Plasma Pharmacokinetics and Cerebrospinal Fluid Concentrations of Idarubicin and Idarubicinol in Pediatric Leukemia Patients: A Children's Cancer Study Group Report

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ABSTRACT

Idarubicin (4-demethoxydaunomycin) is an anthracycline analogue with striking in vitro and in vivo activity against murine leukemias. Based on activity in adults with acute lymphoblastic leukemia, the Children's Cancer Study Group initiated studies to evaluate idarubicin in children with leukemia in second or subsequent relapses. As part of those studies, we have characterized the plasma pharmacokinetics of idarubicin and the major circulating metabolite idarubicinol in 21 patients. Idarubicin plasma elimination was described by a three-compartment open model following i.v. infusion (10–15 mg/m²) on a schedule of weekly for 3 weeks and on a schedule of daily for 3 days every 3 weeks (total dose, 30–45 mg/m²). There was substantial variability in idarubicin elimination among patients, but no indication of dose-dependent or of schedule-dependent changes in pharmacokinetic parameters. The mean terminal half-life, total body clearance, and steady state volume of distribution were 17.6 h, 679 ml/min/m², and 562 l/m², respectively. Idarubicinol elimination was prolonged compared to that of the parent drug with a terminal half-life of 56.8 h. This metabolite clearly accumulated in plasma during the 3 days of treatment on the schedule of daily for 3 days. Urinary recoveries were 2- to 4-fold lower than those of daunomycin against human lymphoblastic leukemia cells in culture (6). Idarubicinol was detected in 20 of those 21 samples. Concentrations in the 20 samples varied from 0.22–1.05 ng/ml with a mean value of 0.51 ng/ml.

INTRODUCTION

Idarubicin (4-demethoxydaunomycin, Fig. 1) is an anthracycline analogue currently under evaluation for the treatment of adult and pediatric leukemias. Early clinical interest in this analogue was based on greater cytotoxicity against murine (1, 2) and human (3, 4) tumor cells in culture when compared to other anthracyclines. For example, idarubicin was 27- to 100-fold and 65- to 200-fold more toxic than daunomycin and doxorubicin, respectively, against HeLa cells (5). We recently determined that the 50% inhibitory dose values for idarubicin were 2- to 4-fold lower than those of daunomycin against human lymphoblastic (CCRF-CEM) and human myelogenous (K-562) leukemia cells in culture (6). Idarubicin was also more active in vivo against murine L1210 and P388 tumors when compared to daunomycin and doxorubicin (7, 8). Also of interest were findings in our laboratory and others that the major circulating metabolite of idarubicin, idarubicinol (Fig. 1), has substantial cytotoxic activity against tumor cells (2, 6, 9). This is in contrast to alcohol metabolites of other anthracyclines, such as daunomycin and doxorubicin, which are much less active than the parent drug (6, 10, 11). Idarubicinol may play a role in the antitumor activity of idarubicin.

In adult clinical trials, idarubicin was active in the treatment of lymphocytic and myelogenous leukemias (12). Based on the preclinical and adult clinical data, the CCSG3 initiated a phase I trial of idarubicin in children with second or subsequent relapses of acute lymphocytic and acute myelogenous leukemias. We now report the plasma pharmacokinetics of idarubicin and the alcohol metabolite idarubicinol as well as the presence of idarubicinol in CSF of these children following administration of idarubicin to patients participating in this phase I trial.

MATERIALS AND METHODS

Chemicals. Idarubicin, idarubicinol, and epirubicin were supplied by Adria laboratories. HPLC grade acetonitrile and methanol (EM Science), desipramine (Sigma Chemical Co.), and monobasic potassium phosphate (Baker analyzed, J. T. Baker) were used as received. Stock solutions of drugs and internal standards were prepared in HPLC mobile phase (see below) containing desipramine (10 μg/ml) in silanized glass vials.

