ONCOLOGY

Regulation of Therapeutic and Toxic Effects of Cardiac Glycosides by Electromagnetic Radiations, Alternating Magnetic and Electric Fields

A. T. Grechko

UDC 616-006.04-085.22:547.918]+615.847.8.09

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 118, № 11, pp. 502-504, November, 1994
Original article submitted January 28, 1994

A model of bioassay of the toxic and therapeutic effects of cardiac glycosides (strophanthin K) was used in experiments with *in situ* isolated hearts of laboratory frogs. This model helped reveal effective parameters of modulating the effects of electromagnetic radiations and of alternating magnetic and electric fields.

Key Words: *electromagnetic radiations; modulation; cardiac glycosides*

Optimizing the methods used in the treatment of oncologic diseases is a high-priority goal of medicine and biology. The search for effective cytostatics which do not have any toxic effects and do not suppress the growth of normal tissues when used in therapeutic doses is ongoing. Some scientists have discovered a selective pattern of the cytostatic action of cardiac glycosides (strophanthin K and digoxin) on cultures of cancerous and nontransformed cells of lymphoid [7] and epithelial [8] tissues. Effective concentrations of these cardiac glycosides causing complete lysis of tumor cell populations are comparable to those used in common therapeutic schemes for the agents of this class [4,6]. However, the use of cardiac glycosides is quite often associated with toxic effects, which are observed in 7.7 to 60% of patients [4,10,11]. Reports about pronounced bioregulatory effects of electromagnetic radiation (EMR) and of alternating magnetic and electric fields (AMF and AEF, respectively) being manifested in the organism during the very first minutes of irradiation [1,3] were the starting point for our research.

Research Department, Military Medical Academy, St. Petersburg. (Presented by S. N. Golikov, Member of the Russian Academy of Medical Sciences)

MATERIALS AND METHODS

The pharmacodynamics of cardiac glycosides and methods of its correction by EMR, AMF, and AEF were studied in 1680 male laboratory frogs. The bioassay method described in the Pharmacopeia of the USSR [2] was used. Groups of 15 animals were fixed on the back to foam plastic plates with plastic pins, after which the hearts were isolated *in situ* and the pericardium was dissected. The cardiotoxic dose of 0.005% strophanthin K causing the characteristic symptom of cardiac arrest in the systole for 30-60 or 60-90 min was determined on the day of the experiment in a separate group of animals of this population. This dose, usually 0.30 to 0.35 ml, was then injected subcutaneously in the femur to animals of the other groups 15 to 30 min before irradiation. The fact that frogs are coldblooded animals greatly simplifies the experiments [9]; moreover, they are highly sensitive to cardiac glycosides [2,5], and the electric properties of their tissues

0007-4888/94/0011-1199$12.50

are similar or identical to those of higher animals and man [3].

The animals were irradiated (or sham-irradiated - controls) at the same times of day at 18°C in a tested echo-free room. The animals were placed at fixed points of free space where the errors of AEF E and H values were no more than 10%. The parameters of irradiation were as follows: 1) ultrahigh frequency (UHF) 3085 MHz, F 400 Hz, τ 1 μsec, Δ 5000, incident AEF 0.3-0.5 and 2-3 mW/cm^2 for H orientation in the distant zone and exposure 1 to 30 min; 2) ultralow frequency (ULF) H 50 to 400 A/m, E 50-400 V/m, F 2-1000 Hz, vertical E polarization, horizontal H to the axis of the animal's position, exposure 1 to 120 min; 3) magnetic field H 0.1-1 kA/m, F 2-50 Hz, horizontal polarization to the axis of the animal's position, exposure 1 to 90 min; 4) electric field of a) low voltage E 580 V/m, F 8 Hz, τ 100 μsec, meander, horizontal polarization, exposure 1 to 90 min; b) high voltage E 50-1000 kV/m, F 2-50 Hz, τ 500 μsec, meander, horizontal polarization, exposure 1 to 120 min.

RESULTS

The majority of tested UHF and ULF parameters of EMR, AMF, and AEF modulated the pharmacodynamics of strophanthin K. However, for some characteristics of the factor these changes were significantly reiterative (Table 1). Prolongation or shortening of the latent period before cardiac arrest and of the duration of cardiac arrest in the systole were recorded here in the course of irradiation, this being followed by recovery of heart automatism. Such changes in strophanthin K pharmacodynamics were recorded after injection of not only standard toxic doses, but of subtoxic doses as well (50 to 75% of toxic doses), which did not induce the above-noted symptoms in the control.

