Pharmacologic Modification of the Metrazol Convulsion

*By Samuel R. Rosen, John B. Ziegler and Bruce Cominole**

Considerable advances have been made in recent years in the study of convulsive phenomena. Increasing attention has been centered in the metrazol seizure. This paper concerns itself with attempts to modify the metrazol convulsion with the purpose of decreasing its usual severity and duration while at the same time preserving its general character and form. The resulting milder seizure may eventually have a clinical application in view of the reports of fractures occurring during metrazol treatment of the psychoses (1), (2), (3), (4), (5). That such lighter convulsions can occur for the most part without producing fractures is supported by the roentgenographic studies on an unpublished series of twenty epileptics which yielded no evidence of fracture although all of these patients had suffered from grand mal attacks for at least five years.

Curare and Beta-erythroidin hydrochloride[1] have been used to relieve various spastic conditions (6). The effect is essentially peripheral, each drug acts apparently by paralysis of the myoneural junction thus interfering with the muscular response to stimulation of the motor nerve. It was accordingly decided to investigate the action of these substances upon the metrazol convulsion.

EXPERIMENTAL

Method.—The convulsant metrazol dosage was determined for each of seven dogs. This was followed the next day by the determination of the intravenous dose of curare requisite for paralysis of the extremities and trunk. The curare effect was then permitted to wear off. On a subsequent day the paralytic intravenous dose of curare was injected, the previously determined convulsant metrazol dose following immediately upon the development of paralysis. Finally, the same dose of metrazol was given separately a day or two later to check against development of tolerance for the drug. The same procedure was carried out with respect to the Beta-erythroidin hydrochloride.

Results and Discussion.—Table I shows dosage of 10% aqueous metrazol which produced optimal convulsions in the dogs used.

Attempts to curarize dogs 1 and 2 met with considerable difficulty. The curare produced frequent fecal vomiting, marked salivation, occasional penile erection, defecation and some clonic twitching of the extremities. In addition, at this stage in the experiment, the development of increased metrazol tolerance made results difficult to interpret. It was eventually found necessary to use 5 cc. and 10 cc. of metrazol on dogs 1 and 2, respectively, to get seizures that could be constantly repeated. Table II shows the disproportionate results obtained with these two dogs.

Table I.—Dosage Which Produced Optimal Convulsions

Dog	Sex	Weight	Dose Metrazol	Seizure: Duration of	Seizure: Intensity of	Remarks
1	M	33.5 Kg.	6 cc.	1 min. 12 sec.	++++[a]	
2	M	17.6 Kg.	4 cc.	1 min. 42 sec.	++++	
3	M	24.5 Kg.	6 cc.	1 min. 35 sec.	++++	
4	M	22.9 Kg.	5 cc.	2 min. 30 sec.	++++	
5	M	12.3 Kg.	3 cc.	2 min. 35 sec.	++++	
6	F	7.8 Kg.	2 cc.	1 min. 16 sec.	++++	
7	M	15.9 Kg.	4 cc.	1 min. 37 sec.	++++	Old dog required 1 hr. to recover

[a] Above indicates very severe seizure characterized by clonic and tonic convulsions, intense opisthotonos, loud clamping of the jaws, etc.

In view of the rather unsatisfactory reactions obtained with this drug, the curare was given up and the Beta-erythroidin hydrochloride was tried instead. Beta-erythroidin hydrochloride has been shown by Unna working at Merck Institute to be the more active optical isomer of a number of erythrina alkaloids previously investigated by Folkers and Koniuszy (7). This is a substance obtained from the seed of the genus Erythrina. It forms a clear colorless solution as opposed to the curare solution which contains a number of impurities. Its action upon the myoneural junction is due to a quaternary ammonium base which it has in common with curare. It has the additional ad-

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[1] Supplies of curare and beta-erythroidin hydrochloride were obtained through the courtesy and kind coöperation of the Merck Institute of Therapeutic Research of Rahway, New Jersey. Part of the Metrazol used was obtained through the courtesy of Bilhuber-Knoll Corporation of Orange, New Jersey.

vantage of being easily obtainable in continental United States. Although there has been reported a marked variability of the effective dose of this drug in humans (6) it was found that consistent paralysis was obtained in dogs with very little variation in dosage. Results are shown in Table III.

