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Short Communications

Leukemic Cell Versus Plasma Levels of Daunorubicin and Daunorubicinol After Infusion of Daunorubicin as Free Drug or the DNA Complex

Börje Andersson and Miloslav Beran

Division of Hematology, Karolinska Hospital,
S-104 01 Stockholm, Sweden

SUMMARY

In two patients with acute non-lymphocytic leukemia, leukemic cell as well as plasma concentrations of Daunorubicin (D) and Daunorubicinol (DOH) were studied after administration of D as free drug or as a complex with DNA.

The peak plasma concentration of D was slightly higher after infusion of the D-DNA complex than after free drug while the intracellular pattern was the opposite. The intracellular peak concentrations were found to be 50-100 fold higher and displayed a kinetic pattern which was completely different from that of D in plasma.

We therefore suggest that assays of the concentrations of the drug and its toxic metabolite in leukemic cells are more relevant than the monitoring of plasma concentrations in the evaluation of the clinical effect of this drug's action.

INTRODUCTION

Monitoring of plasma concentrations of various drugs has proven useful in the development of treatment schedules. It has, however, been of uncertain value in the design of treatment regimes with anticancer drugs, with the notable exception of Methotrexate (5, 8, 13).

The organ distribution pattern of Daunorubicin (D) has shown large time related variations in the local concentrations of the drug, regardless of whether it has been administered as free drug or as a complex with DNA in the hope of a more selective leukaemic cell kill and/or a less pronounced cardiac toxicity (1, 3, 10, 14).

Since the concentrations of the drug in the target tissue along with the sensitivity of the tissue cells determine the drug effect, we were interested in the kinetics of D and Daunorubicinol (DOH) in the leukemic cell mass as compared to the plasma drug levels of patients on this treatment.

PATIENTS AND METHODS

The patients were considered comparable both having an acute myelo-monocytic leukemia. Their serum liver enzymes and kidney function tests were normal and the haematological data are shown in Table I.

Both patients received their first course of D to a total dose of 1.5mg/kg B.W. The female received the D as a free drug infusion for 4.1 hrs, total dose 115 mg. The male received the D-DNA as an infusion for 4.9 hrs, total dose 110 mg (6).

At appropriate time intervals during and after infusion, venous blood samples were taken. They were cooled on ice and after centrifugation at 4000 x G for 10 min at 2-4°C the plasma was aspirated and kept at -80°C until assay. The buffy coats were removed and after weighing (200-400 mg wet weight) they were resuspended in 1.5 ml phosphate buffer (pH 8.1 : u = 0.1) and sonified at 50 W for 30 secs prior to extraction and chromatographic analysis (4).

RESULTS AND DISCUSSION

The plasma and leukemic cell concentrations of D and DOH found in the two patients are shown in fig. 1.

A low D plasma peak was found during the infusion of the free drug. With infusion of the D-DNA the peak level was about twice that seen after the administration of free drug and the D disappeared from plasma at a slightly slower rate. The level of DOH and the pattern of its disappearance was similar after infusion of free and DNA complexed drug.

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TABLE I
PATIENT DATA

AGE / SEX	HEMOGLOBIN g / l	PLATELETS ($x10^9$ / l)	WHITE BLOOD CELLS		SERUM LYSOZYME mg / ml
			TOTAL ($x10^3$ / mm^3)	% BLAST CELLS	
20/M	61	12	58	68	88
45/F	82	106	64	77	158

The higher peak and slower disappearance of D after distribution and/or a slower metabolism of the complexed drug. This is in agreement with previously reported plasma pharmacokinetics of D and DOH in humans and rabbits given free and DNA complexed drug (9, 12) and might suggest that the D-DNA acts as a "slow release" preparation.

In the leukemic cells the D peak values were reached at the end of infusion of the free drug as well as the DNA complex. The initially slight difference in the intracellular D concentration between the patients had disappeared 5 hrs after infusion (Fig. 1).

Weighing of the buffy coat might seem an inexact method to compare the D concentration in plasma and leukemic cells. The advantage is that one ml of plasma can be approximated to one gram of cells. The contaminant of the buffy coat after centrifugation as described, is a little plasma and a few erythrocytes. The plasma was found to contain 50-100 times less DOH than the buffy coat when infusion had ceased. Erythrocytes have also been shown to retain D and DOH to a low degree (7). Thus the differences found using the present method would have been even higher had corrections been made for the plasma and erythrocyte content of the buffy coat.

As can be seen from figures 2 a and b there is a very low correlation between drug and metabolite concentrations in plasma and leukemic cells. The drug is rapidly cleared from plasma and much of it is retained in the leukemic cells which only slowly metabolize and excrete it. The intracellular concentration of D still exceeded 600 mg/g 12 hrs post infusion regardless of the form in which the drug is administered. This is important since a survival of less than 1% of leukemic clonogenic cells exposed for 1 h to a solution of 600 mg of D/ml medium has been reported (2).

It would seem that plasma concentrations of D and DOH poorly reflect drug concentrations in the target tissue in a non-steady state situation. We suggest it is more relevant to monitor concentrations of D and DOH in leukemic cells at the end of infusion and after another 8-10 hrs and to correlate the clinical response to intracellular peak concentrations and to the rate of disappearance of the drug and its metabolite from circulating leukemic cells.

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