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ORIGINAL REPORT

Asparaginase May Influence Dexamethasone Pharmacokinetics in Acute Lymphoblastic Leukemia

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ABSTRACT

Purpose
Dexamethasone is used widely in oncology, but pharmacokinetic studies are lacking. We evaluated dexamethasone pharmacokinetics in children with acute lymphoblastic leukemia.

Patients and Methods
We assessed 214 children with acute lymphoblastic leukemia who received 418 courses of oral dexamethasone (8 mg/m^2/d) on days 1 and 8 of reinduction. Extensive asparaginase use preceded reinduction in the 101 children in the standard/high-risk treatment arm but not in the 113 children in the low-risk treatment arm. A one-compartment model with first-order absorption and disposition was fit to dexamethasone plasma concentrations by using maximum a posteriori probability estimation; we evaluated covariates by using linear mixed models.

Results
Interpatient and intrapatient variabilities in apparent clearance were substantial; they were 46% and 53%, respectively. Variability was explained by the serum albumin concentration ($P < .0001$), concomitant use of fentanyl ($P = .008$) and ketoconazole ($P = .03$), and age ($P = .006$). Apparent clearance was higher in the low-risk arm ($P < .001$) and was related to a greater serum albumin concentration ($P < .001$) and to a lower exposure to asparaginase than in the standard/high-risk arm. Hypoalbuminemia, a biomarker of asparaginase activity, was associated with a lower dexamethasone apparent clearance ($P = .04$) in patients in the standard/high-risk arm that was more pronounced in those not allergic to asparaginase. Ethnicity or gender did not explain apparent clearance variability.

Conclusion
Dexamethasone pharmacokinetics are highly variable and are related to the concurrent use of particular drugs, age, and treatment intensity. Patients allergic to asparaginase may be doubly disadvantaged: they not only suffer from diminished exposure to asparaginase but also, by maintaining high clearance of dexamethasone, may experience fewer antileukemic effects of dexamethasone.

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INTRODUCTION

Glucocorticoids are used extensively in adult and pediatric oncology as antileukemic,[1,2] anti-inflammatory,[3] and antiemetic agents.[4-6] Although dexamethasone is useful in many settings, including in the treatment of childhood acute lymphoblastic leukemia (ALL), adverse events may be dose-limiting.[7] In other patient populations (eg, organ transplant recipients), both desired and adverse effects are dose-related and may be related to pharmacokinetic variability, but there are no prior pharmacokinetic studies of dexamethasone in patients with ALL, and there are few studies in adult patients with cancer.[8,9] To our knowledge, only a single pharmacokinetic study of dexamethasone in children (without ALL) has been reported,[10] which showed a high variation in pharmacokinetics. Because of the limited nature of prior studies, the extent of inter- and intrapatient variability in dexamethasone pharmacokinetics among cancer patients, as well as the covariates for such variability, remains unclear.

Our objectives were to characterize the pharmacokinetic parameters of dexamethasone among children with ALL in a controlled trial, to estimate intrapatient and interpatient variability in the systemic exposure to the drug, and to explore the contribution of covariates to variability in dexamethasone pharmacokinetics.

PATIENTS AND METHODS

Patients

We studied 214 children with ALL who were treated on protocol Total XV at St Jude Children's Research Hospital from July 2000 until December 2005.[11] The institutional review board approved the study, and informed consent was obtained from parents/guardians or from patients.

Patients were assigned to one of three risk categories: low, standard, or high risk, as described previously.[11] Younger children were more likely to be assigned to the low-risk group, whereas older children were more likely to be assigned to the standard- or high-risk groups. Asparaginase allergy was graded by using the National Cancer Institute Common Toxicity Criteria version 2.0, and patients were categorized as those with no toxicity (grade 0) and those with grade 1 to 4 allergy before week 7 of continuation therapy (start of reinduction I).

Treatment Regimen and Sample Collection

Therapy differed by risk arm (Table 1).[11] Patients in the standard/high-risk arms received identical therapy during weeks 1 to 9 of continuation therapy (the period of this analysis).

Dexamethasone 8 mg/m^2/d was given orally as tablets and was divided equally into three doses per day during days 1 through 8 of reinduction. The concomitant use of other drugs in the 72 hours before and 24 hours after dexamethasone was recorded by a pharmacokinetics research nurse (Appendix Table A1, online only).

Blood (3 mL) was drawn into heparin-containing tubes before and 1, 2, 4, and 8 hours after the morning dexamethasone dose on days 1 and 8 of reinduction I, which corresponded to weeks 7 and 8 of continuation treatment, respectively. Plasma was stored at −80°C.

