Cancer Chemother. Pharmacol. 3, 249–251 (1979)

Cancer Chemotherapy and Pharmacology

Evaluation of Early Doxorubicin-induced Cardiotoxicity by Means of Systolic Time Intervals

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Summary. *Systolic time intervals (PEP/LVET ratio) were used for detection of acute variations in myocardial contractility after a single dose of 30, 60, or 75 mg of doxorubicin/m². This drug induces an acute impairment of left ventricular function (increase in the PEP/LVET ratio) detectable 1 h after doxorubicin injection. The phenomenon appears to be dose-related, with a threshold dose of 30–40 mg/m². The decrease in myocardial contractility is fully reversible within 24 h, at least after the first dose. This kind of evaluation appears applicable to phase I studies of new anthracycline derivatives.*

Introduction

Systolic time intervals (STI) are considered a sensitive indicator of the left ventricular function [10]. STI have been extensively used in doxorubicin-treated patients in the hope that they (and especially the PEP/LVET ratio) might be of value in the early detection of doxorubicin-induced cardiomyopathy. The routine use of STI for predicting doxorubicin-induced cardiomyopathy and assessing therapeutic doses of anthracyclines appears questionable, and according to many authors is of very limited value [1, 4–6].

ECG and STI are usually determined in the pretreatment period. The acute effect of doxorubicin on myocardial contractility immediately after drug administration has not been extensively investigated, and conflicting results have been reported [3, 6, 7]. We performed accurate observations in a group of adult patients of both sexes with various neoplastic diseases to investigate the pattern of acute doxorubicin-induced cardiotoxicity after IV administration of the drug.

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Methods and Patients

The study was undertaken in 27 patients of both sexes with various advanced neoplastic diseases. None of them had cardiovascular diseases or hypertension before doxorubicin treatment, or an abnormal ECG before entering the study. Subjects who had previously received radiotherapy to the pericardio-mediastinic area were excluded; no patient was undergoing any treatment that acted on the cardiovascular system. Doxorubicin was administered by IV bolus injection in a 3-min period at a single dose of 30, 60, or 75 mg/m²; further administrations of doxorubicin were planned every 21 days. Heart rate, blood pressure, and STI were recorded before doxorubicin injection while patients were fasting and at rest for at least 20–30 min. One hour after drug administration a new check on blood pressure and STI was taken in the same conditions. The method of recording and calculation of various STI was that described by Weissler et al. [10].

Results and Discussion

In previous reports, we have demonstrated that a single dose of 60–75 mg doxorubicin/m² does not modify the duration of the electromechanical systole but is able to induce a significant prolongation of the pre-ejection period (PEP) and a shortening of the ejection period (LVET): consequently, the PEP/LVET ratio is significantly increased, which means an impairment of left ventricular function [7, 8].

In the present investigation, STI registered in patients receiving three different doses of doxorubicin (30, 60, and 75 mg/m²) were evaluated to ascertain whether there is a dose-dependent change in myocardial contractility (evaluated by PEP/LVET variations) and whether a threshold dose exists. Figure 1 shows a different response of the PEP/LVET ratio after the doxorubicin dosages tested: the mean percentage variation from basal values is 14.1 ± 3.1 after 75 mg/m² and 8.1 ± 1.5 after 60 mg/m² (the difference is statistically significant; $P < 0.05$). In contrast, the mean PEP/LVET ratio recorded after 30 mg/m² was not significantly different

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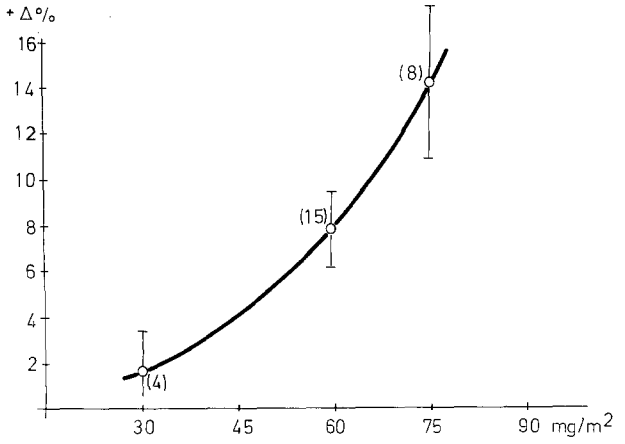

