

Direct negative chronotropic and inotropic effects of curare on isolated and perfused frog's heart

Abdel J. Fuenmayor; Brenda Valero; María A. Farías; Rambal Fuenmayor; Rosalba Caruso; Grisel Rada; Mary Quijada; Abdel M. Fuenmayor.

Department of Physiology and Cardiovascular Research Center of the University of The Andes. Mérida. Venezuela.

Address for reprints: Abdel J. Fuenmayor. Apartado Postal # 154, Mérida, 5101, Venezuela.

Abstract

It has been stated that curare has no direct effect upon the heart because the cardiac muscle is deprived of nicotine receptors. While performing an experimental work, we noticed that when high doses of curare were administered to frogs, a change in cardiac activity occurred. In order to elucidate whether the cardiac effects of curare were the results of a direct action or a reflex response, we studied the effects of increasing doses of d-tubocurarine on the rate and contractility of 8 isolated and perfused frogs' hearts. After testing the d-tubocurarine effects on the heart rate and contractility, we added either acetylcholine, atropine, atenolol or verapamil in order to find out whether any change occurred in the cardiac effects produced by d-tubocurarine. Thirty seven measurements were carried out and it was found that 1) high doses between 1 and 15 micrograms of d-tubocurarine produced a highly significant decrease in heart rate and contractility; 2) d-tubocurarine did not avoid the acetylcholine effect; 3) atropine, atenolol and verapamil did not interfere with d-tubocurarine effects. We conclude that high doses of d-tubocurarine produce «dosis-dependent» heart rate and contractility reductions. These effects are not mediated by muscarinic receptors, beta-1 receptors or the slow calcium channels.

Key words: Curare. Heart. Inotropic. Chronotropic. Frog. Myocardium.

Resumen

Efectos cronotrópicos e inotrópicos negativos y directos del curare sobre el corazón aislado y perfundido del sapo

Se afirma que el curare no tiene efectos sobre el corazón porque en este órgano no hay receptores muscarínicos. Durante un trabajo experimental, observamos que al administrar d-tubocurarina en altas dosis a unos sapos, se producían cambios en la actividad cardíaca. Decidimos estudiar los efectos de la d-tubocurarina sobre la frecuencia cardíaca y la contractilidad de 8 corazones de batracio aislados y perfundidos. Después de probar los efectos de la d-tubocurarina, agregamos acetilcolina, atropina, atenolol o verapamil para investigar el mecanismo de acción de la d-tubocurarina. Encontramos que 1) la d-tubocurarina en altas dosis (1 a 15 mcg) produce una disminución significativa de la frecuencia y la contractibilidad cardíacas; 2) la d-tubocurarina no bloquea el efecto de la acetilcolina, y 3) que la atropina, el atenolol y el verapamil no bloquean el efecto de la d-tubocurarina. Concluimos que la d-tubocurarina, administrada en dosis altas, produce una disminución de la frecuencia y la contractilidad cardíacas directamente relacionadas con las dosis y que dicho efecto no está mediado por receptores muscarínicos, beta-1 o de canales lentos de calcio.

Palabras claves: Curare Cronotropismo, Inotropismo, Acetilcolina, Miocardio.

INTRODUCCION

It has been stated that d-tubocurarine acts by means of a competitive nicotinic receptor blocking action (Ganong 1988, Taylor 1981). Until now, it is believed that the heart is deprived of nicotinic receptors (Ganong 1988, Livingston 1986). Thus, curare should not exert any effect on the heart (Briese 1972, Punnen et al. 1984). However, while performing an experimental work, we observed that when high doses of d-tubocurarine were administered to frogs, the animals' cardiac performance changed. The purpose of the present study was to find out whether d-tubocurarine exerts a direct action on the heart.

METHODS

We used 8 frogs (*Bufo arenanum*) which were captured from their natural environment the night before performing the experiment. The frogs had a mean weight of 69.7 ± 28 g (mean \pm 1 SD). The spinal cord was sectioned; the brain and the remainder of the spinal cord were then destroyed with a stiletto. The anterior chest wall was opened and a pericardiectomy performed. The three caval veins were dissected and a Harvard cannula introduced in the central cava. The aortas were cut; the heart was extracted and connected to a perfusion device which provided a constant perfusion pressure. The heart was then attached to a crowbar with a constant weight on one side and a needle on the other. (Figure 1). The needle was gently applied over a kymograph and each cardiac contraction was registered as a negative deflection (Figure 1). Batrachian's Ringer (Taylor, 1981) was used as the

perfusing solution. When the isolated and perfused heart reached a stable function, cardiac contractions were recorded and the heart rate was measured with a chronometer under direct observation.

Once a control measurement of contractility and heart rate were obtained, we added, under continuous recording, d-tubocurarine to the perfusing solution and waited until the effect had elapsed (i.e. till the heart rate and contractility returned to the control values). The d-tubocurarine doses were gradually increased from 1 to 15 ug/g. Once the effects of d-tubocurarine were recorded, we selected the dose that produced the most prominent modifications and administered it again before adding 25 ug of acetylcholine to the perfusing solution. Finally, so as to find out the origin of the d-tubocurarine actions, we added either atropine (0.04 mg/kg), atenolol (0.15 mg/kg) or verapamil (0.071 mg/kg), before adding d-tubocurarine.