Dexamethasone Concentrations

Dexamethasone and triamcinolone acetonide 10 μL (1 μg/mL in 20% methanol) as a qualitative internal standard were extracted from plasma (500 μL) by solid-phase reversed-phase C_{18} columns. The loaded column was washed with 20% acetonitrile (2 mL), was eluted with methanol, was dried by evaporation, and was reconstituted with 20% methanol (75 μL). The supernatant was injected into the high-performance liquid chromatography system with a diode array detector (Shimadzu, Columbia, MD) and a 150 × 2.0 mm Phenomenex Luna $C_{18}(2)$ column (5 μm; Phenomenex, Torrance, CA). The mobile phase was 83.75% water, 10% acetonitrile, 6.25% 1-butanol, and 0.0985% phosphoric acid (v/v), and the rate was 0.4 mL/min. At 254 nm, the detection limit was 1.36 nmol/L (0.45 pmol on column). Only 15 of 418 courses had 8-hour concentrations less than the detection limit; extracting increased volumes allowed an estimation of the concentration for some of these samples. When using the peak height, the assay was linear from 10 to 200 nmol/L, and the recovery was greater than 95% (as a measured concentration relative to target concentration × 100%). The inter- and intraday coefficients of variation were less than 10% for the high (160 nmol/L) and low (20 nmol/L) controls. Duplicates for the calibrators and controls were reproducible within 100% ± 10%, and they had a coefficient of variation less than 10%. The glucocorticoids prednisone, cortisol, and beclomethasone did not interfere with dexamethasone peak quantification. Periodically, absorbance scans for peaks in unknowns with the proper retention time for dexamethasone were confirmed by using the scanning array feature of the detector.

Pharmacokinetic Model

Pharmacokinetic parameters were estimated by fitting a one-compartment model to the plasma concentration-time data by using maximum a posteriori probability estimation, as implemented in ADAPT II (Biomedical Simulations Resource, Los Angeles, CA).[12] Parameters included the apparent volume (V/F; F was bioavailability), the elimination rate constant (ke), the first-order absorption rate constant (ka), and the time delay between the drug administration and its distribution into the central compartment. Standard equations were used to calculate the apparent clearance (CL/F; equal to ke × V/F) and half-life ($t_{1/2}$; equal to 0.693/ke).

The model-fitted curve for each patient was used to estimate the area under the concentration-time curve (AUC) from time 0 to 8 hours ($AUC_{0\rightarrow 8\ hours}$).

The population pharmacokinetics were determined using a two-stage approach.[13] In the first stage, the pharmacokinetic parameters for each individual course were estimated as above. The variance model of measured data, $C(t)$, was defined as:

$$Var\{V(t)\} = (\sigma_{inter} + \sigma_{slope}\, C(t))^2 \qquad (1)$$

in which $\sigma_{inter} = 0.25$ and $\sigma_{slope} = 0.1$, an error process with a coefficient of variation of 10%.

In the second stage, the population pharmacokinetics were determined by using linear mixed-effects modeling as implemented in R (version 2.4.1; www.R-project.org):

$$\ln(CL_{ij}) = \theta_1 + \sum_{k=2}^{n} \theta_k \cdot \text{covariate}_k + \eta_i + \varepsilon_{ij} \qquad (2)$$

in which CL_{ij} is the CL/F for patient i and course j; θ_1 is the logarithm of the population mean CL/F; θ_k are the coefficients for the effects of each covariate; and η and ε describe the interpatient and intrapatient variability, respectively. (Both are assumed to have a mean of zero.)

Table 1. First 9 Weeks of Continuation Therapy for Protocol Total XV

Week	Treatment Arms: Low Risk	Treatment Arms: Standard/High Risk
1	$DEX_{8\text{-}1}$ + $VCR_{2.0}$ + MP_{75}	DEX_{12} + $VCR_{2.0}$ + MP_{50} + DOX + ASP_{25}
2	MP_{75} + MTX	MP_{50} + ASP_{25}
3	MP_{75} + MTX	MP_{50} + ASP_{25}
4	$DEX_{8\text{-}1}$ + $VCR_{2.0}$ + MP_{75}	DEX_{12} + $VCR_{2.0}$ + MP_{50} + DOX + ASP_{25}
5	MP_{75} + MTX	MP_{50} + ASP_{25}
6	MP_{75} + MTX	MP_{50} + ASP_{25}
7	$DEX_{8\text{-}2}$ + $VCR_{1.5}$ + DOX + ASP_{10} × 3 + IT MHA	$DEX_{8\text{-}2}$ + $VCR_{1.5}$ + DOX + ASP_{25} + IT MHA
8	$VCR_{1.5}$ + ASP_{10} × 3	$VCR_{1.5}$ + ASP_{25} + DOX
9	$DEX_{8\text{-}3}$ + $VCR_{1.5}$ + ASP_{10} × 3	$DEX_{8\text{-}3}$ + $VCR_{1.5}$ + ASP_{25}

Abbreviations: $ASP_{10/25}$, L-asparaginase 10,000 U/m^2 or 25,000 U/m^2 intramuscularly; $DEX_{8\text{-}1/8\text{-}2/8\text{-}3}$, dexamethasone 8 mg/m^2/d orally for 5, 8, or 7 days, respectively; DEX_{12}, dexamethasone 12 mg/m^2/d orally for 5 days; DOX, doxorubicin 30 mg/m^2 intravenously; IT MHA, intrathecal methotrexate, hydrocortisone, and cytarabine; $MP_{50/75}$, mercaptopurine 50 mg/m^2/d or 75 mg/m^2/d orally for 7 days; MTX, methotrexate 40 mg/m^2 intravenously; $VCR_{2.0/1.5}$, vincristine 2.0 mg/m^2/dose or 1.5 mg/m^2/dose intravenously (maximum of 2 mg).

