# THE EFFECTS OF ALIPHATIC SYMPATHOMIMETIC AMINES ON CARDIAC AUTOMATIC TISSUE IN DOGS UNDER CYCLOPROPANE * †

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It is now well known that cyclopropane anesthesia in some way sensitizes ventricular automatic tissue to certain of the cyclic sympathomimetic amines, particularly those having two hydroxyl groups on the ring nucleus (1, 2). It has seemed desirable to study a series of the straight chain amines not only to learn their effects under cyclopropane anesthesia but to find whether there are any marked differences in their stimulating properties.

Since it was intended to compare the effects of the straight chain amines ‡ with the effect of the standard test dose of epinephrine, which is 0.01 mg. per kilogram weight of dog, it was decided to give, first, a dose of amine that would be approximately equal in pressor activity to such a dose of epinephrine. With the exception of 2-methylamino-6-hydroxy-6-methyl-heptane (aranthol) the pressor equivalents could be calculated from the data of Chen based on his experiments with pithed dogs (3, 4). The epinephrine pressor equivalent of aranthol has not been determined but a dose of 10 mg. per kilogram was selected as the maximum for the present study since it was believed from the work of Jackson (5) that this dosage would give maximum pharmacologic results. Of the remaining amines, only 2-methylamino-1-cyclopentyl-propane was given in maximum dosage exceeding the pressor equivalent of 0.01 mg. per kilogram of epinephrine. Both aranthol and 2-amino-heptane (tuamine) were also given in several dosages lower than those expected to give a maximum response. 3-Amino-heptane in a dosage equivalent in pressor activity to the standard dose of epinephrine was found to be so toxic that it was accordingly reduced to one-fourth this amount. 2-Methylamino-1-cyclopentyl-propane and aranthol were supplied in the form of the hydrochloride salt. The remaining amines were in the form of the sulfate salt.

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Each dose of drug was diluted to 5 cc. with distilled water and injected intravenously at a constant rate within a period of fifty seconds. Electrocardiographic records taken at frequent intervals were used to determine cardiac rates and irregularities.

Three drugs, namely, aranthol, tuamine, and 2-methylamino-1-cyclopentyl-propane which are comparatively potent pressor amines, were selected for more detailed study, with especial emphasis on the first two. The cardiac irregularities produced by various dosages of these three amines in dogs under cyclopropane are summarized in table 1.

As judged by the frequency of ventricular tachycardia, both aranthol and tuamine in the maximum dosages used gave evidence of ventricular stimulation. A dose of 10 mg. per kilogram of aranthol stimulates the lower centers of cardiac automaticity to a lesser degree than does our standard test dose of epinephrine, and a dose of 3 mg. per kilogram of tuamine is somewhat less effective than aranthol in stimu-

TABLE 1

PRODUCTION OF CARDIAC IRREGULARITIES IN DOGS UNDER CYCLOPROPANE BY VARIOUS DOSAGES OF: 2-METHYLAMINO-1-CYCLOPENTYL-PROPANE, 2-AMINO-HEPTANE (TUAMINE), AND 2-METHYLAMINO-6-HYDROXY-6-METHYL-HEPTANE (ARANTHOL)

| Amine | | | | After Amine | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Number of Dogs Showing: | | | | |
| Stem Nucleus | Side Chain | Dose, mg./Kg. | Number of Dogs Given Amine | Average Maximum S-A Rate | S-A Tachycardia | No Irregularities but S-A Tachycardia | Atrio-ventricular Tachycardia | Ventricular Extrasystoles | Ventricular Tachycardia |
| Propane | 2-methylamino- | 2* | 6 | 241 | 6 | 6 | | | |
| | 1-cyclopentyl- | 3 | 3 | 231 | 3 | 2 | | 1 | |
| Heptane | 2-amino- (tuamine) | 1 | 9 | 242 | 9 | 6 | 1 | 3 | 1 |
| | | 1.5 | 6 | 260 | 6 | 2 | 1 | 4 | 1 |
| | | 3* | 48 | 268 | 44 | 17 | 6 | 24 | 13† |
| | 2-methylamino-6-hydroxy-6-methyl- (aranthol) | 1.25 | 3 | 158 | 1 | | | | |
| | | 2.5 | 8 | 206 | 7 | 4 | | 4 | |
| | | 5 | 21 | 218 | 19 | 8 | 3 | 10 | 5 |
| | | 10 | 36 | 270 | 36 | 5 | 6 | 29 | 26 |

* Dose of amine approximately equivalent in pressor activity to 0.01 mg. per kilogram of epinephrine as tested on pithed dogs (Chen).

