Disposition of $[^3H]$Actinomycin D in Tumor-bearing Mice

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SUMMARY

A single, nonlethal dose of actinomycin D will cause total regression and cure of Ridgway osteogenic sarcoma in mice. A cure is not obtained with a single dose daily for 7 days. a dose regimen which kills 10% of normal C57BL/6 x DBA/2 mice. This suggests that actinomycin D is more effective on a single high-dose schedule than on chronic daily therapy. Analysis of drug exposure in Ridgway osteogenic sarcoma and normal mouse tissues following the single and multiple-dose regimens suggests the difference in therapeutic response is due to drug exposure at a higher concentration in Ridgway osteogenic sarcoma after the single high dose than after the multiple-dose regimen. This may be related to the higher drug concentration attained in blood following the single-dose regimen than is attained with the multidose regimen.

INTRODUCTION

Following a single, nonlethal dose, actinomycin D will cure罗斯1 mice (14-16). However, actinomycin D failed to produce a cure when administered each day on a 1- to 7-day schedule up to the LD_{50} dose (11). The total doses in both cases are similar (500 and 560 μg/kg).

Toxicity data for mice and rats indicate that the total LD_{50} dose for actinomycin D remains fairly constant over a wide range of dose schedules, provided that the intervals between doses do not allow time for host recovery from drug damage to normal tissues (4, 11). Toxicity studies in dogs indicate that fractionation of the dose reduces drug toxicity (6, 7).

This study was undertaken in order to evaluate drug exposure in tumor and normal mouse tissues following the single and multiple drug-dosing regimens used by Schabel (14) and to correlate tissue drug exposure with drug toxicity in tumorous and normal tissues.

RESULTS AND DISCUSSION

Charts 1 to 3 illustrate the experimental data of selected tissues and tumor for both dose regimens used. A pattern
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Chart 1. Small intestine levels of [3H]actinomycin D in male ROS-bearing AKD2F, mice. est., estimated.

Chart 2. Kidney levels of [3H]actinomycin D in male ROS-bearing AKD2F, mice. est., estimated.

Chart 3. ROS levels of [3H]actinomycin D in male AKD2F, mice. est., estimated.

The results of this investigation are consistent with our previous report (3) that the depletion of actinomycin D from tissues of various mammalian species may be described by a 1st-order process. A comparison of the estimates of tissue drug exposure (Table 1) following the 2 dose regimens suggests greater drug exposure to most normal tissues and tumor following the single-dose regimen. Although the evaluation of tissue drug exposure (C x T) is a useful tool for pharmacodynamic evaluation of drug dosing regimens, the concept (2, 9) must be applied with caution when evaluating cytotoxic agents in vivo. Cellular damage (morphological change) in ROS and some normal tissues following exposure to actinomycin D has been reported previously (15). Since this cellular damage may influence C x T values, and because a vividly conspicuous difference in estimates of total drug exposure in the tissues for the 2 dose regimens is not evident, an explanation for the difference in therapeutic response has not been interpreted from a comparison of C x T values.

Total urinary and fecal excretion of [3H]actinomycin D following single i.p. doses of 80 and 500 μg/kg was 30.5 and 31.5%, respectively, of the administered dose in the 1st 24 hr.

Toxicity. It has been reported that actinomycin D toxicity is cumulative over a wide range of dose schedules (4). This conclusion is largely attributed to results of studies in the mouse and rat, with lethality as the end point. Both drug regimens in this study have similar total doses which approach the highest nonlethal dose in the mouse. For both dose schedules, drug tissue concentrations attained were compatible with in vitro cytotoxic levels reported by Wilkoff et al. (18). Philips et al. (10) suggested that the lethal action of actinomycin D was due to damage of the intestinal mucosa, resulting in penetration of enteric toxins. This leads to the conclusion that in the mouse the toxicity of actinomycin D is cumulative over a wide range of dose schedules because the various schedules used all result in attainment and maintenance of drug levels sufficient to result in the necessary damage to intestinal mucosa to cause death. The long drug-depletion half-life and slow rate
of recovery of the small intestine from actinomycin D damage (10, 15) support this hypothesis.

**Drug Concentrations in Blood.** Serum concentrations of [\(^{3}H\)]actinomycin D following a single i.p. dose of 500 \(\mu\)g/kg were 0.066 at 3 hr and 0.012 \(\mu\)g/ml at 24 hr. Following the initial i.p. dose of 80 \(\mu\)g/kg, serum concentrations of drug were 0.006 and 0.003 \(\mu\)g/ml, respectively, at 3 and 24 hr. Serum concentrations of [\(^{3}H\)]actinomycin D were measured at 3 and 24 hr following subsequent i.p. doses of 80 \(\mu\)g/kg. The highest drug concentration in serum from mice on the multidose schedule was one-eleventh of the concentration following the single-dose regimen than is attained at any time with the multiple-dose regimen. Thus, higher tumor extracellular drug levels (both proximal to and distal from vascular bed) are attained following the single-dose regimen than following the multidose regimen. Following the single high dose, the tumor drug concentration was greater than 7 times the maximum concentration achieved following the multiple-dose schedule. This suggests that a similar higher drug concentration was achieved in all tumor cells, including cells that may exhibit altered drug transport characteristics. In this study, a higher blood level of the drug is attained following the single-dose regimen than is attained at any time with the multiple-dose regimen. Thus, higher tumor extracellular drug levels (both proximal to and distal from vascular bed) are attained following the single-dose regimen than following the multidose regimen. Following the single high dose, the tumor drug concentration was greater than 7 times the maximum concentration achieved following the multiple-dose schedule. This suggests that a similar higher drug concentration was achieved in all tumor cells, including cells that may exhibit altered drug cell membrane transport characteristics.

In progress in this laboratory are studies in the beagle dog comparing blood concentrations of [\(^{3}H\)]actinomycin D with time following a single high dose and a multidose regimen, with a similar total dose. Preliminary results demonstrate that the peak drug concentration in blood is related to the size of the dose and rate of administration. A comparative pattern similar to that reported for mice has been observed in dogs.

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