Covariate Analysis

Covariates (demographics, treatment arm, week of therapy, concomitant drugs [Appendix Table A1, online only], and serum albumin concentration) were investigated for their ability to significantly improve the model fit (by a reduction of at least 3.84 [$P < .05$] in the -2 log-likelihood, on the basis of the F test) and for the significance of corresponding parameter estimates θ_k (by θ_k differing from zero [$P < .05$], on the basis of the t test). Concomitant medications were grouped into 10 categories on the basis of the frequency of use and the likely pharmacokinetic consequences: doxorubicin, fentanyl, propofol, vincristine, antiviral agents, ketoconazole, antacid agents, CYP3A substrates, steroids, and inducers (Appendix Table A1, online only). The final regression model was selected by using stepwise regression.

Recursive partitioning (ie, classification and regression tree) also was used to test the interaction of covariates on dexamethasone CL/F. Because serum albumin concentration was a continuous variable, a cutoff value was chosen by using the model to split observations into two subgroups that best distinguished those with high versus low CL/F. At each step, the most predictive variable was determined by using linear mixed-effects modeling, and a cutoff for the predictive variable was chosen to split observations into two subgroups. This process was repeated for each subgroup until no variables were found to further accentuate the difference in CL/F between the groups.

Statistics

Analyses were performed by using R and Statistica software (version 7.0, 1995; StatSoft Inc, Tulsa, OK). The Wilcoxon rank sum and two-sample tests were used to test possible differences between groups. Population mean, regression coefficient, and intrapatient and interpatient variability were assessed by linear mixed-effects modeling. P values less than .05 indicated statistical significance.

RESULTS

Observed Demographics

We studied 212 courses on week 7 and 206 courses on week 8 in 214 patients (99 females and 115 males). Altogether, 407 courses were assessable, and 11 courses were excluded because the patients vomited within 1 hour of the dose, problems occurred with the IV line, or there was poor compliance in dosing or in blood sample collection.

One hundred thirteen patients were assigned to the low-risk arm (median age, 4.17 years; range, 1.25 to 18.4 years), and 101 patients were assigned to the standard/high-risk arms combined (median age, 8.17 years; range, 1.00 to 18.8 years).

Pharmacokinetic Parameter Estimates

There was substantial interpatient variability in dexamethasone pharmacokinetics (Fig 1, inset). Seven courses displayed an extreme CL/F, that is, a CL/F more than six-fold less than or greater than the population mean. Although no clear reason could be identified to explain these outlying data, the cause was likely a cryptic problem with dosing rather than extreme clearance. Interpatient and intrapatient variabilities in pharmacokinetics were extensive both when all observations (N = 407) and only those that excluded extreme outliers (n = 400) were analyzed (Appendix Table A2, online only).

Glucocorticoids are substrates for and inducers of drug-metabolizing enzymes and transporters.[14-17] Daily dexamethasone could cause autoinduction of clearance, inhibition of clearance, or a combination of both. To address intrapatient variability, we studied each patient twice, on day 1 (week 7) and day 8 (week 8) of an 8-day course of dexamethasone. The population mean CL/F at week 7 (15.5 L/h/m^2; standard error, 0.84 L/h/m^2) was greater than that at week 8 (12.4 L/h/m^2; standard error, 0.54 L/h/m^2; $P = .004$; Appendix Fig A1, online only). The mean ka was 1.5 hours^{-1}; mean V/F was 46.8 L/m^2; mean ke was 0.3 hours^{-1}; and mean $t_{1/2}$ was 2.3 hours (Appendix Table A2, online only).

Analysis of Covariates

There was a large range of dexamethasone systemic exposures despite administration of the same dose to all patients (Fig 1, inset). In the univariate analyses, we examined whether clinical or laboratory characteristics explained the variability in CL/F (Appendix Table A3, online only). A greater CL/F was associated with a younger age ($P < .001$) and a greater serum albumin concentration ($P < .001$; 355 courses in 207 patients; Fig 1). In the low-risk arm, the week of therapy (week 7); the concurrent use of fentanyl, propofol, doxorubicin, or ketoconazole; and the absence of antacid drugs or other steroids were associated with a greater CL/F (Appendix Table A3, online only). Other concomitant medications, ethnicity, and gender were not significant covariates for CL/F.

