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Action of Aminoacetic Acid in Preventing Convulsions Produced by Metrazol.

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In searching for another anticonvulsant that will not at the same time produce a narcotic effect, we have studied the effect of previous administration of aminoacetic acid upon the convulsions usually following the injection of metrazol in the rabbit. For the purpose of study, the severity of the observed attacks was defined and classified numerically as follows: Only a hunching backward as type 1; twitching of ears and head as type 2; myoclonic jerking of the muscles of the head, neck and extremities, the animal remaining erect as type 3; a more severe myoclonic jerking of these parts, the animal remaining erect as type 4; and a complete clonic-tonic-clonic convulsion, the animal falling to the ground as type 5.

As control experiments we induced convulsions in 100 rabbits by means of intravenous injection of metrazol. The minimal convulsant dose was found to be 13.2 mg of metrazol given intravenously per kilo of body weight of rabbit. After administration

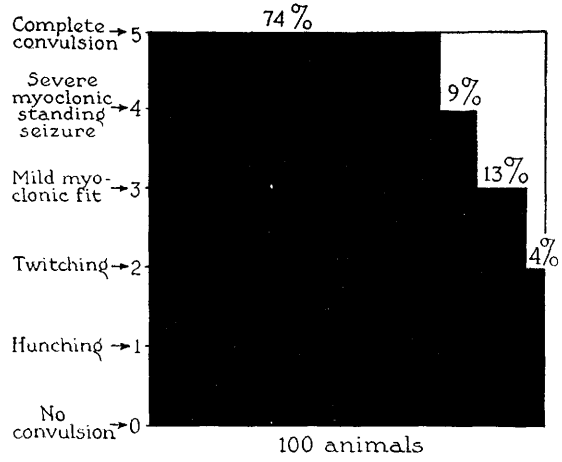

FIG. 1.

Percent distribution of degree of severity of convulsions in 100 animals which received an intravenous injection of 13.2 mg metrazol per kilo.

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of this dose, there ensued 74 (74%) complete convulsions (type 5), severe myoclonic standing seizures (type 4) in 9 (9%), 13 (13%) mild myoclonic standing seizures (type 3) and in 4 (4%) only twitchings (type 2). Fig. 1.

In 43 rabbits, 220 to 880 mg of aminoacetic acid per kilo weight were injected intravenously 5 minutes before the intravenous administration of a minimal convulsant dose of metrazol. Some protective action against convulsions produced by metrazol was found. In this group the injection of metrazol produced 53.5% of complete convulsions (type 5), 16.2% of mild myoclonic seizures (type 3), 11.6% of only twitches (type 2), 2.3% of hunching (type 1), and in 16.2% no motor disturbance was observed. Fig. 2. However, a great variability was seen in the action of aminoacetic acid in different groups of animals. Although aminoacetic acid prevented attacks in a significant number of instances and diminished the severity of attacks when they occurred, its anticonvulsant property is not as marked as other agents studied by us, such as pyridine, nicotinamide, some other pyridine derivatives and phenylcinchoninic acid.[1]

When metrazol was administered subcutaneously, the convulsion appeared only after a certain length of time sufficient for the absorption of a convulsive dose; in these cases previous injection of aminoacetic acid appears to be more effective in preventing convulsions than in these instances where metrazol is given intravenously.

The responses of rabbits to the subcutaneous injection of convulsive doses of metrazol shows a greater variation than those

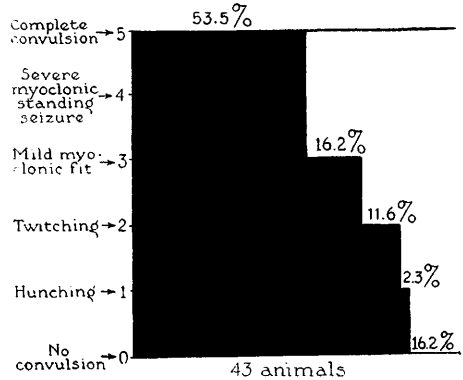

FIG. 2.

Percent distribution of degree of severity of convulsions in 43 animals which received 220 to 880 mg per kilo of aminoacetic acid intravenously 5 min. previous to the injection of a minimal convulsant dose of metrazol.

[1] Pollock, L. J., Finkelman, I., and Tigay, E., to be published.

observed after intravenous injection of the same agent. A number of seconds after the intravenous administration of a minimal convulsant dose of metrazol there usually appears a single clonic-tonic-clonic convulsion. However, the subcutaneous injection of a convulsant dose of metrazol (36.5 to 55 mg per kilo of body weight) is followed by phenomena of a different nature.