It will be seen from Table III that an optimal dosage of 4 mg. per Kg. weight in dogs was found. The desired effect of the drug in this dosage appeared

Table II.—Disporportionate Results with Dogs

Date	Dog	Dose Metrazol	Degree of Paralysis	Dose of Curare	Duration of Seizure	Intensity of Seizure
7/5/39	2	4.5 cc.	±	5 mg.	1 min. 50 sec.	++++
7/6/39	2	4.5 cc.	+	10 mg.	1 min.	++++
7/8/39	2	4.5 cc.	+++	15 mg.	2 min.	+++[a]
7/10/39	2	4.5 cc.	++++	25 mg.	2 min. 12 sec.	++[b]
7/13/39	2	4.5 cc.	++++	28 mg.	2 min. 25 sec.	+[c]
7/3/39	1	6.0 cc.	.....	8 mg.	None	.....
7/5/39	1	8.0 cc.	.....	None	None	.....
7/6/39	1	10.0 cc.	.....	10 mg.	1 min. 50 sec.	++++
7/7/39	1	10.0 cc.	+++	20 mg.	2 min. 40 sec.	++

[a] Opisthotonos absent. [b] Opisthotonos absent, clonic phase much weaker. [c] Brief seizure followed by very weak clonic twitches.

Table III.—Consistent Paralysis with Little Variation in Dosage

Date	Dog	Dose Er-HCl	Degree of Paralysis	Time of Drug Action	Duration of Paralysis	Remarks
7/24/39	2	100 mg. (6 mg./Kg.)	++++[a]	5 sec.	27 min.	Dog almost died; marked respiratory impairment
7/25/39	2	50 mg. (3 mg./Kg.)	No action	....	.....	No effect
7/26/39	2	78 mg. (4 mg./Kg.)	++++	15 sec.	16 min.	Completely limp
7/25/39	1	100 mg. (3 mg./Kg.)	++[b]	25 sec.	4 min.	Holds head up only
7/27/39	1	134 mg. (4 mg./Kg.)	++++	50 sec.	10 min.	Completely limp
8/31/39	3	96 mg. (4 mg./Kg.)	++++	35 sec.	5 min.	Completely limp
8/31/39	4	92 mg. (4 mg./Kg.)	++++	5 sec.	13 min.	Clonic twitches noted, a few
8/31/39	5	50 mg. (4 mg./Kg.)	++++	8 sec.	7 min.	Completely limp
8/31/39	6	32 mg. (4 mg./Kg.)	++++	15 sec.	4 min.	Completely limp
8/31/39	7	65 mg. (4 mg./Kg.)	++++	6 sec.	Death	Very old dog; cataract, resp. failure

[a] Animal completely paralyzed. [b] Animal unable to support weight but can still hold up head or move limbs and tail.

Table IV.—Results with Convulsant Doses of Metrazol

Date	Dog	Dose Er-HCl	Degree of Paralysis	Duration of Paralysis	Dose Metrazol	Seizure: Duration of	Seizure: Intensity of	Remarks
7/27/39	2	78 mg.	++++	16 min.	5 cc.	3 min. 20 sec.	++	Seizure reduced, clonic phase almost gone
7/27/39	1	134 mg.	++++	12 min.	10 cc.	1 min. 10 sec.	+	Very marked diminution
9/2/39	3	95 mg.	++++	18 min.	6 cc.	Not measured	+	No opisthonus, mild clonics, very mild seizure
9/1/39	4	95 mg.	++++	31 min.	5 cc.	1 min. 40 sec.	+	Only few clonics, very mild seizure
9/2/39	5	55 mg.	++++	11 min.	3 cc.	Not measured	+	Mild clonics only
9/1/39	6	32 mg.	++++	15 min.	2 cc.	30 sec.	+	Only 2 or 3 seconds with mild clonics

++ = Opisthotonos absent.
+ = Opisthotonos absent, clonic phase much weaker.

