged from 39 to 409 minutes, the average being 124.9 minutes and the median, 104 minutes. In the rats receiving the pentothal sodium-d-

tubocurarine chloride combination, the narcosis time ranged from 15 to 371 minutes, the average being 123.75 minutes and the median, 86 minutes.

The mortality rate in the group of rats receiving pentothal sodium was 0 per cent while in the group receiving the pentothal sodium-d-tubocurarine chloride combination it was 32 per cent.

Guinea Pigs.—Two hundred and ten experiments were done on 104 mature male guinea pigs. In 81 experiments the animals received 0.4 mg. of pentothal sodium per 100 Gm. of body weight and 129 received 0.4 mg. of pentothal sodium plus 0.004 mg. d-tubocurarine chloride per 100 Gm. In 34 of the latter group of experiments, the guinea pigs died, leaving 95 experiments in which a narcosis time could be recorded.

In the group receiving pentothal sodium alone, the narcosis time ranged from 3 to 55 minutes, the average being 11.25 minutes while the median was 9.5 minutes. In the group receiving the pentothal sodium-curare combination, the narcosis time ranged from 1 to 39 minutes, the average being 10.2 minutes and the median, 9 minutes.

In the group of guinea pigs that received pentothal sodium alone, the mortality rate was 0 per cent, while in the group of those that received the pentothal sodium-d-tubocurarine chloride combination, the mortality rate was 26.35 per cent.

Rabbits.—Forty-seven mature rabbits were used in doing a total of 164 experiments. A dose of 12.5 mg. of pentothal sodium per kilogram of body weight was given in 76 experiments while in 88 experiments a dose of 12.5 mg. of pentothal sodium plus 0.14 mg. d-tubocurarine chloride per kilogram of body weight was given.

In the group of animals that received pentothal sodium alone, the narcosis time ranged from 3 to 71 minutes, with an average of 12.86 minutes and a median of 10.75 minutes. In the group that received 12.5 mg. of pentothal sodium plus 0.14 mg. of d-tubocurarine chloride per kilogram of body weight, the time of narcosis ranged from 4 to 39 minutes, with an average of 13.75 minutes and a median of 12.5 minutes. There were no rabbits in either group that died as a result of the drugs administered.

Dogs.—Nine mature mongrel dogs were used in doing 28 experiments. In 14 experiments a dose of 20 mg. of pentothal sodium per kilogram of body weight was used and in the 14 other experiments a dose of 20 mg. of pentothal sodium plus 0.2 mg. of d-tubocurarine chloride per kilogram of body weight was employed.

In those dogs that received pentothal sodium alone, the time of narcosis ranged from 25 to 58 minutes, with an average of 36.75 minutes and a median of 35.25 minutes. In those dogs that received the pentothal sodium-d-tubocurarine chloride combination, the time of narcosis ranged from 22 to 67 minutes, with an average of 36.42 minutes and a median of 34 minutes.

While doing these experiments, we felt that if a potentiating effect

occurred as a result of mixing the pentothal sodium and curare before injecting them as a single solution, this point might be emphasized by the occurrence of a shorter time of narcosis if the two drugs were injected separately, allowing mixture to occur in the blood stream.

Eight dogs were given 20 mg. of pentothal sodium per kilogram of body weight and through the same needle immediately after this injection, 0.2 mg. of d-tubocurarine chloride per kilogram was injected. This was the same proportionate dose of each drug that was given to the dogs when the curare and pentothal sodium were in solution together and given as a single injection.

When the two drugs were injected separately, the time of narcosis ranged from 21 to 73 minutes, with an average of 41 minutes and a median of 39 minutes. As can be seen, the narcosis time by this method was definitely not shorter than that in the experimental series, and it was therefore concluded that there was no significant difference in the results of the two methods of administering the drugs.

None of the dogs in either group died as a result of the drugs administered in doing these experiments.

SUMMARY

Experiments on rats, guinea pigs, rabbits and dogs were designed to determine whether anesthesia with pentothal sodium was prolonged when combined with d-tubocurarine chloride.

Effective doses of pentothal sodium and d-tubocurarine chloride per kilogram were determined. The amount of pentothal sodium used was that amount necessary to cause loss of the righting reflex. The amount of d-tubocurarine chloride used was that amount necessary to cause generalized paralysis of the animal without respiratory paralysis.

In the control series, pentothal sodium was given in the effective dose as described in the preceding paragraph, and the narcosis time was determined.

In the experimental series, the same dose of pentothal sodium was given as in the control series, but an effective dose of curare as described above was contained in the pentothal sodium solution. The narcosis time was determined and compared with that of the control series.

All injections in the guinea pig, rabbit and dog were intravenous and were given in one minute. In the white rat, all injections were intraperitoneal and the injection time was not controlled.

The only animals that died as a result of the experiments were some of the guinea pigs and white rats that received the pentothal sodium-d-tubocurarine chloride solution. No animals died from pentothal sodium alone in the doses used.

No significant difference was found between the narcosis time in the pentothal series and the narcosis time in the pentothal-d-tubocurarine series in any of the four species of animals used.

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II. PENTOTHAL SODIUM-MYANESIN NARCOSIS

INTRODUCTION

WHILE our studies with curare and pentothal sodium were being done, Berger and Bradley (1, 2) and Mallinson (3) reported the results of their investigation of α:β-dihydroxy-γ-(2 methylphenoxy)-propane (myanesin) a new muscle-paralyzing agent. In their report, they referred to their use of myanesin in combination with hexobarbitone (evipal) and the resultant potentiation of the narcotic effects of the hexobarbitone by the myanesin. It was this report that prompted the studies of the possible potentiation of pentothal sodium narcosis with myanesin that we are presenting in this paper.

Of one hundred and forty-three alpha-substituted glycerol ethers, myanesin seemed to be the most potent and the safest. It was therefore subjected to rather extensive laboratory studies, the results of which are found in the reports by Berger and Bradley (1, 2).

The property of myanesin which attracted the most attention was