Effect of Toxic Doses of 4,4'-Diamidino-Stilbene (Stilbamidine) on the Electrocardiogram in Mice. (17630)

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Diamidine compounds upon rapid intravenous administration produce severe cardiovascular symptoms. Studies on simultaneous multiple electrocardiographic and pulse tracing in patients with multiple myeloma injected with 4,4'-diamidino-stilbene (stilbamidine)* revealed changes indicative of possible myocardial or peripheral origin associated with tachycardia and hypotension(1). To investigate the cardiac effects of the drug in the toxic range, stilbamidine was given parenterally to mice and the effects were observed in three simultaneous electrocardiograms.

Method. Twelve experiments were conducted using Strain A mice, 5 to 10 months old, and approximately 25 g in weight. Standard leads I, II and III were taken, employing needle electrodes inserted subcutaneously into the appropriate extremities of restrained but unanesthetized mice. The impulses were amplified and applied to mirror-type galvanometers† in a recording oscillograph. The tracings were made simultaneously, with the recording paper moving at 8 inches per second.

The reproducibility of electrocardiograms was determined in 16 mice by taking frequent records over a period of 6 weeks. After at least 2 control records had been taken, stilbamidine dissolved in sterile distilled water was injected intraperitoneally. Records were taken continuously during the first 5 minutes after injection and at progressively longer intervals thereafter. The materials were injected intraperitoneally in all studies.

Results. Intraperitoneal injections of 2 mg (80 mg/kg) or less of stilbamidine did not

TABLE I.
Effect of Intraperitoneal Stilbamidine in Mice.

Mouse No.	Stilbamidine		Effect	
	mg	mg/kg	On electrocardiogram	Mortality
1	1.2	48	No significant change.	Survived.
2	2.5	100	Slight transient sino-auricular depression.	"
3	2.5	100	Shift in auricular pacemaker.	"
4	4	160	Progressive reverse Wenkebach; shifting pacemaker; A-V nodal rhythm. Rate slowed to 350/min. in 20 min.	Died overnight.
5	4	160	Complete A-V dissociation with I-V conduction defect.	Respirations ceased, 5.5 min.
6	5	200	Shifting pacemaker, progressive A-V block, to final bundle branch block and complete A-V dissociation.	" " 4 "
7	5	200	Progressive A-V, S-A, and I-V block to complete A-V dissociation.	" " 4.5 "
8	5	200	Flattening of T wave with slowing of rate to 480/min. within 30 min.	Died within 24 hrs.
9	5	200	Flat T waves, rate slowed to 600/min. in 25 min.	" " " "
10	5	200	Abrupt slowing of rate at 10.5 min.; 6:1 A-V block at 16 min.	Died, 35 min.
11	10	400	Progressive S-A, A-V, and I-V block.	Respirations ceased, 4 min.
12	20	800	" " " " " "	" " 3.5 "

* Furnished by Merck and Co., Inc., Rahway, N.J.

1. Bierman, H. R., and Sokolow, M., *J. Nat. Cancer Inst.*, 1949, v10, 279.

† No. 7-120-CEC, Pasadena, Calif. Frequency response 0-500 cps.

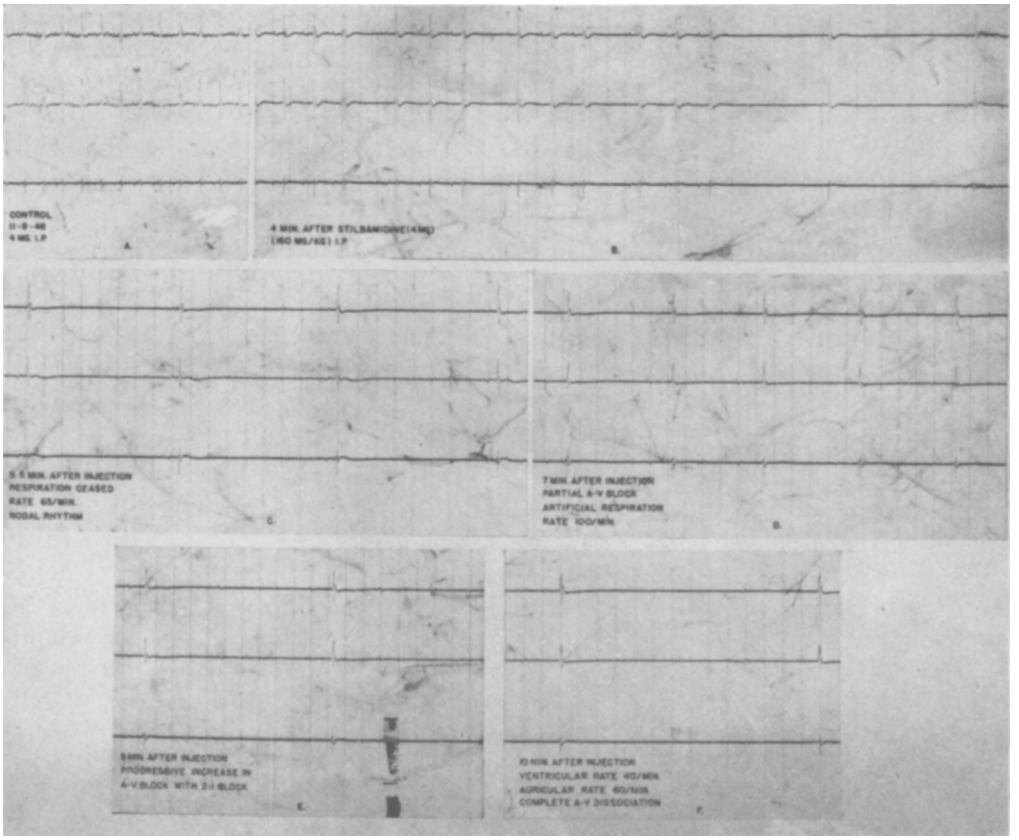

FIG. 1.