Contractility was measured as the mean height in mm of 4 cardiac contractions spikes and heart rate as the number of beats per min. The heart rate and contractility variations were computed with the following formula.

$$PV = [(MA \times 100) / MB] - 100$$

(where PV = percent variation, MA = measurement after intervention and MB = measurement before intervention).

The data were statistically analyzed by means of a t-test, a regression and a correlation analyses. Statistically significant differences were those with a p value $\leq .05$.

RESULTS

We carried out 37 measurements in the 8 animals (Table 1). When d-tubocurarine was added, the heart rate and contractility decreased significantly ($P < .0001$). The decrease was «dosis-dependent» and exhibited a pattern of negative linear correlation (Figure 2 and 3). It was also found that d-tubocurarine did not interfere with acetylcholine effect and that atenolol, verapamil and atropine did not block the d-tubocurarine effect.

DISCUSSION

Since the heart was isolated and perfused out of the animal's body, this experimental model allowed us to evaluate the direct actions of d-tubocurarine on the heart. The observed effects cannot be attributed to variations in autonomic tone, preload, after load or perfusing fluid composition.

The depressant effects of d-tubocurarine on the heart rate and contractility were only seen when high doses of the drug were administered and they showed a «dosis-dependent» pattern with a negative linear correlation. The aforementioned effects cannot be understood as the result of muscarinic receptor stimulation because atropine did not modify the d-tubocurarine action, and d-tubocurarine did not block the acetylcholine effect. The negative chronotropic and inotropic effects were not mediated by beta-1 cardiac receptors since atenolol was not found to interfere with d-tubocurarine action. The same holds true for slow calcium channels as verapamil did not block the d-tubocurarine effect.

We used very high doses of d-tubocurarine which exceed by far those used in therapeutic applications of the drug. In the literature there are reports of arterial hypotension in patients who have been submitted to d-tubocurarine overdoses. (Taylor 1981). The arterial hypotension has been explained by an hypothetical peripheral sympathetic blockade. On the light of our findings, we can also suppose that the hypotension could be, in part, the result of a direct action of d-tubocurarine on the heart.

CONCLUSION

In the isolated and perfused frog's heart, high doses of d-tubocurarine produce a direct negative chronotropic and inotropic effects which are mediated neither by muscarinic or sympathetic beta-1 receptors nor by slow calcium channel action.

REFERENCES

- BRIESE, E. 1972. Perfusion de Corazón Aislado de Batracio. In *Prácticas de Fisiología*. PP 132. Consejo de Publicaciones de la Universidad de Los Andes. Mérida.
- GANONG, W .F. 1988. Sistema nervioso autónomo. In *Fisiología Médica*. Editorial El Manual Moderno . Mexico. 186-191.
- LIVINGSTON, R.B. 1986. Mecanismos de control visceral. In *Best & Taylor. Bases Fisiológicas de la Práctica Médica*. (J.B. West, Ed.) Editorial Médica Panamericana. Buenos Aires. 1414-1442.
- PUNNEN, S., GONZALEZ, ER., KRIEGER, A. J., SAPRU, H.N. 1984. Cardiac vagolytic action of some neuromuscular blockers. *Pharmacol. Biochem & Behavior* 20: 85-89.
- TAYLOR, P. 1981. Agentes bloqueadores neuromusculares. In *Las Bases Farmacológicas de la terapéutica*. (Goodman & Gilman, Ed.), pp 229-242. Editorial Médica Panamericana. Buenos Aires.

ACKNOWLEDGMENT

We are grateful to Dr. Françoise Meyer and to Marino Sanchez for their invaluable help.

TABLA I.

DOSIS	HR-B	HR-A	% Variation	C-B	C-A	% Variation
1	24	20	-17	18	17	-5.56
1	20	20	0	18	18	0
1	48	48	0	19	19	0
1	40	40	0	19	19	0
3	20	20	0	18	16	-11.11
3	24	24	0	6	4	-33.33
3	24	20	-17	19	15	-5.88
3	44	44	0	19	19	0
3	48	48	0	18	18	0
3	56	48	-14	17	16	-5.88
5	24	24	0	4	4	0
5	32	28	-12	6	4	-33.33
5	28	24	-14	13	12	-7.69
5	44	44	0	16	6	-62.5
5	48	40	-16	16	3	-81.25
7	44	40	-9	19	8	-57.89
7	44	24	-45	16	5	-68.75
8	44	26	-41	11	6	-45.45
10	24	20	-16	18	4	-77.77
10	36	18	-50	8	2	-75
10	36	24	-33	8	2	-75
10	60	48	-20	7	2	-71.42
10	42	24	-43	7	2	-71.42
10	40	32	-20	19	7	-63.15
13	48	28	-42	19	3	-84.21
13	44	20	-9	20	7	-65
13	44	32	-27	21	2	-90.47
13	44	32	-27	24	2	-91.66
13	40	32	-20	11	5	-54.54
13	20	20	0	16	13	-18.75
13	29	29	-7	17	13	-23.52
13	16	16	0	16	12	-25
13	44	40	-9	19	5	-73.68
15	36	32	-11	15	4	-73.33
15	36	24	-33	18	9	-50
15	40	36	-10	20	10	-50
15	32	24	-25	23	2	-91.3