Albumin concentrations of patients on the standard/high-risk arms were less than those of patients on the low-risk arm at week 7 ($P < .001$); the means ($\pm$ standard deviations) were 3.13 $\pm$ 0.63 g/dL and 4.14 $\pm$ 0.32 g/dL, respectively (Fig 2A). This finding is consistent with hypoalbuminemia caused by asparaginase, to which patients on the standard/high-risk arm were more exposed (Table 1). Moreover, there was a substantial decrease in the albumin concentration in patients in the low-risk arm from weeks 7 to 8 ($P < .001$), which reflected the reintroduction of asparaginase during week 7 to the low-risk arm (Fig 2A).

An allergy to asparaginase before reinduction was more common among patients in the standard/high-risk arms (31 of 101) than among those on the low-risk arm (1 of 113). In the standard/high-risk arms, serum albumin and dexamethasone CL/F were significantly greater in patients who had developed an allergy to asparaginase than in those who had not ($P = .002$ and .04, respectively; Fig 2B). Allergy may inactivate asparaginase, and this inactivation results in lower systemic exposure to asparaginase. The net result would be less asparaginase-mediated inhibition of protein synthesis and, thus, a greater serum albumin.[18]

We built multivariate models to assess how covariates of CL/F might interact when we included all patients (n = 355 courses in 207 patients) and when we excluded the outlying courses (n = 348 courses in 204 patients; Table 2). The treatment arm, use of ketoconazole or fentanyl, age, and serum albumin were associated with CL/F. The inter- and intrapatient variabilities (expressed as a CV %) for CL/F of the final model decreased to 40% and 45%, respectively, from 51% and 51%, respectively, for CL/F of the base model when the outliers were included and to 32% and 41%, respectively, from 44% and 46%, respectively, when the outliers were excluded.

Classification and regression tree analysis was also used to assess covariates for CL/F. Serum albumin was the most significant predictor; results were similar when the outlying values (n = 7) were excluded (Fig 3) or included (data not shown). The best cutoff value for distinguishing those with low CL/F from those with high CL/F was 3.35 g/dL. In patients with low serum albumin, only age (with a cutoff of 10 years) was a significant predictor of CL/F. In those with high serum albumin, the most important determinant of CL/F was treatment arm: patients in the standard/high-risk arms had a lower CL/F than those in the low-risk arm. In patients in the low-risk arm, CL/F was lower at week 8 than at week 7 (Fig 3).