Here, in about 60 seconds after injection, the animal becomes restless, raises the ears, hunches backward, sits on the hind legs, shakes the head and appears frightened. During this period the respirations become rapid and deep. These are followed by a period in which the animal shivers, becomes rigid and at times ataxic. Twitching and myoclonic jerking appear at different time intervals after injection; in some these occur as early as 2 minutes after injection; in others up to 19 minutes. In some a complete convulsion follows the twitching and myoclonic jerking; in others a seizure of lesser intensity may ensue and these milder seizures may be repeated at intervals of from 2 to 31 minutes. When the first seizure is complete it may appear as early as 2 minutes after injection and as late as 27 minutes afterward. Usually these severe seizures are repeated at intervals of an hour or more, and in a few instances these seizures occurred one after another as in a status.

Schoen,[2] Camp,[3] and Lendle[4] stated that the convulsive dose of metrazol administered subcutaneously is 50 mg per kilo of body weight. Hildebrandt and Voss[5] and Schubel and Gehlen[6] place this dosage at 40 mg and Hildebrandt and Mugge[7] concluded after a large number of experiments that 35 mg is sufficient.

In our experiments with a group of 28 rabbits used as a control (Fig. 3A) the subcutaneous injection of from 36.5 to 55 mg of metrazol per kilo of body weight produced, after an interval of varying length, a complete convulsion (type 5), in 39.3%, a severe standing myoclonic seizure (type 4) in 7.1%, a mild standing myoclonic seizure (type 3) in 4.3%, twitches only (type 2) in 17.8%. No motor manifestations were seen in 21.4%.

Five minutes before the subcutaneous administration of a convulsant dose of metrazol, 25 animals were given aminoacetic acid intravenously in doses of from 330 to 440 mg per kilo of body weight. In these, there resulted (Fig. 3B) a complete convulsion

[2] Schoen, R., *Arch. f. exp. Path. u. Pharm.*, 1926, **113**, 257.

[3] Camp, W. J. R., *J. Pharm. and Exp. Therap.*, 1928, **33**, 81.

[4] Lendle, L., *Arch. f. exp. Path. u. Pharm.*, 1936, **181**, 408.

[5] Hildebrandt, F., and Voss, J., *Munch. Med. Wschr.*, 1926, **73**, 862.

[6] Schubel, K., and Gehlen, W., *Arch. f. exp. Path. u. Pharm.*, 1928, **133**, 295.

[7] Hildebrandt, F., and Mugge, H., *Schwerz Narkose—Anaesthesie*, 1936, **9**, 25.

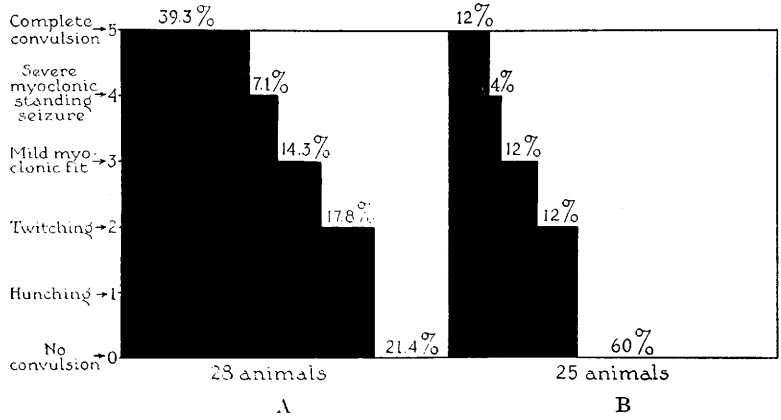

FIG. 3A.

Percent distribution of degree of severity of convulsions in 28 animals which received a subcutaneous injection of metrazol, 36.5 to 55 mg per kilo.

FIG. 3B.

Percent distribution of degree of severity of convulsions in 25 animals which received 330 to 440 mg of aminoacetic acid per kilo 5 min. before the subcutaneous injection of 36.5 to 55 mg per kilo of metrazol.

(type 5) in 12%, a severe standing myoclonic seizure (type 4) in 4%, a mild standing myoclonic seizure (type 3) in 12%. In 12% only twitches (type 2) were observed and 60% showed no motor manifestations.

Most significant is the observation that in the group treated with aminoacetic acid 12% had complete convulsions induced by metrazol, while in the group not so treated, 39.3% had complete convulsions. Further, in the treated group 60% showed no motor manifestations, while in the untreated group this ratio was 21.4%.

We have not been able to determine the reason for this anticonvulsant property. Aminoacetic acid as well as glucuronic acid contributes significantly to the detoxication of many substances by conjugation as for example Borneol. It may be possible that aminoacetic acid acts as a detoxicant when metrazol is injected subcutaneously and thereby diminishes the severity of and at times prevents the convulsions often seen after such injections.

Conclusions. Aminoacetic acid affords some protection against convulsions produced by the intravenous injection of metrazol. It is insignificant as compared to other substances, as pyridine, nicotinamide and phenylcinchoninic acid. Aminoacetic acid affords a great deal of protection against convulsions produced by the subcutaneous injection of metrazol.