Standard leads I, II, and III recorded simultaneously on Strain A mouse following 4 mg intraperitoneally of stilbamidine (160 mg/kg of mouse). Note progressive slowing of rate and development of A-V block. Ventricular complex contour is maintained.

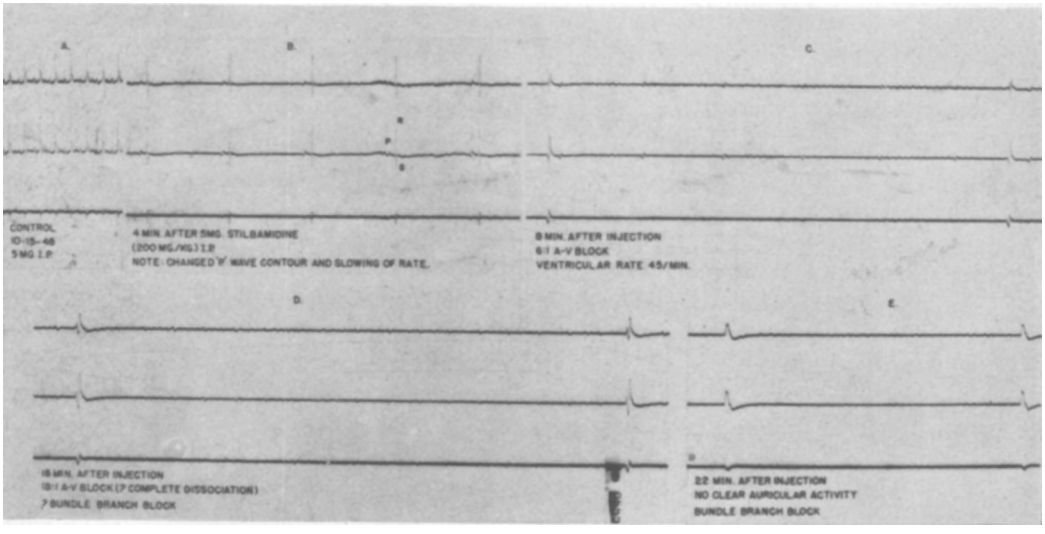

FIG. 2.

Simultaneous electrocardiographic leads I, II, and III on Strain A mouse. Note progressive development of A-V block and change in auricular and ventricular complex contour.

produce any toxic signs or electrocardiographic changes. Transient and minor electrocardiographic changes were observed with doses of 2.5 mg (100 mg/kg). Doses above 5 mg (200 mg/kg) were lethal. Striking electrocardiographic abnormalities followed by cessation of respiratory and cardiac activity occurred with 4 to 20 mg (160 to 800 mg/kg) in most animals (Table I). Respirations usually stopped within 4 to 6.5 minutes, and cardiac action usually ceased approximately 18 minutes after intraperitoneal injection with higher doses. Artificial respiration was not effective when respirations had ceased.

The most striking electrocardiographic findings following the intraperitoneal administration of stilbamidine were progressive and varying degrees of sino-auricular, auriculo-ventricular, and intraventricular block, occurring in that order. During the development of sino-auricular block, the cardiac rates slowed from the usual control rate of 600 per minute to as low as 10 per minute (Fig. 1).

Varying degrees of auriculo-ventricular block from 10 to 1 to complete auriculo-ventricular dissociation were noted (Fig. 2). After respirations had ceased and the cardiac rate had slowed materially, intraventricular and possibly bundle-branch block occurred. There was no discordant relationship noted between any of the 3 electrocardiographic leads following lethal doses of stilbamidine. The electrocardiographic changes preceded respiratory cessation by 2 to more than 30 minutes. Anoxia following the respiratory cessation may contribute to the late electrocardiographic changes.

Conclusions. 1. Stilbamidine administered intraperitoneally to mice in doses of 4 to 20 mg (160 to 800 mg/kg) caused cessation of respirations in 4 to 6.5 minutes, accompanied by progressive and varying degrees of sino-auricular, auriculo-ventricular and intraventricular block eventuating in death. No significant ST-T changes occurred.

2. The constancy and reproducibility of the electrocardiogram in the normal mouse indicates that the effect of drugs upon the electrocardiogram may profitably be studied in this animal.

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Relationships of Availability of Oxygen to Physical Fitness in Patients with Cardio-respiratory Diseases.* (17631)

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The concept of physical fitness in either normal subjects or patients with various cardio-respiratory diseases refers to the integrated capacity of the heart, lungs, blood and regulatory mechanisms to meet exertional demands. Fitness is measured by the least variable characteristics of the cardio-respiratory responses to exercise(1). The latter is standardized by walking on a motor-driven treadmill at a fixed velocity; hence the rate of energy expenditure is proportional to the body weight(2). Although this work load is only moderate for normal subjects, it may be

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