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Evaluation of Cardiac Activity and Pharmacokinetic Analysis of ^{3}H-Adriamycin in Patients Pretreated with Beta-Methyldigoxin

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Summary. *The consequences at the cardiac level of adriamycin treatment alone or in association with the cardiac glycoside beta-methyldigoxin, were evaluated with reference to the PEP/LVET ratio, heart rate, and minimum blood pressure. The variation usually seen in the PEP/LVET ratio when adriamycin is administered alone was not observed when pretreatment with beta-methyldigoxin was also given. A similar situation is found with variations in blood pressure and heart rate. From a pharmacokinetic point of view, this treatment scheme does not seem to affect the general behavior of the antibiotic.*

Introduction

Therapy with adriamycin, an antibiotic of the anthracycline group, has frequently been associated with cardiomyopathy and congestive heart failure [1]. Various approaches have been used to reduce the cardiotoxicity of the antibiotic, but the only practical result achieved so far as protection of the patient is concerned, is the conclusion that the dose should be reduced to a total dosage of 500 mg/m^2 [1, 4, 6]. Recently, preliminary clinical observations have suggested that pretreatment with cardioactive glycosides might reduce adriamycin-induced cardiomyopathy [5, 8]. In fact, it has been demonstrated that pretreatment with beta-methyldigoxin significantly reduced the impairment of left ventricular function, evaluated by the measurement of systolic time intervals, after adriamycin injection [8]. These results suggest that cardiac glycosides could prevent the early cardiotoxic effect or avoid late dose-related cardiomyopathy, competitively inhibiting adriamycin at the receptor site of the cardiac muscle.

The aim of this study is to contribute to the prevention of negative inotropic effects from adriamycin by means of a proper pretreatment of patients with beta-methyldigoxin and also to investigate the pharmacokinetic properties of the antibiotic when administered in such a therapeutic scheme.

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Materials and Methods

The study included two groups of five and 20 patients, respectively. The ages of the patients ranged from 35 to 60 years. All had advanced neoplastic disease of various types; none suffered from cardiovascular insufficiency or had an abnormal ECG upon entering the study. No patient had been previously treated with radiotherapy on the mediastinopericardial area, nor had any patient received drugs active on the cardiovascular system other than beta-methyldigoxin.

The first group of patients received a single IV dose of ^{3}H-adriamycin (specific activity 3727 dpm/γ; Farmitalia Laboratories, Milan, Italy) after pretreatment with beta-methyldigoxin. This treatment consisted in the administration of 0.4 mg/day for 4 days and 0.2 mg on the fifth day, exactly 1 h before the antibiotic injection. The second group received nonradioactive adriamycin without digitalis pretreatment. Blood pressure, ECG, and polygraphic tracings were taken prior to the beginning of treatment (baseline values), immediately before, and 60 min after adriamycin injection. The method of registration and calculation of the systolic time interval was according to Weissler [9[.

Blood samples were drawn 2, 5, 8, 10, 15, and 30 min and 1, 2, 4, 8, 16, 24, 48, 72, 96, 120, 144, and 168 h after the injection; urine samples were collected 1, 2, 4, 8, 16, 24, 48, 72, 96, 120, 144, and 168 h after the injection, and feces were collected every day for one week. Heparinized blood samples were centrifuged at 200 *g* for 10 min to separate plasma. Aliquots of plasma, urine, and feces were burned in duplicate in an IN 4101 Sample Oxidizer (Intertechnique, Plaisir, France), and the tritiated water was collected. The radioactivity was determined in a Packard model 3255 liquid scintillation spectrometer using a scintillation cocktail made up of 7 g butyl PBD, 300 ml 2-ethoxyethanol, and toluene to give 1 liter. The counts per min were corrected for efficiency by the external standard method. Chromatographic analysis of the injected ^{3}H-labeled drug and of the plasma samples was performed on silica gel thin-layer plates (250 μ) in an ascending fashion in the two alternative systems: chloroform : methanol : acetic acid : water (80 : 20 : 14 : 6); and chloroform : methanol : acetic acid (100 : 2 : 5). Chromatographs showed the lack of significant degradation products and metabolites.