Patients. The 21 patients eligible for this study were between 1 and 21 years of age with leukemia in second or subsequent bone marrow relapse and had failed higher priority CCSG protocols or other standard therapy. Patients had a Karnofsky performance status >30, normal organ function, and a life expectancy of 4 weeks or more. All patients had recovered from the toxicity of previous therapy, had received <325 mg/m² of anthracyclines, had not previously received idarubicin, and had not received anticancer therapy for at least 3 weeks (unless their disease progressed during that period as evidenced by an increasing peripheral blast cell count or an increasing percentage of marrow blast cells). Patients were required to have measurable disease without clinical signs of CNS relapse at the initiation of treatment. Three patients were found to have blast cells in their CSF. Fourteen of the 21 patients had received CNS radiation prior to study, and 15 had received intrathecal therapy. Signed, institutionally approved informed consent was obtained from all patients and/or their guardians. Idarubicin (10, 12.5, 13.5, and 15 mg/m²) was administered by i.v. infusion (10–45 min) once daily for 3 days every 3 weeks or once weekly for 3 weeks.

Samples. Patient whole blood samples (4 ml) were collected in heparinized tubes and cooled immediately in ice-water. Plasma was isolated by low speed centrifugation, transferred to plastic tubes, capped, and immediately frozen. Samples were obtained prior to drug administration and 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 h after drug administration on day 1 of the schedule of once weekly for 3 weeks or on day 3 of the schedule of once daily for 3 days every 3 weeks. Samples were also obtained prior to drug administration and 12 h after drug administration on days 1 and 2 of the once daily for 3 days every 3 weeks schedule.

As specified in the protocol, lumbar puncture was done 18–30 h after the first dose during the once weekly for 3 weeks schedule and 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 h after drug administration for patients receiving once daily for 3 days every 3 weeks.

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3 The abbreviations used are: CCSG, Children's Cancer Study Group; CSF, cerebrospinal fluid; HPLC, high performance liquid chromatography; CNS, central nervous system; Vdss, total body clearance; t1/2, mean terminal half-life; Vdss, steady state volume of distribution.

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after the third dose during the once daily for 3 days every 3 weeks schedule in patients without signs or symptoms of CNS disease. An aliquot of that clinical CSF specimen (2 ml) was frozen for determination of idarubicin and idarubicinol.

Urine was collected only during the weekly schedule in separate containers from 0–24 h and from 24–48 h after the administration of the first dose of idarubicin. The specimens were refrigerated during the collection period. Following each collection period the total volume was noted and an aliquot frozen for determination of idarubicin and idarubicinol.

Sample Preparation. Epirubicin (100 ng/20 μl) was added to standard curve or thawed patient plasma aliquots (1.5 ml) as internal standard. Plasma was diluted with an equal volume of 25 mM potassium phosphate buffer (pH 3.0). All three molecules were isolated from biological samples by solid phase extraction with 1-ml Baker C18 SPE columns. Prior to sample addition, columns were rinsed with 2 ml each methanol, distilled water, and 25 mM potassium phosphate buffer (pH 3.0). Following sample application, columns were washed with 2.5 ml 25 mM potassium phosphate buffer (pH 3.0), 2 ml distilled water, and the three anthracyclines eluted with 1 ml methanol/25 mM potassium phosphate buffer, pH 3.0 (9/1). Solvent was evaporated under a gentle stream of nitrogen and the residue reconstituted in 0.25 ml mobile phase containing desipramine (10 μg/ml) added to prevent adsorption to glassware. CSF (2 ml) and urine (0.1 ml) diluted with normal saline (0.9 ml) were extracted by the same column procedure and the residue was reconstituted in 0.2 ml (CSF) or 0.25 ml (urine) mobile phase. Recoveries of idarubicin, idarubicinol, and epirubicin from plasma were 92, 91, and 93%, respectively. Idarubicin and idarubicinol concentrations were determined by fit of unknown sample drug/internal standard peak height ratios to the linear regression equations derived from standard curves.