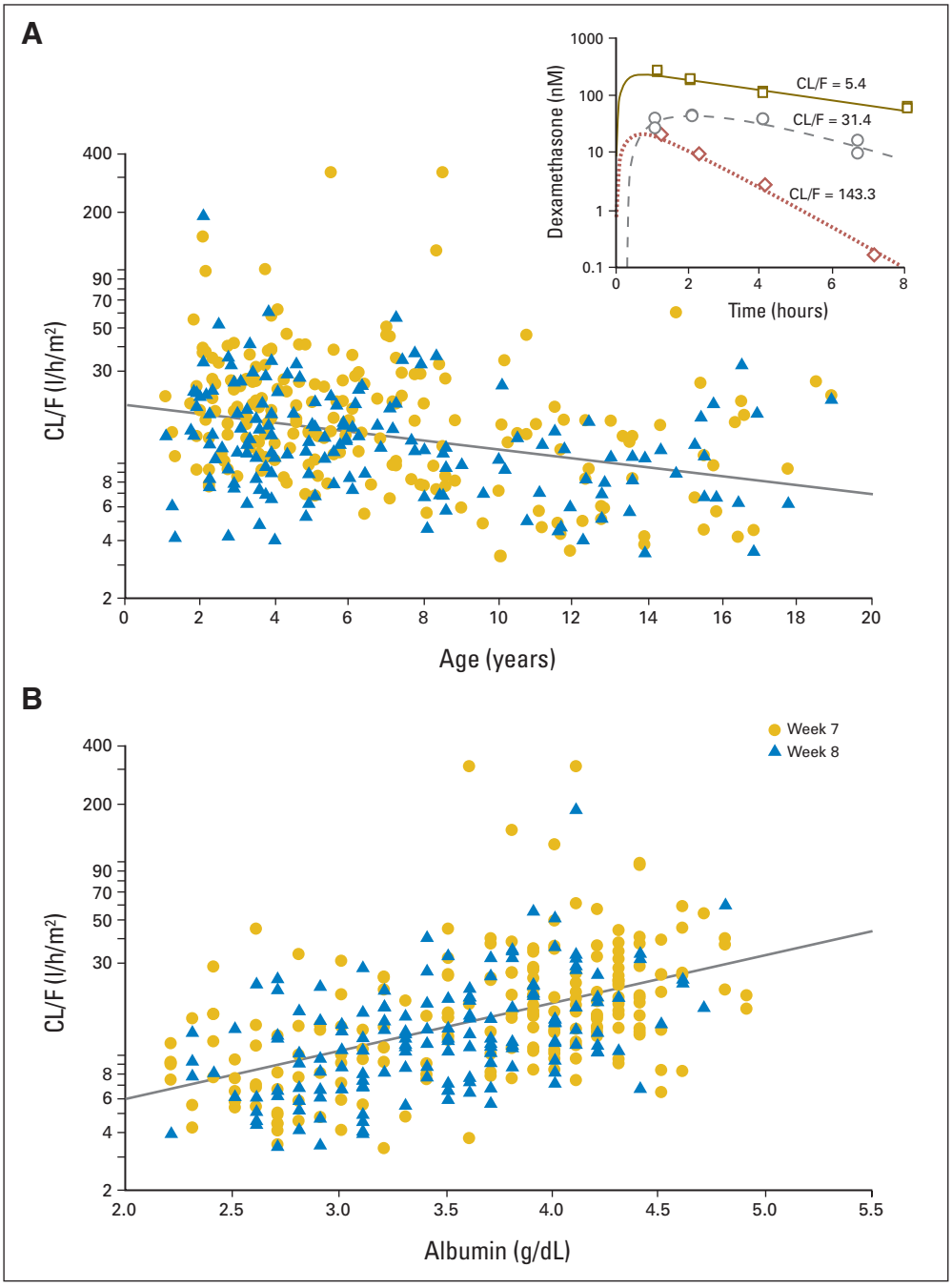

Fig 1. Upper inset: Dexamethasone concentration-time (nM·hour) plots for representative patients with a low, medium, and high apparent oral clearance (L/h/m^2). Dexamethasone apparent clearance (CL/F) is (A) negatively related to age ($P < .01$; $r = 0.14$) and (B) positively related to serum albumin concentration ($P < .001$; $r = 0.25$). Individual data points are shown for week 7 (circle) and week 8 (triangle), and the regression line is for all courses (n = 355).

DISCUSSION

Dexamethasone pharmacokinetic data in patients with cancer have been lacking. The present study is the first pharmacokinetic evaluation of dexamethasone in children with cancer or in any group of patients with ALL. The paucity of prior data is surprising, given the extent of dexamethasone use in oncology. Dexamethasone is a critical component of modern chemotherapy regimens for ALL, but there is uncertainty as to the optimal dosage; most trials use 6, 8, 10, or 12 mg/m^2/d. We observed high inter- and intraindividual pharmacokinetic variabilities (CV of 46% and 53%, respectively) in dexamethasone CL/F, which resulted in a more than 10-fold variability in systemic exposure to the drug at a uniform dosage of 8 mg/m^2/d; this variability dwarfs that anticipated when weighing, for example, 8 versus 12 mg/m^2/d for administered doses. The extensive variability led to an examination of covariates for CL/F, especially of predictors likely to change within patients and thus to explain the high intraindividual variability. The multivariate analysis showed that serum albumin and the treatment arm were strongly associated with CL/F; both covariates were plausibly linked by the more intensive use of asparaginase in the standard/high-risk arms than in the low-risk arm. Univariate