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Pharmacokinetic compartmental analysis of the data was performed with NONLIN (a program kindly supplied by Upjohn Co., Kalamazoo, Michigan, USA) on an IBM 370 computer.

Results

The values of the three parameters obtained from patients pretreated or not with beta-methyldogoxin are shown in Fig. 1. A direct comparison between the two groups of patients is not possible because of the difference in the basal values, but a Student's *t*-test can be applied within the single groups of patients to show whether or not the differences among mean values at various times have a statistical significance.

While adriamycin alone causes a significant increase in minimum blood pressure and a decrease in heart rate, a certain degree of restoration toward normal values can be observed as a consequence of the pretreatment with beta-methyldigoxin. Since the PEP/LVET ratio can be considered the most important parameter, because of its good correlation with injected fraction, cardiac index, and clinical status, the mean values of this ratio are plotted in Fig. 2, together with the individual values for the five predigitalized patients. Even if different patterns of values can be observed among the patients, analysis of the mean values demonstrates a substantial 'buffer effect' of beta-methyldigoxin pretreatment on adriamycin-induced cardiac activity variations.

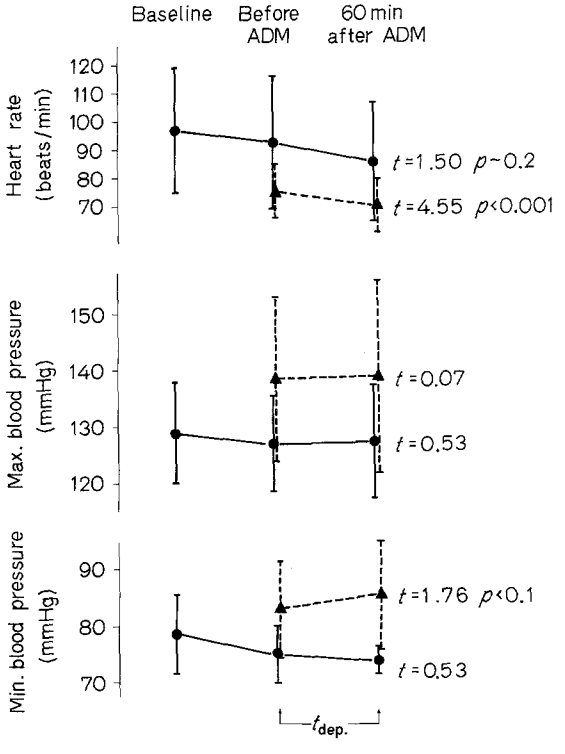

Fig. 1. Mean values and standard deviations of heart activity parameters in a group of 20 cancer patients treated with 60 mg adriamycin/m² alone (▲) and in a group of five cancer patients treated with the same dose of antibiotic but after a pretreatment with beta-methyldigoxin (●; *arrow* shows time of pretreatment). Student's *t*-test was applied to data obtained before adriamycin and 60 min after adriamycin administration

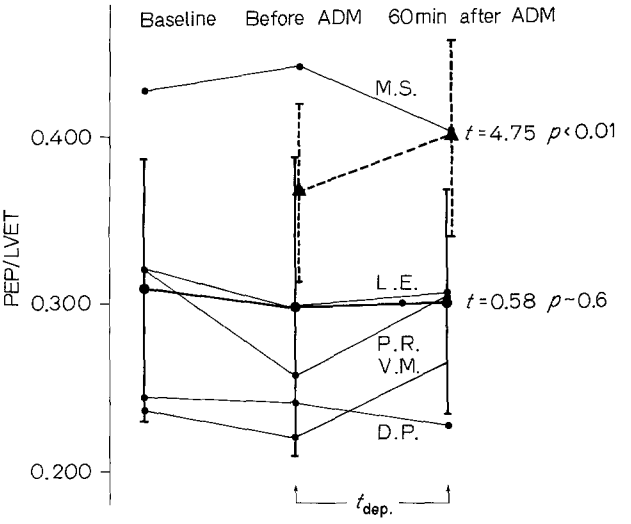

Fig. 2. PEP/LVET ratio values for cancer patients treated with 60 mg of adriamycin/m² alone (▲) or after pretreatment with beta-methyldigoxin (●; *arrow* indicates time of pretreatment). For the first group of 20 patients only the mean values and standard deviations are reported, while for the second group of five patients the individual values (•) are also reported. Student's *t*-test was applied to data obtained before adriamycin and 60 min after adriamycin administration