Table V.—Results with Metrazol Alone

Date	Dog	Dose of Metrazol	Seizure: Duration of	Seizure: Intensity of	Remarks
8/2/39	2	5 cc.	1 min. 45 sec.	++++	Severe opisthotonos, 12 sec. with 1 min. 35 sec. of severe clonic convulsions
8/2/39	1	10 cc.	2 min. 27 sec.	++++	Very severe opisthotonos and clonic convulsions
9/5/39	3	6 cc.	1 min. 30 sec.	++++	Opisthotonos and clonics very severe
9/5/39	4	5 cc.	1 min. 10 sec.	++++	Severe tonic seizure, opisthotonos, clonics, fecal vomiting, defecation
9/5/39	5	3 cc.	2 min. 12 sec.	++++	Severe tonics, opisthotonos severe clonics
9/5/39	6	2 cc.	1 min. 10 sec.	++++	Severe tonics, opisthotonos severe clonics

in from 5 to 50 seconds, the average being 19 seconds. The duration of paralysis is from 4 to 16 minutes, averaging 9 minutes and 10 seconds. The one death which occurred can probably be explained on the basis of the marked age of the animal. It will be noted that the duration of the paralysis is short enough to fall entirely within the post-metrazol confusion period. The dogs were next erythroidinized and then give previously determined convulsant doses of metrazol with results shown in Table IV:

The final recheck with metrazol alone to rule out the possible development of tolerance to the drug in the dosage previously used is given in Table V.

CONCLUSIONS

The results as indicated in Table IV show that a standard dosage of Beta-erythroidin hydrochloride about 4 mg. per Kg. was effective in markedly reducing the intensity of the metrazol seizure in dogs. The duration of the convulsion was variable but in the more prolonged instances included pauses between brief clonic seizures. In general the duration appeared to be decreased. Table V demonstrates the potency of the metrazol dosages used with the Beta-erythroidin hydrochloride thus proving that this drug has a paralytic action upon the animals that had received an otherwise convulsant dose of metrazol. No untoward side reactions such as fecal vomiting, defecation, etc., were observed.

Work is now in progress on the application of the method to schizophrenic patients.

SUMMARY

1. Paralytic doses of curare were given to two dogs on successive days without harmful effects. The curare, however, was found unsatisfactory because of difficulties in standardization and undesirable side-actions. The same procedure was followed with Beta-erythroidin hydrochloride, a substance having a curare-like action. The one death that occurred was in an aged dog who had reacted very poorly to a metrazol dose on the previous day and who died following Beta-erythroidin hydrochloride and metrazol.

2. A previously determined convulsant dose of metrazol was given to a series of seven dogs already paralyzed by Beta-erythroidin hydrochloride. The severity and, to some extent, the duration, of the metrazol convulsion were drastically reduced.

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Comparative Study of Vitamins and Constants of Free and Extracted Oils from Canned Sockeye Salmon*,†

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Canned salmon is recognized as an important staple of food and commerce in all parts of the world. The world's output during the last ten years has reached an annual average of over ten and a half million cases. Every year a portion of the pack is stored and the greater part sold prior to the arrival of the new pack. It is of immense interest to know if the product undergoes any changes during this period. This led to the inception of a study, which is in progress, of the effects of storage upon the oil in canned salmon. The present report, however, concerns an investigation as to the proper procedure of removing the oil from the salmon and a comparative study of certain properties of the free oil (that which drains from the salmon upon opening the can) and the extracted oil (obtained by ether extraction). Of the five species used for canning, sockeye

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