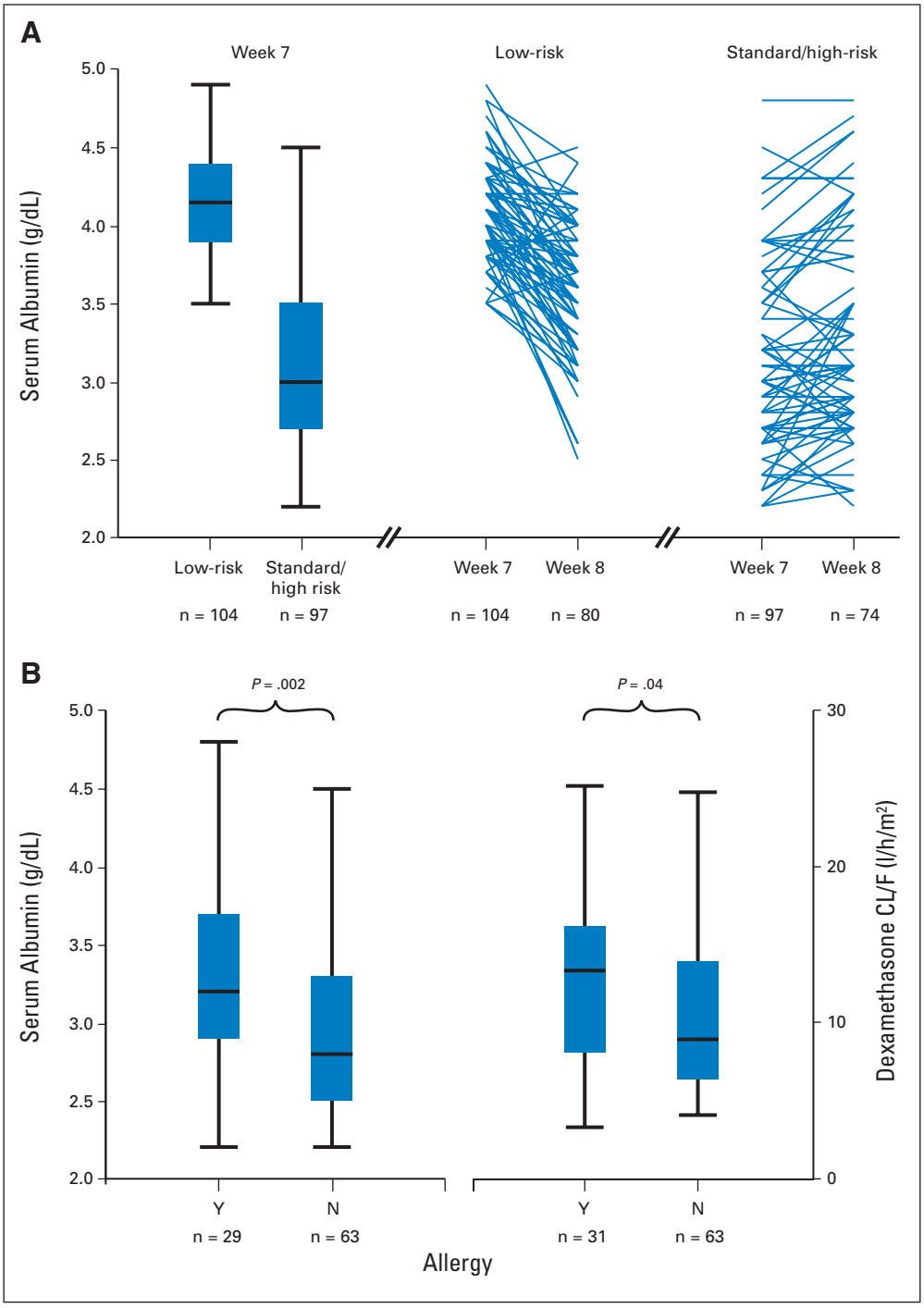

Fig 2. (A) Serum albumin concentrations were lower in the standard/high-risk arms than in the low-risk arm at week 7 ($P < .001$; box plots: quartiles, median, nonoutlier range). Decreases in albumin from weeks 7 to 8 were greater for the low-risk arm ($P < .001$) than for standard/high-risk arms ($P < .01$; n = 355 courses). (B) Serum albumin concentration and dexamethasone apparent clearance (CL/F) in patients (Y) who were allergic to asparaginase before week 7 and in patients (N) who were not.

analyses of other covariates indicated additional variables that may impact dexamethasone pharmacokinetics in other clinical settings.

Serum albumin was positively associated with CL/F (Fig 1B). A correlation between pharmacokinetic parameters and serum albumin has also been found for other drugs that are eliminated hepatically.[19-21] Serum albumin is a measure of hepatic function[22-24] and reflects the hepatic capacity to synthesize protein. Hypoalbuminemia is a well-recognized effect of asparaginase.[25] Although hypoalbuminemia may be caused by other factors, we hypothesize that albumin was variable partly because of prior asparaginase use and that decreased albumin may be a biomarker of impaired hepatic synthesis of proteins involved in dexamethasone clearance.[26]

The albumin concentration on the standard/high-risk arms was approximately 25% lower than on the low-risk arm (Fig 2A), which was consistent with greater prior exposure to asparaginase in the former group (Table 1). The dexamethasone CL/F (Fig 2B) and the serum albumin changes (Fig 2A) as a result of asparaginase explain much of the inter- and intraindividual variabilities in CL/F. Low albumin predicted low clearance; however, among those with low albumin concentrations, age predicted clearance (Fig 3). In those with

Table 2. Final Model to Predict Apparent Clearance With a Combination of Forward Selection and Backward Elimination Methods

Variable	Analysis			
	θ*	SE	t†	P
Including outliers (n = 355)‡				
Intercept	1.15§	0.22	5.28	< .0001
Low-risk arm	0.13	0.09	1.43	.15
With ketoconazole	1.19	0.55	2.15	.03
With fentanyl	0.14	0.05	2.69	.008
Age	−0.03	0.01	−2.78	.006
Albumin	0.43	0.06	7.05	< .0001
Excluding outliers (n = 348)				
Intercept	1.23§	0.19	6.57	< .0001
With fentanyl	0.10	0.05	2.14	.03
Low-risk arm	0.19	0.08	2.32	.02
With ketoconazole	1.14	0.49	2.33	.02
Age	−0.02	0.01	−2.61	.01
Albumin	0.39	0.05	7.18	< .0001

NOTE. Covariates tested include demographic features, treatment arm, week of therapy, albumin concentration, and concomitant drug use.