As regards the pharmacokinetic aspect of the treatment scheme tested, a comparison between the two groups of patients was not performed because of the slight differences expected from such a general analysis. On the other hand, a pharmacokinetic description of the treatment with adriamycin associated with a digitalis therapy is undoubtedly important for clinical practice.

The plasma levels of ^{3}H-adriamycin found in the five patients whose cardiac activity was recorded are plotted in Fig. 3, and the excretion data are shown in Fig. 4. After IV injection, the drug rapidly disappears from the plasma within the first 30 min, then there is a slow equilibrating phase and, after the fourth hour, a certain stability of the levels.

As previously reported for adriamycin administered alone [3], the majority of the patients show a fecal excretion of the drug that markedly exceeds that in the urine. As a mean evaluation, after 168 h about 70% was excreted through the biliary route, while 25% was excreted in the urine.

The log-plot of plasma levels shows the presence of three exponential components in the fitting curve for all the patients. For this reason the three-compartment

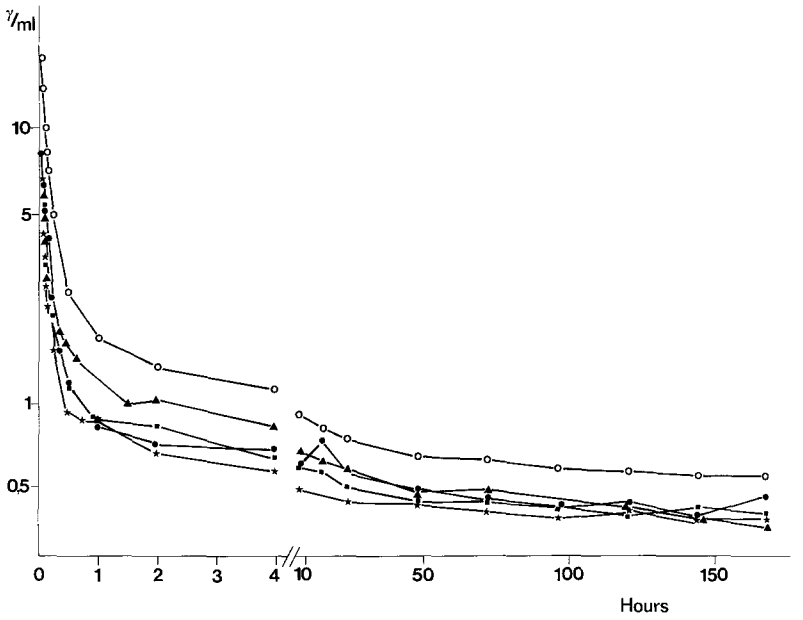

Fig. 3. Plasmatic concentrations of ^{3}H-adriamycin injected IV to five cancer patients after pretreatment with beta-methyldigoxin

