Studies on Myocardial Glucose Metaboltsm of Adriamycin-Administered Rats Using Positron-Emitting Radiopharmaceuticals

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Introduction

Glucose, as an energy source of tissue metabolism, is more extensively taken up by tumors, the myocardium or the brain than by any other tissues. The similar nature is found in F-18-labeled-2-deoxy-glucose(F-18FDG), a glucose analog.

Adriamycin(ADR) is usually given alone or in combination for the treatment of leukemia and various solid tumors and its marked efficacy has been appreciated. However, the long-term administration of ADR should be discontinued due to two kinds of side effects: One is myelosuppression frequently seen also in other anticancer drugs and the other is cardiotoxicity. The latter is distinctively seen in anthracycline antibiotics like ADR. Although a possible mechanism and prediction of cardiotoxicity of this drug have been explored, any reliable conclusion has not been reached yet. The most practical way to prevent the toxicity would be to predict the onset of the toxicity and to discontinue administration of the drug early enough.

The following report deals with our experimental studies on glucose metabolic dysfunction of the myocardium induced by ADR and our trial to detect ADR-induced cardiomyopathy by using F-18FDG. By utilizing the results obtained imaging ADR-induced cardiotoxicity will become possible using positron-emission tomography(PET).

Materials and Methods

1. Animals

Male Donryu rats, 5 weeks old, weighing 140-160g were used in the following experiments.

2. Induction of Acute & Chronic Toxicity by ADR

ADR was dissolved in physical saline and intravenously injected into the tail veins at the dose of 0.1cc/100g of weight.

i) Acute Toxicity

The lethal toxicity by a single administration of ADR was studied as a preliminary experiment. Since it was known in the prior experiment that the maximum tolerated dose(MTD) was approximately 3 mg/kg 7 or 13 days after the administration, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4.25 mg/kg and 5.5 mg/kg of ADR were intravenously injected. On days 1, 3, 5 & 7 after the injection of ADR, the animals were sacrificed by cervical dislocation one hour after the administration of F-18FDG at the dose of 10-20 μCi/rat which was supplied by Cyclotron and Radioisotope Center, Tohoku University. The whole body weight after the ADR administration and weight of the heart at the sacrifice were measured. Blood glucose concentration was determined by dextrometer. The distribution of F-18FDG in blood, the heart, the liver, the kidney, the thigh muscle and the brain was measured by auto-gamma counter and expressed by % injected dose/g tissue. The uptake of F-18FDG in the heart of the ADR-administered animals was compared to that of the control normal heart without ADR administration and the uptake ratio was defined as follows: Uptake ratio = % injected dose/g tissue of the heart(ADR-administered)/ mean of % injected dose/g tissue of the heart(not ADR-administered)

ii) Chronic Toxicity

0.25 mg/kg, 0.5 mg/kg or 1 mg/kg of ADR were injected every 7 days ranging from 4 to 41 times and they were provided for the experiments over 6 days after the final administration. Similar studies were made as described in the studies on acute toxicity.

Results and Discussion

1. Studies on Acute Toxicity

i) Changes of heart weight and ratio of heart to body in weight are shown in Fig. 1 & 2: Heart weight and ratio of heart to body in weight both showed the identical tendency and reached the nadir 5 days after the administration.

ii) Uptake ratio of F-18FDG in the heart shown in Fig. 3: The uptake ratio after a single administration of ADR was below 1.0 in the groups given 3 mg/kg and 4.25 mg/kg of ADR. The decrease in the uptake ratio was evident in acute toxicity.

2. Studies on Chronic Toxicity

i) Changes of body weight are shown in Fig. 4: Until ten weeks after the onset of administration, all the animal groups given 1 mg/kg, 0.5 mg/kg, 0.25 mg/kg or none(control) of ADR indicated a similar tendency of body weight increase, but after ten weeks the body weight decreased as shown in Fig. 4.

ii) Changes of heart weight are shown in Fig. 5 and ratio of heart to body in weight in Fig. 6: Heart weight appeared to reduce as the administration dose of ADR increased, but there was no difference in the ratio of heart to body in

weight between the respective groups. Accordingly, it may be considered that reduction of heart weight due to administration of ADR is attributed to nonspecific protein synthesis dysfunction.

iii) F-18FDG uptake ratio in the heart is shown in Fig. 7: F-18FDG uptake ratio was below 1.0 in the frequently administered groups, namely, 0.25 mg/kg 25, 0.5 mg/kg × 22, and 1 mg/kg × 14.

