# A STUDY ON THE COMPARATIVE DEPRESSANT EFFECTS OF HYPNOTIC DRUGS (MEDOMIN, SECONAL AND PHENOBARBITAL) ON HEART MUSCLE AND CARDIAC VAGUS NERVE *†

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THE fact that barbituric acid derivatives depress structures other than the central nervous system has been known for some time. In 1925 de Waele (1) first demonstrated that somnifene affected the peripheral part of the inhibitory mechanism of the heart. Four years later Lieb and Mulinos (2) reported not only a depression of the cardiac vagus nerve following the administration of amytal but an actual paralysis of the nerve which lasted as long as two hours. Their results have been confirmed by Garry (3), Shafer, Underwood and Gaynor (4), Koppanyi, Linegar and Dille (5), and Swanson and Shonle (6). Koppanyi and his associates noted similar changes with the use of pentobarbital sodium, barbital sodium and phenobarbital sodium.

Kennedy (7) studied the effect of evipan upon the irritability of the cardiac vagus nerves and reported negative results. His observations were supported by those of Storm (8) who experimented with monkeys. According to Gruber and his associates (9), all of the barbiturates which they studied (evipal sodium, pentobarbital sodium, ortal sodium and amytal sodium) depressed the cardiac vagus nerves in cats, dogs and monkeys. The thiobarbiturates (pentothal sodium, sodium thioethamyl and sodium thiopentobarbital) in some instances, however, increased the responsiveness of the heart to vagus nerve stimulation.

Thirteen different barbiturates were studied by Gruber, Haury and Gruber (10). They found the actions of all of these on the cardiac vagus nerve to be similar qualitatively and different quantitatively. Their observations were confirmed by Gruber and Keyser (11) whose studies of three additional barbiturates produced similar findings. Gruber and his associates found the point of action of the barbiturates, in producing a depressive effect of cardiac vagus nerves, to be on the

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endings of the postganglionic nerve fibers (12). Whether the preganglionic fibers as well as the ganglions were paralyzed could not be determined.

In addition to depressing the cardiac vagus nerves the barbiturates also depress cardiac muscle (13), whereas the thiobarbiturates appear to make the heart muscle more irritable (14).

In a previous communication we were able to show that cycloheptenylethyl barbituric acid injected intravenously in dogs caused some acceleration but no noticeable change in the force of the contractions of the heart (15).

This investigation was carried out on hearts of frogs of the species Rana pipiens to determine whether cycloheptenylethyl barbiturate (medomin) is free of cardiac effects and upon terrapin (Chrysemys marginata) to determine whether it has a depressant action on the cardiac vagus nerve similar to that produced by all other barbiturates (9, 10, 11, 12, 16). The method used with the frogs was the same as that previously described by one of us (13). The concentrations of the barbiturate used were M/5,000, M/2,500, M/2,000, M/1,000 and M/500. In order to compare the activity of this barbiturate with that of other barbiturates, similar molecular concentrations of seconal sodium and phenobarbital sodium were studied on the same hearts.

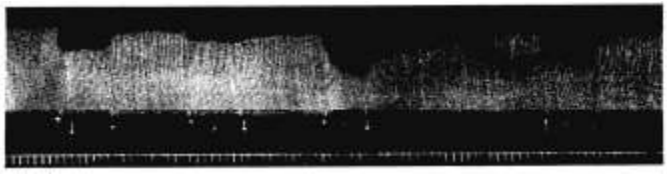

FIG. 1. Excised frog heart. The top curve shows cardiac contractions, the up stroke being systole; the bottom curve shows time in intervals of twenty seconds. The drugs were applied between the arrows ↑↓, at 1, cycloheptenylethyl barbiturate, at 2, phenobarbital sodium and at 3, seconal sodium. In each instance the concentration was 1/2,000 molar.

The method of preparation of the terrapin and the apparatus used in this research were similar to those previously described (10). The sodium salt of cycloheptenylethyl barbiturate (medomin) was freshly prepared and dissolved in Ringer's solution. The molecular concentrations varied from M/2,000 to M/100. The action of this drug was compared with that of similar molecular concentrations of seconal sodium and phenobarbital sodium.