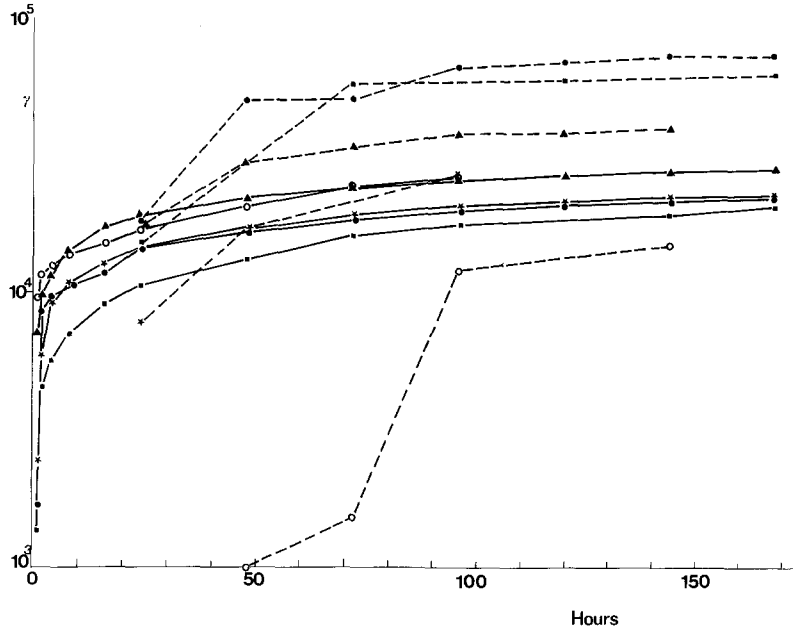

Fig. 4. Cumulative excretion of ^{3}H-adriamycin by the fecal (– – –) and urinary (——) routes in five patients who received IV injections after pretreatment with beta-methyldigoxin

open model shown in Fig. 5 was chosen for the interpretation of the distribution and excretion data [7]. The data are elaborated separately for each patient, and the optimal values for the fitting parameters, together with the calculated microconstants of the compartmental model, are reported in Table 1. The mean values and standard deviations calculated are also reported. Among the parameters, the microconstant, alpha, and its half-life are the ones with the smallest standard deviation (variation coefficient ~ 48% and 4%, respectively), followed by the rate constants, K_{21} and K_{12} (variation coefficient 12% and 23%, respectively). This suggests that the initial phase characterized mainly by the distribution of the drug between the central and the external compartment, which is more rapidly accessible, is the most common among the various parameters.

On careful consideration of the values of the various pharmacokinetic parameters, it can be noted that the rate constants responsible for the transport of the drug from the inner to the outer compartments are greater

Table 1. Pharmacokinetic three-compartment open model parameters for five cancer patients treated with ^{3}H-adriamycin after a pretreatment with beta-methyldigoxin

Parameter and unit		Patient					
		DP	PR	MS	VM	IE	Mean ± SD
D	γ	100,000	100,000	100,000	90,700	100,000	98,280 ± 4,248
A	γ/ml	10.21	4.54	19	10.30	10	10.81 ± 5.19
α	h^{-1}	9.49	9.82	8.99	9.61	10	9.58 ± 0.38
B	γ/ml	1.43	0.84	1.99	1.53	1.02	1.36 ± 0.45
β	h^{-1}	0.53	0.04	0.79	0.59	1.04	0.60 ± 0.37
C	γ/ml	0.44	0.10	0.90	0.28	1.02	0.55 ± 0.40
γ	h^{-1}	0.018	0.0042	0.0043	0.007	0.011	0.0089 ± 0.0058
$t_{1/2\alpha}$	h	0.073	0.07	0.077	0.07	0.07	0.072 ± 0.003
$t_{1/2\beta}$	h	1.3	17.44	0.88	1.17	0.67	4.29 ± 7.35
$t_{1/2\gamma}$	h	38.56	164.78	162.75	98.00	65.84	105.99 ± 56.79
K_{el}	h^{-1}	0.43	0.12	0.10	0.28	0.12	0.21 ± 0.14
K_{12}	h^{-1}	5.74	7.93	4.39	5.50	5.08	5.73 ± 1.33
K_{13}	h^{-1}	1.91	0.086	3.39	2.47	3.22	2.22 ± 1.33
K_{21}	h^{-1}	1.84	1.72	1.73	1.89	2.26	1.89 ± 0.22
K_{31}	h^{-1}	0.12	0.008	0.17	0.08	0.4	1.156 ± 0.149
V_1	ml	8276	18,223	4572	7500	8344	9383 ± 5175
AUC	γ/ml × h	82	82.4	104.5	70.9	77.2	83.4 ± 12.7
AUX1	γ × h	235,000	837,860	986,345	321,575	827,955	641,747 ± 339,055
AUX3	γ × h	733,368	3,871,930	2,493,990	934,877	1,865,930	1,980,019 ± 1,275,046
AUX4	γ × h	3,877,040	9,047,830	19,495,900	10,493,400	6,682,160	9,919,266 ± 5,911,605
PC	ml/h	3,522	2,175	464	2,115	1,015	1,818 ± 1,182

