Original Articles

Uptake and Distribution of Daunorubicin and Daunorubicin-DNA Complex in Mice as Studied by Whole-Body Autoradiography and Liquid Chromatography

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Summary. The tissue distribution of daunorubicin (D) and daunorubicin-DNA complex (D-DNA) was studied in mice by means of whole-body autoradiography (WBA) and high-performance liquid chromatography (HPLC).

A higher accumulation of radioactivity in the blood after 1 min and a lower initial accumulation in the cardiac muscle were found after administration of 3H-D-DNA than after the injection of free drug.

Comparative studies of plasma levels of daunorubicin and daunorubicinol (DOH) in D- and D-DNA-treated animals by HPLC showed that the initial differences were negligible from 2 h onward.

A rapid accumulation of D in bone marrow occurred in both D- and D-DNA-treated mice. D reached its maximum level after 1 h and was almost constant for 12 h.

A new WBA finding was a rapid and specific accumulation of radioactivity in the pituitary gland, in the thyroid, and in the pancreatic islets, which might be of some interest in consideration of possible late endocrine side effects of anthraquinone glycoside therapy.

Introduction

The anthraquinone glycoside daunorubicin (D) has found widespread use in the treatment of acute leukemias. However, the use of the drug has been limited by its cardiotoxicity (e.g., Bonadonna et al., 1969; Jaenke, 1974). The mechanism responsible for the cardiac toxicity is unknown, although several hypotheses have been put forward (for review see Chabner et al., 1977). Chemical modification of the anthracycline molecule (Hurwitz et al., 1975; Israel et al., 1975; Lenaz et al., 1974) and an adjustment of the treatment schedule (Weiss et al., 1976) have been proposed to attenuate this severe side effect.

Another approach is to link D to deoxyribonucleic acid (DNA) (Trouet et al., 1972). The D-DNA complex is thought to be preferentially taken up by cells capable of extensive endocytosis, thereby minimizing the localization of the drug in the cardiac muscle and increasing the uptake in the tumor tissue. The D-DNA complex has been shown to retain an antileukemic effect in mice (Trouet et al., 1972; Henry, 1974; Ohnuma et al., 1975) and has recently been tested in humans (Sokal et al., 1973; Cornu et al., 1974). The work on rats (Langslet et al., 1974) and rabbits (cited in Chabner et al., 1977) indicates that daunorubicin and adriamycin complexes with DNA are less cardiotoxic. However, the scarcity of data on the distribution of D-DNA in the body (Ohnuma et al., 1975) and the cardiotoxicity of the drug make it imperative to pursue further studies of this therapeutic approach.

In the present investigation the uptake and distribution of 3H-D and 3H-D-DNA in the heart and other tissues of mice have been studied with whole-body autoradiography (1) to obtain more detailed information on the specific sites of accumulation and to focus attention on any possible new site of action of the drugs in the body, and (2) to elucidate further the possible differences in the accumulation of D and D-DNA in heart muscle and its relation to other tissues. We used whole-body autoradiography for its superiority in detecting the drugs within organs composed of heterogenous tissues, such as pancreas or gastric wall. The concentration of D and its main reduced metabolite daunorubicinol (DOH) in plasma and bone marrow was studied by liquid chromatography (Eksborg, 1978).

Materials and Methods

Labeled Compounds

3H-Daunorubicin (H-D) randomly labeled (specific activity 0.1 mCi/mg) was supplied by Pharma-Rhodia (Copenhagen). The radiochemical purity was checked by thin-layer chromatography with ra-
Fig. 1. Whole-body autoradiogram of a female mouse 1 min after an IV injection of $^3$H-D (A) and $^3$H-D-DNA (B). Light areas correspond to the high uptake of radioactivity. Note the difference in concentration of isotope in the blood. In the heart muscle a higher uptake of radioactivity can be seen after the injection of $^3$H-D (A) than after $^3$H-D-DNA (B). Exposure time: 29 days. Section thickness: 20 μm