HPLC Assay. Idarubicin and idarubicinol were determined by a modification of the reverse phase HPLC procedure of Pizzorno et al. (13). Separation was achieved on an IBM C18 HPLC column (25 cm x 4.6 mm i.d.; 5 μm) and Brownlee guard column (15 x 3.2 mm i.d.; 7 μm). The mobile phase consisted of acetonitrile, methanol, and 50 mM potassium phosphate buffer, pH 4.5 (45/10/45). Eluting materials were detected by fluorescence (excitation wavelength, 254 nm; emission wavelength, >440 nm). Plasma and urine standard curves were linear over the range of 0.25–100 ng/ml for idarubicin and idarubicinol. CSF standard curves were linear from 0.15–5.0 ng/ml. Representative patient plasma chromatograms from blood samples obtained prior to and after administration of idarubicin are illustrated in Fig. 2.

Analysis of Pharmacokinetic Data. Plasma idarubicin concentration data were fitted to the equation \( Y = A e^{-\alpha t} + B e^{-\beta t} + C e^{-\gamma t} \) by nonlinear regression using the program NONLIN (14) on a CDC Ciber 170–720 computer equipped with interactive graphic analysis. A weighting factor of 1/\( Y \), where \( Y \) is the plasma concentration at time \( t \) following administration of the drug was used. \( A, B, \) and \( C \) are intercepts at \( t = 0 \) and \( \alpha, \beta, \) and \( \gamma \) are the disposition rate constants. The plasma elimination half-life of idarubicin was estimated by graphic analysis. Values of \( Cl_{\text{ra}} \) and \( Vd_{\text{a}} \) were adjusted for duration of infusion and multiple dosing (15).

RESULTS

Plasma Pharmacokinetics. Plasma elimination of idarubicin and idarubicinol were characterized following i.v. administration of idarubicin (10–45 min) on the once daily for 3 days every 3 weeks and the once weekly for 3 weeks schedules. Representative patient plasma profiles for idarubicin and idarubicinol following administration of idarubicin once weekly for three weeks and once daily for three days are shown in Figs. 3 and 4, respectively. Individual patient pharmacokinetic data are summarized in Table 1. Plasma elimination of idarubicin was described by a three-compartment open model with \( t_{1/2\gamma} \), \( Cl_{\text{ra}} \), and \( Vd_{\text{a}} \) values of 17.6 h, 679 ml/min/m², and 562 liters/m², respectively. There was significant interpatient variability in the pharmacokinetic data (Table 1). Pharmacokinetic data were similar for repeated weekly courses of idarubicin in the two patients in whom pharmacokinetic studies were repeated (data not shown). Idarubicinol was detected soon after parent drug administration, and concentrations of idarubicinol were greater than those of parent drug within 4–6 hours of drug administration. Plasma elimination of the alcohol (\( t_{1/2\gamma} \) 56.8 h) was greatly prolonged relative to that of parent drug (\( t_{1/2\gamma} \) 17.6 h). Following daily administration of idarubicin, plasma concentrations of idarubicinol were 5- to 10-fold greater than parent drug during most of the 3-day treatment period. Idarub-
of the weekly regimen were analyzed for idarubicin and idarubicinol. Similar analyses were done with plasma obtained from blood samples drawn at approximately the same time as the CSF sample.

Idarubicin was detected in CSF from only 2 of 21 patients from whom CSF samples were obtained during the study (Table 2). Both patients received idarubicin by the once daily for 3 days every 3 weeks treatment schedule. Idarubicinol was detected in 20 of the 21 patients as detailed in Table 2. Idarubicinol CSF concentrations varied over the range 0–1.05 ng/ml, with a mean value of 0.51 ng/ml. On average, CSF concentrations of idarubicin were 4% of metabolite concentrations in plasma samples obtained at the same time. Insufficient CSF samples were available from the 12.5 mg/m² dose to determine the relationship between dose and idarubicinol CSF concentration on the once weekly for 3 weeks schedules. For the once daily for 3 days every 3 weeks schedule, the average (±SD) idarubicinol CSF concentrations were 0.57 (0.29) and 0.70 (0.27) ng/ml for the 12.5- and 13.5-mg/m² doses, respectively.

