Disposition of DX-52-1, a novel anticancer agent, after intravenous administration to mice and dogs

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SUMMARY

DX-52-1 is a new derivative of a quinocarmycin analogue. The disposition of [³H]-DX-52-1 was investigated in mice and dogs after intravenous administration (4 and 0.15 mg/kg, respectively).

The plasma concentration of non-volatile radioactivity was 7.4 μg eq/ml 3 min after administration to mice, then declined biphasically until 2 h. The distribution of non-volatile radioactivity into blood cells was 20% 3 min after administration, being maintained until 30 min. The plasma concentration of unchanged drug was almost equal to that of the radioactivity 3 min after administration and the unchanged drug ratio decreased rapidly. High radioactivity was found in the gall bladder, kidney, liver, and lung 15 min after administration. No radioactivity was detected in most tissues 24 h post-administration. The cumulative excretion of total radioactivity into urine and feces after administration was 68 and 28% within 96 h, respectively.

The plasma concentration of non-volatile radioactivity was 0.65 μg eq/ml 3 min after administration to dogs. The distribution of non-volatile radioactivity into blood cells was about 20% 3 min after administration and this level tended to increase with time. The cumulative excretion of total radioactivity into urine and feces after administration was 62 and 24%, respectively.

INTRODUCTION

A novel antibiotic, quinocarmycin, demonstrating moderate activity against Gram-positive but not Gram-negative bacteria, was isolated from a culture broth of Streptomyces melanovinaceus (1,2). The compound exhibited cytotoxic activity in a variety of murine and human tumors (1–6). In particular, it was shown to exhibit specific activity against the melanoma and breast carcinoma subpanels in the National Cancer Institute (NCI) human tumor line screen (7,8). DX-52-1 was a more stable analogue of quinocarmycin and was formed by hydrocyanation of quinocarmycin (9,10). Because of the lack of effective agents for the treatment of human melanoma, DX-52-1 was a candidate for clinical study by the NCI. In the present study, we investigated the blood/plasma concentration, distribution and excretion in male mice and the blood/plasma concentration and excretion in dogs after intravenous
bolus administration of [3H]-DX-52-1 (4 and 0.15 mg/kg, respectively). The disposition of DX-52-1 was studied in mice treated with 12 mg/m² (4 mg/kg), which represents a toxic dose low in beagle dogs on the basis of body surface area, following a 6 h i.v. infusion on days 1, 8 and 15 involving a total dose of 36 mg/m². The disposition of DX-52-1 was studied in dogs treated with 3.3 mg/m² (0.15 mg/kg), which represents one-tenth a minimal lethal dose (1.5 mg/kg) in beagle dogs, following an intravenous bolus administration. The total radioactivity may contain volatile components, mainly 3H₂O and so the non-volatile radioactivity after freeze-drying plasma/blood was measured. Both total and non-volatile radioactivity in urine and feces were measured.

MATERIALS AND METHODS

Chemicals

DX-52-1 (NSC 607097) and the radiolabeled compound ([3H]-DX-52-1, Fig. 1) were synthesized in our laboratories. Radiochemical purity was determined by thin-layer chromatography (TLC, Silica gel 60F, CH₃CN:H₂O:CH₃COOH - 90:10:1 v/v/v) was over 97% and the specific activity was 0.32 TBq/mmol (0.90 GBq/mg). The labeled compounds were diluted with non labeled DX-52-1 before each experiment. All other reagents and solvents were of analytical grade.

Animals

Male CDF1 strain mice of 5 weeks of age (Charles River Japan, Inc., Yokohama, Japan) weighing 21–24 g and male beagle dogs of 36 months of age (HRP, Kalamazoo, MI, USA) weighing 10–11 kg were used. Mice were given a standard diet (CL-2, Clea Japan, Inc., Tokyo, Japan) and water ad libitum, housed in a temperature (22 ± 1°C), and humidity (55 ± 5%) controlled environment with a 12 h light/dark (light : 7:00–19:00) cycle for 6 days. Dogs were given a standard diet (ED-1, Sanwa Chemical Research Co., Nagoya, Japan) and water ad libitum, housed in a temperature (23 ± 3°C) controlled environment with a 12 h light/dark (light : 7:00–19:00) cycle for 29 months. The animals without any abnormality were used for the experiments. The numbers of mice for blood/plasma concentration and distribution measurement were 3 and 1 per designated time point, respectively. The number of mice for the excretion measurement was 4. The number of dogs was 2.

Drug administration

After drying [3H]-DX-52-1 in toluene-ethanol (70:30 v/v) under nitrogen, unlabeled DX-52-1 in physiological saline solution was added to the residue. The drug solution was injected into the tail vein of mice and the cephalic vein of dogs at a dose of 4 mg/0.2 ml/kg and a dose of 0.15 mg/0.2 ml/kg, respectively. Drug was administered to the animals under non-fasting conditions.

Blood/plasma concentration

Blood was collected from the femoral artery and vein of each mouse under light ether anesthesia at intervals until 96 h after dosing. As for dogs, blood was withdrawn from the cephalic vein opposed to the dosed vein. After freeze-drying (Laboconco freeze dryer, Laboconco Co., Kansas City, MO, USA), the samples were dissolved in 5 times their volume of Soluene-350/isopropyl alcohol (1:1, v/v) under 50°C overnight, and decolorized with 30% H₂O₂, twice the blood volume overnight. After adding Hionic Fluor (Packard Japan Co. Ltd, Tokyo, Japan) 100 times the volume of the blood samples, the samples were kept in the dark for several days and their non-volatile radioactivity was counted. The plasma samples obtained from the remaining blood were freeze-dried and dissolved in 40 times their volume of liquid scintillator, Ultima Gold (Packard Japan) and their non-volatile radioactivity was counted. Collection time points were as follows: 0.05, 0.1, 0.167, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 24, 48, 72 and 96 h for mice and 0.05, 0.1, 0.167, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 24, 48 and 72 h for dogs.