Fig. 1. Dose-dependent change in PEP/LVET ratio 60 min after doxorubicin injection (mean ± SD). Figures in parentheses give number of patients

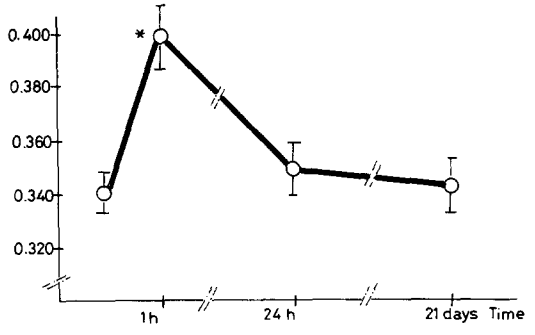

Fig. 2. Time course of STI modifications (PEP/LVET) induced by the first dose (75 mg/m²) of doxorubicin (mean ± SD of eight patients). *, Value statistically different from basal values ($P < 0.05$)

from the mean basal values. The results clearly demonstrate the existence of a dose-dependent relationship and a threshold dose of 30–40 mg/m² for this drug-induced phenomenon.

These results are not in agreement with those reported by Björchem and Garwicz [3], who evaluated alteration in left ventricular function by echocardiographic assessment: according to these authors, no immediate effect of doxorubicin on left ventricular function could be shown. In reality, the contrast is only apparent: in fact, it must be stressed that the observations recorded by Björchem and Garwicz were limited to the first 10 min after doxorubicin injection, while experimental data indicate that the negative inotropic effect on the myocardium requires more time to become evident [9]. Secondly, these authors limited their observations to a range of doses (30–40 mg/m²) that our results clearly indicate to be around the threshold dosage.

However, data recently published by Balcueva et al. [2] and obtained by use of impedance cardiography give evidence of a drug-dependent decrease in cardiac output between 4 and 6 h after the administration of doxorubicin, with recovery after 24 h.

The time course of STI variation after doxorubicin administration was also investigated. For this purpose, patients who received 60 or 75 mg/m² were also monitored 24 h and 21 days after doxorubicin injection. In a limited number of patients, a check of STI after 7 and 14 days was also performed. Patients were also separately analyzed according to the amount of doxorubicin administered. Figure 2 shows only the results obtained in eight patients who received the highest dose (75 mg/m²) of doxorubicin, since the same pattern of PEP/LVET variation was detected in 15 subjects after 60 mg/m². Figure 2 shows that values detected 1 h after doxorubicin administration appear significantly different from the mean basal values, but the slight increase in the PEP/LVET ratio observed at 1, 7, 14, and 21 days after doxorubicin injection was not significant when statistically analyzed. This means that the impairment of left ventricular function is almost completely reversible at least after the first dose of doxorubicin.

On the basis of reported data, it can be concluded that doxorubicin almost consistently induces an acute impairment of left ventricular function; the phenomenon is detectable within 60 min after doxorubicin administration and appears to be dose-related, with a threshold dose of 30–40 mg/m². The decrease in myocardial contractility appears to be fully reversible within 24 h and it is no longer detectable during the following 21 days, at least after the first dose of doxorubicin. The observed temporary decrease in myocardial contractility has no clinical significance, since it is not expressed by any clinical signs or symptoms of cardiovascular impairment.

These results suggest that further investigation of the dose-dependent response of STI after different cumulative dosages of doxorubicin is called for, to ascertain whether acute PEP/LVET variations recorded after different cumulative dosages could be predictive before clinical signs of doxorubicin-induced cardiomyopathy appear. Furthermore, this method could be applied to clinical investigation of acute effects produced by new anthracycline analogues and derivatives, and even the effects of other pharmacological manipulations in doxorubicin-treated patients.

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Received August 13, 1979