TABLE I: The heart rate and contractility, before and after d-tubocurarine administration. DOSIS = μ g/g. HR-B= Heart rate (beats/minute) before d-tubocurarine administration. HR-A= Heart rate (beats/minute) after drug administration. C-B= Contractility before curare (mm) C-A= Contractility after curare (mm). % Variation = Percentual variation in heart rate and contractility.

¡Escriba en MedULA!

MedULA publica artículos originales de investigación, de revisión y de opinión, así como de información general sobre aspectos de interés para el sector salud. La revista, en principio, está dirigida al médico general, aun cuando en cada número se incluyen artículos de interés para los especialistas. Envíenos artículos o información relevante que tenga cabida en MedULA al apartado 870, Mérida.

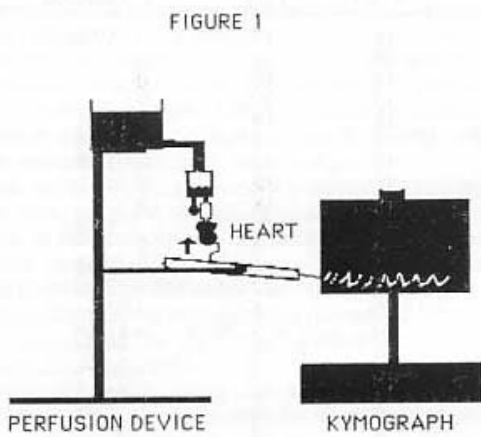


Figure 1. Perfusion device and kymograph for cardiac activity recording.

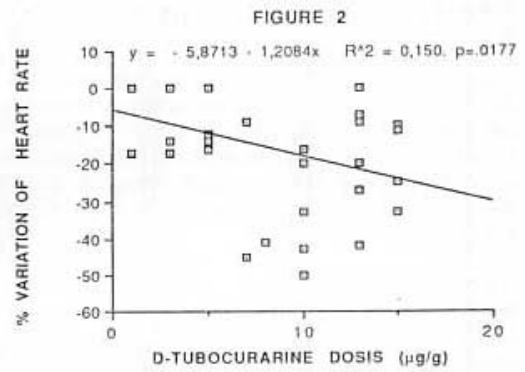


Figure 2. Correlation between the d-tubocurarine doses ($\mu\text{g/g}$) and the percentual variation of heart rate.

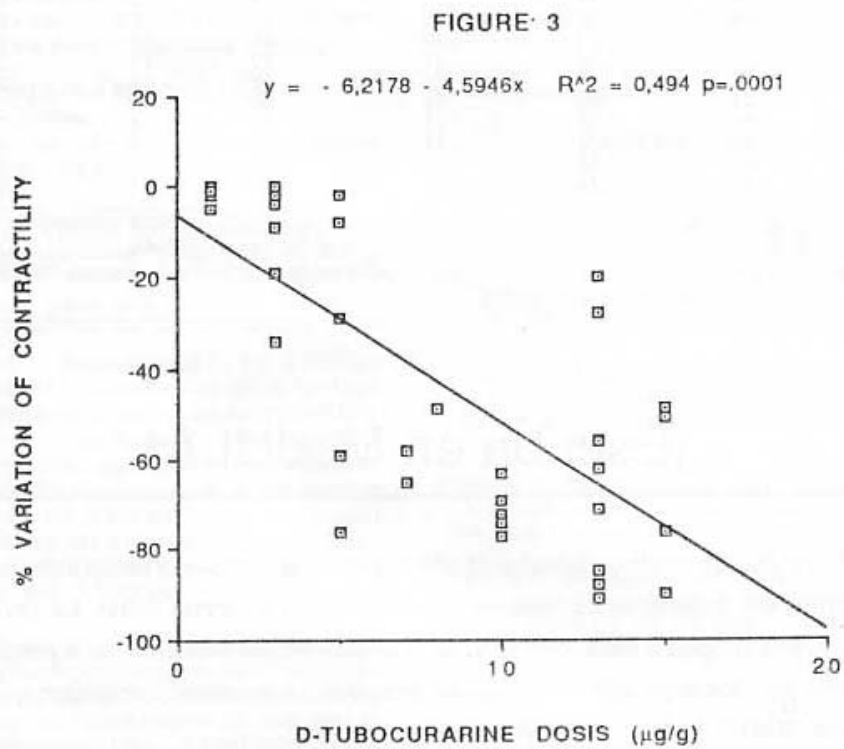


Figure 3. Correlation between the d-tubocurarine doses ($\mu\text{g/g}$) and the percentual variation of contractility.