Abbreviation: SE, standard error.

*Sign for θ values indicates the negative or positive effect of each variable (eg, fentanyl use is associated with an increased CL/F, and increased age is associated with a decreased CL/F).

†The t value is number of standard errors the regression coefficient is away from zero. The greater the absolute t value, the greater the confidence in the coefficient as a predictor.

‡As blood chemistries were not tested for all patients at week 8 of continuation therapy, 52 observations with missing albumin concentrations were removed from the dataset when univariate, multivariate, and classification and regression tree analyses were performed.

§θ represents logarithm of the population mean parameter.

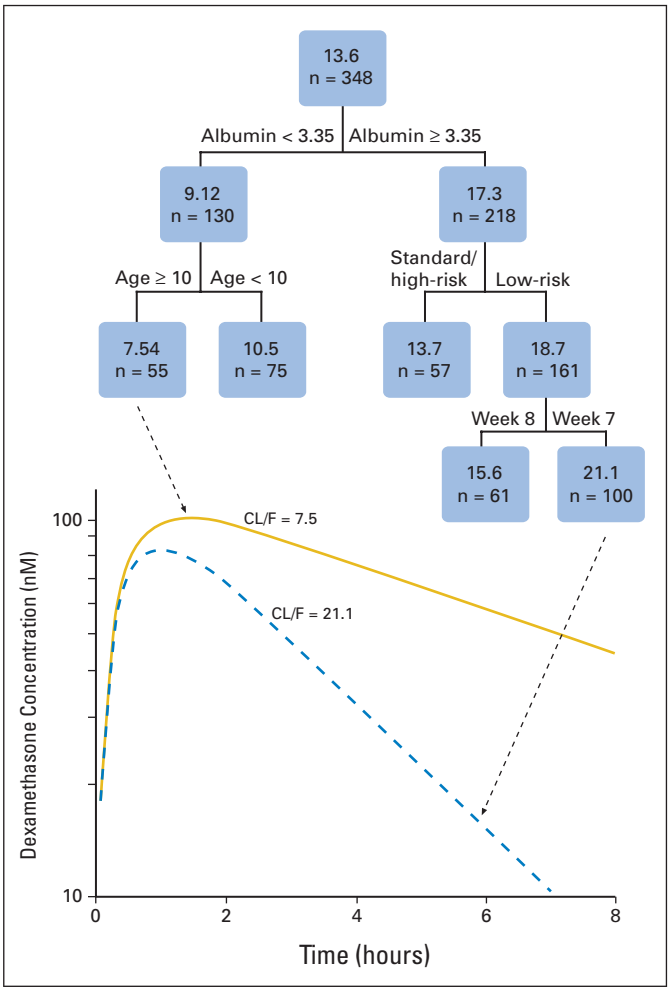

Fig 3. Classification tree indicating variables associated with apparent clearance. Each number indicates the average CL/F in the indicated number of courses (n = 348 courses that excluded 7 outliers). Plots indicate predicted plasma dexamethasone concentration versus time after 2.7 mg/m^2 for patients predicted to have a low CL/F of 7.5 L/h/m^2 (low albumin, older age) and those predicted to have a higher CL/F of 21.1 L/h/m^2 (high albumin, low-risk, week 7).

greater albumin, patients on the low-risk arm (who were younger and with less asparaginase) had a greater CL/F, and clearance at week 8 was less than that at week 7, possibly because of the asparaginase received during week 7 (Fig 3). The decrement in albumin from weeks 7 to 8 was much more impressive on the low-risk arm than on the standard/high-risk arms (Fig 2A). This result is consistent with the idea that the intensive asparaginase on the standard/high-risk arms had already caused hypoproteinemia by week 7; further treatment had minimal further effects on serum albumin, whereas patients on the low-risk arm were more susceptible to a decrement in albumin by the time they received asparaginase in week 7.

Asparaginase plasma exposure is lowered by allergy, which is often accompanied by inactivating antibodies.[18,27] At the time of dexamethasone pharmacokinetic analyses, allergy was more common on the standard/high-risk arms than on the low-risk arm. Serum albumin was greater in patients with clinical allergy by the start of the reinduction phase; this result is consistent with the hypothesis that systemic exposure to asparaginase was lower in patients with an asparaginase allergy (Fig 2B). Likewise, the dexamethasone CL/F was greater in those who had an asparaginase allergy (Fig 2B). Thus, patients with an allergy to asparaginase may be doubly disadvantaged in terms of an antileukemic effect—the allergy may be associated with the direct antibody-mediated inactivation of asparaginase, and the lower exposure to asparaginase may result in less hypoproteinemic effects and greater clearance of dexamethasone.