If 0.25 mg/kg ADR is administered 25 times, the total dose amounts to 6.25 mg/kg in case of rats and 312.5 mg/body in case of 50 kg man. Suppose the surface area of a body is 1.2 m^2-1.5 m^2, the total dose per surface area would be 260 mg/m^2-208 mg/m^2 in man. Likewise, when 0.5 mg/kg is given to a rat 22 times, the equivalent dose in man would be 458 mg/m^2-366 mg/m^2. In case of 1 mg/kg × 14 times in a rat, cumulative dose in man would amount to 580 mg/m^2-470 mg/m^2. It has been reported that in clinical studies the frequency of cadiomyopathy caused by ADR is 3 % with the total dose of 400 mg/m^2, 7 % with 550 mg/m^2 and 18 % with 700 mg/m^2, and with over 450-550 mg/m^2 rapid increase of the frequency is observed.[1,2)]

The reported critical total dose in man and the dose in man calculated from the total dose of ADR in rats in the present studies on chronic toxicity were surprisingly similar. The uptake of F-18FDG decreased as the administration dose of ADR increased.

Conclusion

The decrease in F-18FDG uptake was observed in the heart of the rats both in acute and chronic toxicity caused by ADR. The results obtained with chronic toxicity seemed to resemble actual clinical conditions and might serve as an experimental model of chronic heart toxicity caused by ADR. Decrease in F-18FDG uptake in the heart is thought to suggest that the administration of ADR induces dysfunction of myocardial glucose metabolism. By utilizing a short-lived positron emitter F-18FDG myocardial dysfunction by ADR may be predicted in terms of changes of myocardial images with PET.

Further studies are necessary to elucidate the correlation between myocardial toxicity and glucose metabolic dysfunction.

Acknowledgment

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References

1) Von Hoff D. D. et al., Ann. Intern. Med. 91 (1979) 710-717.
2) Praga C. et al., Cancer Treat. Rep. 63 (1979) 827-834.

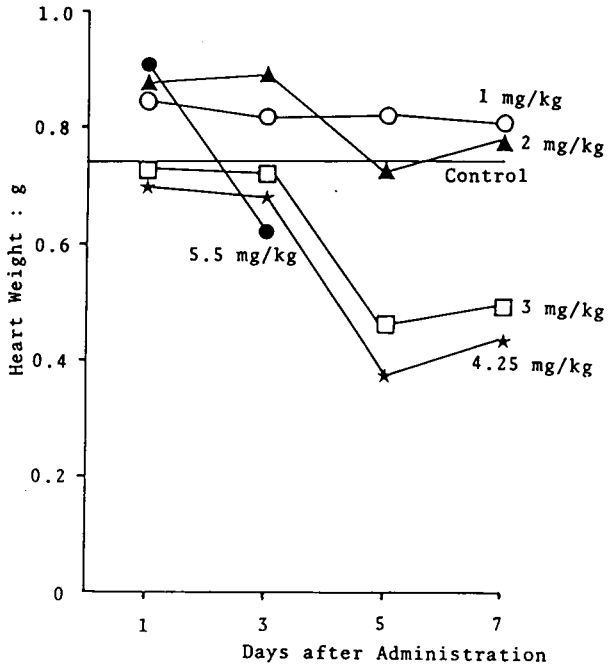

Fig. 1. Changes in heart weight of rats after a single administration of ADR.