† Ventricular fibrillation followed ventricular tachycardia in one dog.

lating ventricular tissue. Ventricular fibrillation never occurred following this dose of aranthol but it occurred once following the 3 mg. per kilogram dose of tuamine. In no case did ventricular irregularities of any kind appear for more than five minutes beyond the completion of the injection of the amines. There was no evidence of ventricular stimulation by 2-methylamino-1-cyclopentyl-propane in dosages equivalent in pressor activity to 0.01 mg. per kilogram of epinephrine and only occasional scattered ventricular extrasystoles resulted when the dosage was increased by 50 per cent. Regardless of whether or not ventricular irregularities appeared, a marked S-A tachycardia, averaging 254 beats per minute and lasting for twenty-five or more minutes, followed the injection of these three amines.

As the dosages of tuamine and aranthol were reduced, the evidence of ventricular stimulation became less apparent. When the dose of tuamine was reduced to 1 mg. per kilogram, 6 of 9 dogs showed no irregularities other than S-A tachycardia. The dosage of aranthol was reduced to 2.5 mg. per kilogram, before ventricular tachycardia failed to appear. At these low dosages, however, neither drug could be considered very potent in its pressor activity. In three experiments it was found that the blood pressure rise from 1 mg. per kilogram of tuamine averaged only 25 mm. of mercury. The 2.5 mg. per kilogram dose of aranthol resulted in an average blood pressure rise of 39 mm. of mercury in three experiments. Further experiments indicated that a good pressor response usually could not be expected with a dosage less than 1.5 mg. per kilogram of tuamine or 5 mg. per kilogram of aranthol, which is one-half the maximum dosage of these drugs used in these experiments. Although there was much less evidence of ventricular stimulation by these dosages than that produced by the maximum dosage used, still only 2 of 6 dogs after administration of 1.5 mg. per kilogram of tuamine and 8 of 21 dogs after 5 mg. per kilogram of aranthol were entirely free of ventricular irregularities.

Experiments were carried out to determine whether the cardiac irregularities produced by tuamine and aranthol depend upon the sensitization of the ventricle by cyclopropane. Five dogs that had previously shown ventricular tachycardia under cyclopropane when tuamine was injected were given the same dose at weekly intervals while unanesthetized, under ether, and under nembutal. Five dogs known to show ventricular tachycardia under cyclopropane when given a dose of 10 mg. per kilogram of aranthol were tested under the same conditions. The results of these experiments appear in table 2 and parallel those known to occur when epinephrine is injected in dogs under similar conditions. With the exception of Dog 1, both amines produce reflex vagal slowing, nodal rhythm, and escape phenomena in the unanesthetized dog. Dog 1 was the only dog out of a total of 18 that have been given tuamine in the unanesthetized state that has shown ventricular tachycardia. Under ether there was almost no evidence of

ventricular stimulation with either tuamine or aranthol. While ventricular tachycardia occurred only once under nembutal, and that when tuamine was injected, there was evidence of increased sensitivity of the ventricle under this anesthetic as shown by the occurrence of numerous ventricular extrasystoles. These results make it seem probable that cyclopropane in some manner sensitizes the heart to tuamine and aranthol as it does to epinephrine.

TABLE 2

THE EFFECTS OF TUAMINE AND ARANTHOL ON VENTRICULAR IRRITABILITY UNDER CYCLOPROPANE, ETHER, NEMBUTAL AND IN UNANESTHETIZED CONTROLS

| Amine | Dog No. | Unanesthetized Control | Cyclopropane | Nembutal | Ether |
|---|---|---|---|---|---|
| 3 mg./Kg. Tuamine | 1 | VT | VT | SAT | SAT |
| | 2 | SAT | VT | AVT | VExs |
| | 3 | A-V Block | VT | VT | AVT |
| | 4 | AVB | VT | SAB | AVT |
| | 5 | AVB | VT | VExs | AVT |
| 10 mg./Kg. Aranthol | 1 | VExs | VT | SAT | SAT |
| | 6 | AVB | VT | A-V Block | SAT |
| | 7 | AVB | VT | VExs | SAT |
| | 8 | VB | VT | VExs | SAT |
| | 9 | AVB | VT | A-V Block | SAT |

SAB—SA bradycardia
AVB—AV bradycardia
VB—Ventricular bradycardia
AVT—AV tachycardia
VT—Ventricular tachycardia
VExs—Ventricular extrasystoles.