**DISCUSSION**

We have characterized the plasma pharmacokinetics of idarubicin and the alcohol metabolite idarubicinol in children receiving idarubicin as single agent therapy for relapsed leukemia. An important issue in such studies is the pharmacokinetic behavior of the drug in pediatric patients as compared to adult patients. While it is always difficult to compare results from widely divergent studies, data from this study and from published reports suggest that there are no major differences in idarubicin and idarubicinol pharmacokinetics in children (17) as compared to adults (18, 19). Our pediatric data for 21 patients were qualitatively similar to those of Tan et al. (17) for 7 patients. The terminal half-life value was somewhat prolonged in our study when compared to their results (17.6 versus 11.3 h). Of equal importance is the age dependence of pharmacokinetic parameters in pediatric patients receiving equivalent doses of the drug. In the limited number of patients studied, no
relationship was found between the age of the patients and the pharmacokinetic behavior of idarubicin and idarubicinol.

For both adult and pediatric patients, plasma elimination of idarubicin was characterized by a three-compartment open model, substantial exposure to the metabolite idarubicinol, and much slower elimination of the alcohol when compared to parent drug. The elimination half-life of idarubicin may be overestimated since the alcohol continues to be formed while idarubicin is present in the body. This pattern of prolonged alcohol elimination relative to parent drug elimination is similar to that observed for anthracyclines, such as daunomycin (20), and in contrast to anthracyclines, such as Adriamycin. Daunomycin has a greater affinity for aldo-keto reductase than does doxorubicin, and this may be the case for idarubicin as well. In the latter case, the alcohol metabolite is eliminated at essentially the same rate as parent drug, and plasma concentrations of the alcohol are rarely greater than those of the parent drug (20).

The findings with regard to idarubicin are important not only as a mechanism of idarubicin elimination but also in light of data concerning the cytotoxicity of idarubicinol and idarubicin against tumor cells. Most side chain alcohol metabolites of anthracycline-like agents are much less potent than the parent drugs in terms of cytotoxicity against tumor cells in culture (10, 11). We found this to be true in studies with Adriamycin, daunomycin, and epirubicin using human lymphoblastic and myelogenous leukemia cells. In marked contrast, idarubicinol was almost equitoxic with idarubicin in both cell lines (6). These data suggest that idarubicin is an atypical anthracycline anticancer agent in that patients are exposed to two very cytotoxic species rather than to an active parent drug and a much less active major circulating alcohol metabolite.

Discussions of anthracycline pharmacology rarely note their presence in the CNS following parenteral administration, and they are not considered in the treatment of CNS disease. Our analysis of CSF samples was based primarily on one report that idarubicin was detected in CSF following i.v. administration to an adult leukemia patient (16). It was particularly surprising to detect idarubicinol in all but one patient given its greater polarity compared to idarubicin.

It is difficult to predict the relationship between CSF and plasma concentrations of idarubicin at times other than those (18–30 h) for which we obtained samples. However, we would predict that idarubicin would be detectable in CSF at earlier time points following i.v. administration. More important, based on plasma elimination data, we would predict that idarubicinol is present (most likely at higher concentrations) at times earlier than 18–30 h and that levels may be sustained for several days due to the slow plasma elimination half-life (57 h). We have preliminary data showing that exposures of 0.5–1.0 ng/ml idarubicinol for 3–5 days are cytotoxic to human leukemia cells in culture (6). Those exposure conditions may well underestimate the CSF exposure in patients. Thus, the presence of idarubicinol in CSF may warrant consideration in the treatment of diseases with CNS components.

4 M. J. Kuffel, J. M. Reid, and M. M. Ames, manuscript in preparation.

REFERENCES


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