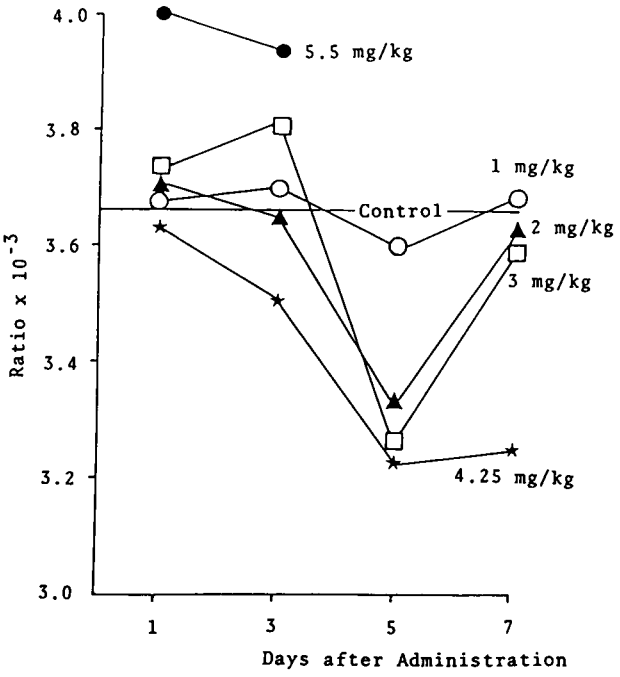

Fig. 2. Changes in ratio of heart to body in weight of rats after a single administration of ADR.

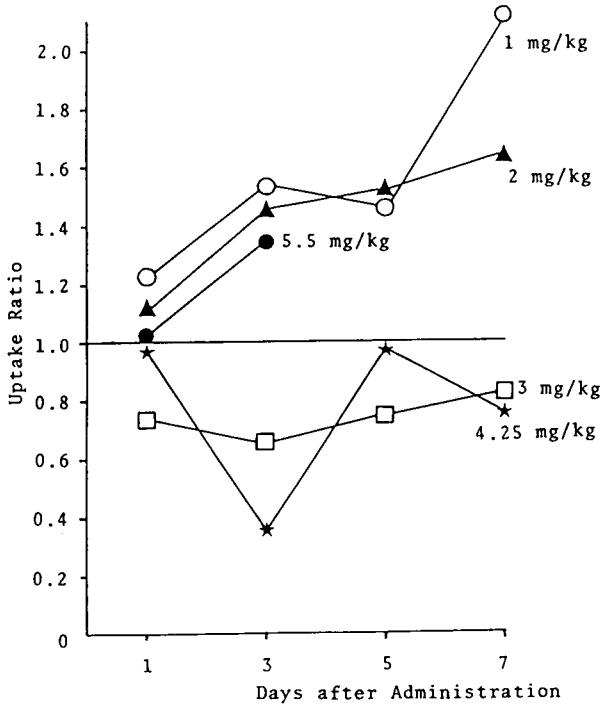

Fig. 3. Changes in F-18FDG uptake ratio.
Uptake ratio = % injected dose/g tissue of heart(ADR-administered)/
mean % injected dose/g tissue of heart(not ADR-administered).

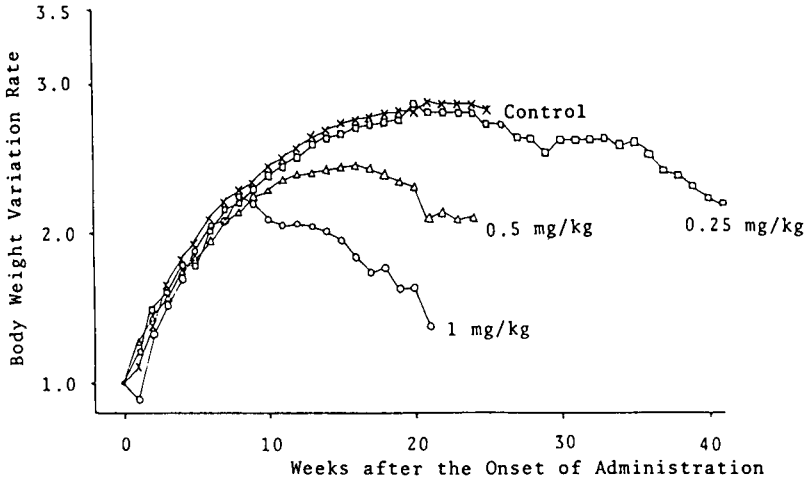

Fig. 4. Body weight variation rate of frequently ADR-administered rats.
Body weight variation rate = body weight after onset of
administration/body weight at onset of administration.
The rats were given ADR administration weekly.