Fifty-six experiments were made with cycloheptenylethyl barbituric acid, 44 with seconal sodium, and 46 with phenobarbital sodium on excised perfused frog hearts. Cycloheptenylethyl barbiturate, like other barbiturates, when added to the perfusate caused a decrease in the height of the contractions of the perfused isolated frog heart. In

TABLE 1

EFFECTS OF SECONAL SODIUM, CYCLOHEPTENYLETHYL BARBITURATE AND PHENOBARBITAL SODIUM UPON THE TERRAPIN CARDIAC VAGUS NERVE

| Barbiturate | No. of Experiments | M/2,000 | | | | M/1,000 | | | | M/500 | | | | M/250 | | | | M/200 | | | | M/100 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | − | −+ | +− | + | − | −+ | +− | + | − | −+ | +− | + | −+ | +− | + | | −+ | +− | + | | −+ | +− |
| Seconal sodium | 55 | 1 | 2 | 5 | 1 | | 4 | 10 | 5 | | | 4 | 6 | | 1 | 5 | | | 1 | | | | |
| Cycloheptenylethyl barbiturate | 25 | | | | | 1 | 5 | 2 | | 1 | 2 | 9 | | 1 | 2 | | | | 2 | | | | |
| Phenobarbital sodium | 51 | | | | | 3 | 4 | | | 4 | 12 | | | 8 | 5 | 4 | | 3 | | 1 | | 2 | 5 |

− Complete cessation of heart beat upon vagus stimulation; −+ vagus nerve depressed less than 50 per cent; +− vagus nerve depressed more than 50 per cent; complete block of cardiac vagus effect upon the heart.

many experiments it also decreased the rate of heart beat. In figure 1 may be seen the comparative actions of this barbiturate at 1, phenobarbital sodium at 2 and seconal sodium at 3. In each instance an M/2,000 solution was used. It may be noted that phenobarbital caused the least and seconal sodium the greatest changes in the height and rate of contraction of the heart. Our results indicate that approximately twice the molecular concentration of phenobarbital sodium is required to produce the same depression as is produced by cycloheptenylethyl barbiturate and that twice the concentration of this barbiturate is required to produce the same degree of depression as is produced by seconal sodium.

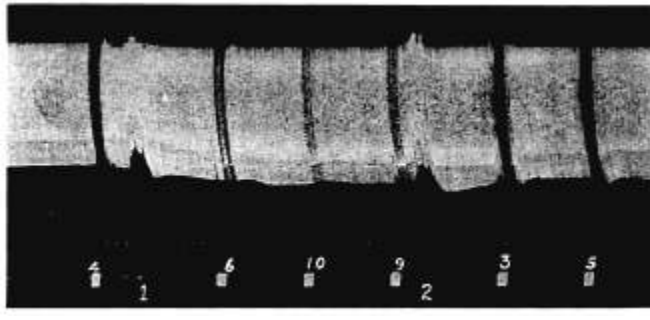


FIG. 2. Intact terrapin heart. The top curve indicates the contractions of the ventricle; the up stroke of the lever is systolic and down stroke diastolic. The bottom line indicates the time and duration of stimulation of the right cardiac vagus nerve and the points of application and removal of the drug. The middle line shows the time in intervals of twenty seconds. Cycloheptenylethyl barbiturate was applied to the heart between 1 and 2. At 4 the right vagus nerve was stimulated before the application of the drug and at 6, 10 and 9 during the time the drug was applied. At 2 the heart was washed with Ringer's solution and the vagus nerve was stimulated again at 3 and 5.

In studying the action of cycloheptenylethyl barbiturate on the cardiac vagus nerve in the turtle, 25, 55, and 51 experiments were performed with cycloheptenylethyl barbiturate, seconal sodium and phenobarbital sodium, respectively. As in the experiments on frog hearts, the first barbiturate appears to be approximately twice as depressant as phenobarbital sodium, whereas seconal sodium appears to be twice as active as cycloheptenylethyl barbiturate (table 1).

The effect of M/250 cycloheptenylethyl barbiturate on the cardiac vagus nerve is shown in figure 2. In this experiment the heart was exposed to the drug from 1 to 2 as seen in the record. During this exposure, instead of complete cessation of the heart beat being produced during vagal nerve stimulation as at 4 in the control, there were 6, 10 and 9 contractions of the heart during vagal stimulation as seen at 6, 10 and 9 in the record. Six minutes after the drug was removed the heart again responded to electrical excitation of the right vagus nerve (at 5) by complete cessation of heart beat.

## CONCLUSIONS

Cycloheptenylethyl barbiturate (medomin), like other barbiturates, depresses both rate and height of contraction of the excised, perfused heart of the frog. These effects are less than those produced by seconal sodium but greater than those produced by phenobarbital sodium.

When this barbiturate is applied to the terrapin heart in adequate concentration, it depresses the cardiac vagal inhibitory effects of vagal stimulation on the heart. This effect is less than that produced by seconal sodium in equal molecular concentration but greater than that produced by phenobarbital sodium.

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