Each of 14 other pressor amines prepared by Chen and his associates was given to dogs under cyclopropane. The cardiac effects are summarized in table 3. Nine of these resembled the action of tuamine and aranthol in that they produced marked S-A tachycardia and gave evidence of ventricular stimulation. These drugs were: 2-amino-1-cyclopentyl-ethane, 1-amino-3-methyl-butane, 2-amino-4-methyl-hexane, 2-amino-5-methyl-hexane, 2-amino-6-methyl-heptane, 2-amino-6-methyl-heptene-5, 1-amino-3,4-dimethyl-pentane, 2-amino-5-methyl-heptane, and 1-amino-3-methyl-heptane. Three more of these amines, namely: 2-amino-1-cyclohexyl-propane, 2-amino-5-methyl-hexene-5, and 2-amino-3, 6-dimethyl-heptane, resembled in their action 2-methylamino-1-cyclo-

TABLE 3

PRODUCTION OF CARDIAC IRREGULARITIES IN DOGS UNDER CYCLOPROPANE BY ALIPHATIC PRESSOR AMINES IN DOSAGES APPROXIMATELY EQUIVALENT IN PRESSOR ACTIVITY TO 0.01 MG. PER KILOGRAM OF EPINEPHRINE*

| Amine | | Dose mg./Kg. | Number of Dogs Given Amine | Cardiac Effects |
|---|---|---|---|---|
| Stem Nucleus | Side Chain | | | |
| Heptane | 3-amino- | 18** | 3 | No ventricular stimulation. Moderate S-A stimulation. (Maximum acceleration to average rate of 177/min.) |
| Octane | 2-amino- | 20† | 5 | |
| Propane | 2-amino-1-cyclohexyl- | 6 | 3 | No ventricular stimulation. Marked S-A stimulation. (Maximum acceleration to average rate of 222/ min.) |
| Hexene-5 | 2-amino-5-methyl- | 20 | 3 | |
| Heptane | 2-amino-3, 6-dimethyl- | 11 | 8 | |
| Ethane | 2-amino-1-cyclopentyl- | 8 | 3 | Ventricular stimulation. (Ventricular extrasystoles and ventricular tachycardia). Marked S-A stimulation. (Maximum acceleration to average rate of 240/min.) |
| Butane | 1-amino-3-methyl- | 40 | 3 | |
| Pentane | 1-amino-3, 4-dimethyl- | 6 | 3 | |
| Hexane | 2-amino-4-methyl- | 3 | 11 | |
| | 2-amino-5-methyl- | 6 | 3 | |
| Heptane | 1-amino-3-methyl- | 8 | 3 | |
| | 2-amino-5-methyl- | 10 | 3 | |
| | 2-amino-6-methyl- | 4 | 3 | |
| Heptene-5 | 2-amino-6-methyl- | 25 | 3 | |

* Calculated from data of Chen (as tested on pithed dogs).

** ¼ pressor equivalent to 0.01 mg. per kilogram of epinephrine. Toxic drug; 1 out of 3 dogs died.

† Depressor drug under cyclopropane at this dosage.

pentyl-propane in that they produced a marked S-A tachycardia but gave no evidence of ventricular stimulation.

Only two of the drugs in this group of 14 seemed to differ in action from the three amines that were more thoroughly studied. These drugs which were: 3-amino-heptane and 2-amino-octane, produced a moderate degree of cardiac acceleration and gave no evidence of ventricular stimulation. 3-Amino-heptane, however, proved to be too toxic in dosages that would produce good pressor response. Even when the dose was reduced to one-fourth the calculated equivalent of epinephrine, one of 3 dogs died within ten minutes after the injection

of the drug. The maximum dosage used by Chen, which was approximately 4 mg. per kilogram, had only weakly pressor action under cyclopropane. 2-Amino-octane under cyclopropane proved to be a depressor drug in the dosage employed.

## SUMMARY

Regardless of a rise in blood pressure the sympathomimetic amines of the aliphatic series are likely to cause a marked S-A tachycardia. The exceptions were the toxic 3-amino-heptane and 2-amino-octane which is a depressor drug under cyclopropane.

In dosages equivalent in pressor activity to 0.01 mg. per kilogram epinephrine, six of the amines did not produce ventricular irregularities under cyclopropane. These were: 3-amino-heptane, 2-amino-octane, 2-amino-1-cyclohexyl-propane, 2-methylamino-1-cyclopentyl-propane, 2-amino-5-methyl-hexene-5, and 2-amino-3, 6-dimethyl-heptane.

In dosages equivalent in pressor activity to 0.01 mg. per kilogram of epinephrine, eleven of the amines caused varying degrees of ventricular stimulation as evidenced by ventricular extrasystoles and ventricular tachycardia. These were: 2-amino-1-cyclopentyl-ethane, 1-amino-3-methyl-butane, 1-amino-3,4-dimethyl-pentane, 2-amino-4-methyl-hexane, 2-amino-5-methyl-hexane, 1-amino-3-methyl-heptane, 2-amino-heptane, 2-amino-5-methyl-heptane, 2-amino-6-methyl-heptane, 2-methylamino-6-hydroxy-6-methyl-heptane, and 2-amino-6-methyl-heptene-5.

Dogs showing ventricular tachycardia under cyclopropane when either tuamine or aranthol was given showed very few ventricular irregularities when given the same drug while unanesthetized or etherized. Both these amines produced more ventricular irregularities in dogs given nembutal than in those unanesthetized or given ether, but not nearly as many irregularities as in dogs under cyclopropane.

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