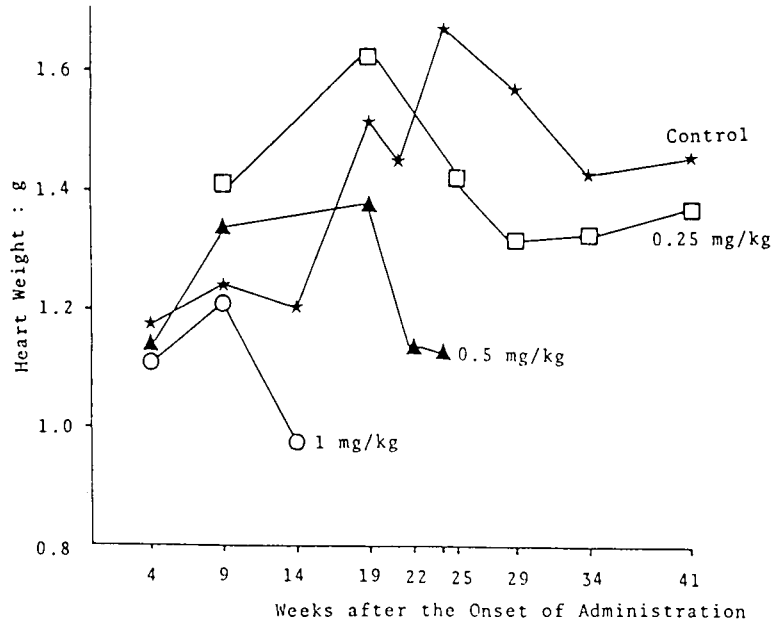

Fig. 5. Changes in heart weight of frequently ADR-administered rats. The rats were given ADR-administration weekly.

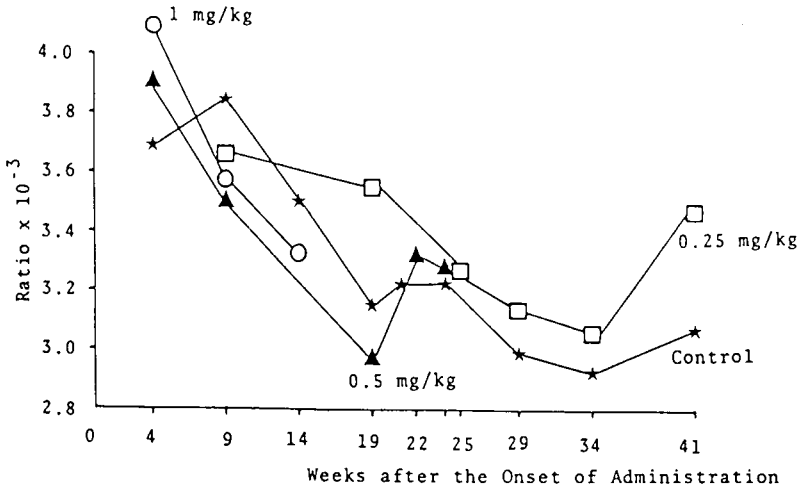

Fig. 6. Changes in ratio of heart to body in weight of frequently ADR-administered rats.
The rats were given ADR administration weekly.

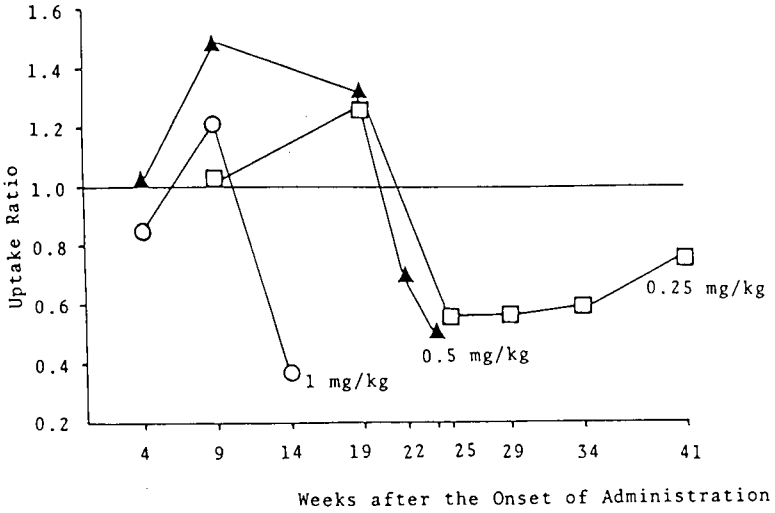

Fig. 7. Changes of F-18FDG uptake ratio of frequently ADR-administered rats. Uptake ratio = % injected dose/g tissue of heart(ADR-administered/ mean % injected dose/g tissue of heart(not ADR-administered). The rats were given ADR-administration weekly.