Although dexamethasone is bound (approximately 80%) to plasma proteins, a finding of hypoalbuminemia in association with decreased CL/F is not consistent with a plasma protein-binding mechanism. Lower albumin concentrations would result in increased concentrations of unbound dexamethasone, but, because dexamethasone is a restrictively cleared drug, this increase in the unbound dexamethasone concentration should be accompanied by an increase in the clearance of the free drug, which would result in no net increase in exposure or total drug clearance.[28] However, we observed increased clearance with an increased serum albumin concentration. Thus, at least in this setting, it appears that albumin's effect on CL/F is more likely to reflect hepatic clearance than plasma protein- binding.

As is true for other agents,[29] dexamethasone had a faster CL/F in younger than in older children. Although the effect of age on clearance was complicated by the fact that younger children were more likely to be treated on the low-risk arm rather than the standard/high-risk arms, the multivariate analyses (Table 2; Fig 3) suggest an independent effect of age. The dexamethasone CL/F in a patient at 19 years was 102.5% less than in a patient at 5 years (from 7.8 to 15.8 L/h/m^2), which was consistent with greater toxicity among older children.

Table 3. Pharmacokinetic Studies of Dexamethasone

Study	No. of Patients	Condition	Age Range (years)	Dose	CL/F	V	$t_{1/2}$ (hours)
Puisset et al 2005[8]	20 adults	Solid malignancies	41-74	20 mg IV infusion	5.68 (1.98) L/h/m^{2*}	51.7 (8.3) L	3.0 (1.1)
Puisset et al 2005[9]	21 adults	Solid malignancies	19-71	20 mg IV infusion	Range, 3.3-11.7 L/h/m^{2*}	—	3.1 (range, 1.9-4.8)
O'Sullivan et al[31]	10	Healthy controls	25-65	1 mg orally	2.96 (0.89) L/h/m^{2*}	—	5.6 (1.4)
O'Sullivan et al[31]	9	Depressed patients	19-67	1 mg orally	3.63 (0.65) L/h/m^{2*}	—	5.4 (1.4)
Richter et al[10]	12	Children with croup airway obstruction or head injury	0.25-16.83	0.1 or 0.3 mg/kg IV	—	2.07 (2.24) L/kg	4.34 (4.14)
Rose et al[30]	13 adults	Healthy male smokers	25-65	4 mg orally	12.1 (3.5) L/h/m^{2}†‡	—	3.6 (1.0)
Rose et al[30]	13 adults	Healthy male nonsmokers	25-65	4 mg orally	10.3 (4.2) L/h/m^{2}†‡	—	3.1 (1.1)
Current§	165	Children < 10 years with ALL	1-9.92	2.67 mg/m^2/dose orally	15.5 (SE, 0.70) L/h/m^2	47.9 (SE, 1.52) L/m^2	2.14 (SE, 0.08)
Current§	49	Children ≥10 years with ALL	10-18.8	2.67 mg/m^2/dose orally	9.78 (SE, 0.76) L/h/m^2	42.9 (SE, 2.59) L/m^2	3.06 (SE, 0.14)

NOTE. Data are the mean (SD), except as indicated.
Abbreviations: SD, standard deviation; CL/F, apparent clearance; V, volume; t, half-life; IV, intravenously, ALL, acute lymphoblastic leukemia.
*Results in L/h/m^2 were obtained by multiplying the CL values in L/h by 0.43.
†Results in L/h/kg were obtained by multiplying the CL values in mL/min/kg by 0.06.
‡Results in L/h/m^2 were obtained by multiplying the CL values in L/h/kg by 30.
§Data are the population means and SEs.

Moreover, the dexamethasone clearance observed in adult studies (Table 3) was closer to that which we observed in older rather than younger children. Thus, adults are exposed to twice the active drug as children are when given the same dose.

The univariate analysis (Appendix Table A3, online only) of drug interactions may have been confounded by covariance with other characteristics (eg, serum albumin), as the dexamethasone CL/F paradoxically increased with the use of CYP3A4 substrates or inhibitors and decreased with the use of CYP3A4 inducers. In the multivariate analysis (Fig 3), however, these drugs had negligible effects on CL/F relative to more penetrant influences, such as albumin, age, week of therapy, and treatment arm (ie, prior asparaginase use).

Plasma sampling was limited to five samples over 8 hours. For this reason, confidence intervals for pharmacokinetic parameters estimates were wide. Nevertheless, estimates of CL/F were comparable to or slightly greater than those reported in adults (Table 3). Likewise, our estimates of ka and V/F (Table 3) were also comparable to those found previously.[10,30,32]

In conclusion, dexamethasone pharmacokinetics displayed substantial inter- and intrapatient variability. Much of the variability was accounted for by variability in the serum albumin concentration, which in turn was affected by the intensity of prior asparaginase treatment. The dexamethasone CL/F was greater in younger than in older children, which resulted in almost twice the systemic exposure in adults than in younger children given the same dose. Our findings indicated that host- and treatment-related factors greatly affect systemic exposure to dexamethasone and could account for variable responses to this widely used agent.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).