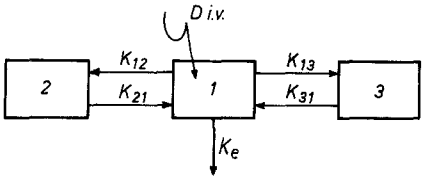

Fig. 5. Three-compartment pharmacokinetic open model, with rapid IV injection of the drug (D i.v.) in the central compartment

than the opposite ones. The areas under the theoretical curves of compartments two and three are also much greater than those calculated for the central one. Another observation is that the value of the volume of the central compartment is greater than the simple blood volume in the majority of cases.

Discussion

The consequences at the cardiac level of adriamycin treatment alone or in association with the cardiac glycoside, beta-methyldigoxin, have been evaluated with reference to the PEP/LVET ratio, heart rate, and minimum and maximum blood pressure. Since it is known that an increase in the PEP/LVET ratio represents an impairment of left ventricular function, particular attention has been paid to this parameter. It has thus been found that in contrast to the results obtained when adriamycin is given alone, when pretreatment with beta-methyldigoxin is given the variation in the PEP/LVET ratio that is normally observed with adriamycin does not occur. A similar situation is also found regarding the variations in blood pressure and heart rate usually found as a consequence of adriamycin injection. These observations prove that in all the patients tested the proposed treatment scheme did not cause any impairment of myocardial function.

With regard to the pharmacokinetic analysis of adriamycin in these conditions, our results are substantially consistent with the ones obtained in previous studies [2], where the high affinity of adriamycin for the tissues and its mainly fecal excretion from the body were pointed out. The kinetic parameters showed wide variations in different patients, except for those that concerned the early distribution of the drug.

Finally, we can confirm that pretreatment with beta-methyldigoxin actually reduces the incidence of early cardiac side effects of adriamycin, and also that this treatment scheme does not seem to affect the general pharmacokinetic behavior of the antibiotic.

References

1. Blum, R. H., Carter, S. K.: Adriamycin. A new anticancer drug with significant clinical activity. Ann. Intern. Med. **80,** 249 (1974)

2. Di Fronzo, G., Gambetta, R. A., Lenaz, L.: Distribution and metabolism of adriamycin in mice. Eur. J. Clin. Biol. Res. **16,** 572 (1971)
3. Di Fronzo, G., Lenaz, L., Bonadonna, G.: Distribution and excretion of adriamycin in man. Biomedicine [Express] **19,** 169 (1973)
4. Gottlieb, J. A., Lefrak, E. A., O'Bryan, R. M.: Total adriamycin cardiomyopathy: prevention by dose limitation. Proc. Am. Assoc. Cancer Res. **14,** 88 (1973)
5. Guthrie, D., Gibson, A. L.: Doxorubicin cardiotoxicity: possible role of digoxin in its prevention. Br. Med. J. **2,** 1447 (1977)
6. Lefrak, E. A., Pitha, J., Rosenheim, S., Gottlieb, J. A.: A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer **32,** 302 (1973)
7. Rescigno, A., Segre, G.: La Cinetica dei Farmaci e dei Traccianti Radioattivi. Torino: Boringheri 1961
8. Villani, F., Beretta, G., Pagnoni, A., Guindani, A.: Adriamycin cardiotoxicity in man: effect of pretreatment with beta-methyldigoxin. A polygraphic study. In: Chemotherapy, Vol. 8. Hellmann, K., Connors, T. A. (eds.), p. 491. New York: Plenum Press 1976
9. Weissler, A. M., Harris, W. S., Schoenfeld, D. C.: Bedside technic for the evaluation of ventricular function in man. Am. J. Cardiol. **23,** 577 (1969)

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