TABLE 1. The Most Significant Values of Strophanthin K Pharmacodynamics Modulation in the Course of Animal Exposure to UHF and ULF EMR, AMF, or AEF ($M \pm m$)

Group of animals (acting factor)	Exposure duration, min	Duration of strophanthin K action before frog cardiac arrest	
		time, min	vis-a-vis control
Deceleration of strophanthin K pharmacodynamics			
1. Control	–	69.9±3.4	1.00
Experiment (strophanthin + UHF EMR 0.3–0.5 mW/cm^2)	1	81.7±3.0	1.17
	15	72.0±2.7	1.03
	30	88.8±2.6*	1.27
2. Control	–	91.3±3.4	1.00
Experiment (strophanthin + ULF EMR H 400 A/m, E 400 V/m, F 6, 10, 100, and 500 Hz)	60	116.9±4.1	1.28
	180	119.4±3.9*	1.31
3. Control	–	32.5±1.4	1.00
Experiment (strophanthin + AMF H 1 kA/m, F 6, 8, 10 Hz)	1	46.7±1.7*	1.44
	15	40.0±1.4	1.23
4. Control	–	49.3±1.9	1.00
Experiment (strophanthin + AEF E 500 kV/m, F 2, 4, 6, 8, 10, and 25 Hz)	5	54.7±2.0	1.11
	30	68.0±2.4*	1.38
Acceleration of strophanthin K pharmacodynamics			
1. Control	–	95.8±2.9	1.0
Experiment (strophanthin + UHF EMR 2–3 mW/cm^2)	10	71.7±2.1*	0.75
2. Control	–	117.4±3.3	1.00
Experiment (strophanthin + ULF EMR H 400 A/m, E 400 V/m, F 2, 8, 25, and 40 Hz)	60	101.0±3.1	0.86
	120	90.4±3.0*	0.77
3. Control	–	88.7±2.2	1.00
Experiment (strophanthin + AMF H 1 kA/m, F 25, 30, 40, and 50 Hz)	10	81.6±1.9	0.92
	90	69.2±1.8*	0.78
4. Control	–	67.3±2.1	1.00
Experiment (strophanthin + AEF E 500 kV/m, F 30 and 40 Hz)	30	56.5±2.0*	0.84
	60	57.2±2.2*	0.85

Note. Asterisk shows values reliably ($p<0.05$) differing from control.

The most marked (by 17-44%) prolongation of the latent period before cardiac arrest in the systole with a short interval of systolic arrest was observed after low-power UHF irradiation of animals (0.3 to 0.5 mW/cm²). The effect was boosted as the field intensity increased: ULF EMR 50-400 V/m, A/m; AMF 0.1-1 kA/m, and AEF 50-1000 kV/m, as well as with prolongation of exposure to UHF EMR (1-30 min) and ULF EMR (60-180 min), AMF 1 kA/m (1-90 min), and AEF 500 kV/m (5-30 min) at frequency modulations 6, 10, 100, and 500 Hz (ULF EMR); 6, 8, and 10 Hz (AMF); and 2, 4, 6, 10, and 25 Hz (AEF).

The most appreciable (by 10-25%) shortening of the latent period of the drug's effect with a stable cardiac arrest was observed for exposure to: UHF EMR 2-3 mW/cm²; ULF EMR E 400 V/m, H 400 A/m, F 2, 8, 25, and 40 Hz; AMF H 1 kA/m, F 25, 30, 40, and 50 Hz; AEF 500 kV/m, F 8, 30, and 40 Hz. Similarly as in previous experiments, a direct relationship was observed between the intensity of the bioeffect, on the one hand, and the exposure duration, intensity of E and H, and frequency characteristics of the factor, on the other.

The results of some experiments coincided with published data which characterize stable species-specific energy and frequency "windows" of a high biological reactivity to an electromagnetic field, among other variants, in the frequency modulation band of 2 to 10 Hz [3]. The use of a pharmacological analyzer of strophanthin K made it possible to reproduce this effect clearly in mass parallel investigations and to extend the characteristics of the ranges of frequency and energy (dose-dependent) "windows" of biological reactivity to EMR, AMF, and AEF. These data can be used in various areas of medicine and biology, specifically, for the development of optimal combined methods of oncotherapy (treatment with lower doses of cardiac glycosides and reduction of their toxic effects), as well as for action on other organs and tissues containing receptor "targets" for cardiac glycosides [4-6].

REFERENCES

1. *Topics in Experimental and Practical Electromagnetobiology*, Eds. I. G. Akopaev and V. V. Tyazhelov [in Russian], Pushchino (1983).
2. *State Pharmacopeia of the USSR*, 10th ed., Moscow, (1968), pp. 917-921, 931-932.
3. B. I. Davydov, V. S. Tikhonchuk, and V. V. Antipov, *Biological Effects of, Norm-Setting, and Protection from Electromagnetic Radiation* [in Russian], Moscow (1984).
4. V. V. Zakusov, *Clinical Pharmacology* [in Russian], Moscow (1978).
5. G. M. Kitaigorodskaya, M. R. Mukumov, and N. V. Dmitrieva, *Farmakol. Toksikol.*, **47**, No. 1, 38-44 (1984).
6. M. D. Mashkovskii, *Drugs* [in Russian], Moscow (1986).
7. A. A. Narimanov and B. K. Gavrilyuk, *Radiobiologiya*, **29**, No. 2, 188-191 (1989).
8. A. A. Narimanov, *Eksp. Klin. Farmakol.*, **55**, No. 3, 22-23 (1992).
9. V. P. Terent'ev, *The Frog* [in Russian], Moscow (1950).
10. Y. A. Bristol and D. B. Evans, *Med. Res. Rev.*, **3**, No. 3, 259-287 (1983).
11. E. Steiness, *Acta Med. Scand.*, Suppl. 707, 63-64 (1986).