Cancer Chemother Pharmacol (2005) 55: 237–243
DOI 10.1007/s00280-004-0836-8

ORIGINAL ARTICLE

Xueyu Chen · Robert R. Bies · Ramesh K. Ramanathan
Eleanor G. Zuhowski · Donald L. Trump
Merrill J. Egorin

Population pharmacokinetic analysis of 17-(allylamino)-17-demethoxygeldanamycin (17AAG) in adult patients with advanced malignancies

Received: 25 December 2003 / Accepted: 7 April 2004 / Published online: 19 October 2004

Abstract *Purpose*: 17-(Allylamino)-17-demethoxygeldanamycin (17AAG) is a novel anticancer agent in clinical development. The objectives of this study were to develop a population pharmacokinetic model for 17AAG and its major metabolite, 17AG, and to investigate influences of patient characteristics and biochemical markers on pharmacokinetic parameters estimated for 17AAG and 17AG. *Experimental design*: In a phase I clinical study, 17AAG was administered by intravenous infusion to 43 patients with refractory, advanced malignancies. Plasma concentrations of 17AAG and 17AG were determined by high-performance liquid chromatography. Plasma concentration vs time data were modeled using NONMEM. Nine covariates (age, sex, performance status, weight, height, body surface area, AST, bilirubin and serum creatinine) were investigated for their influences on individual pharmacokinetic parameters. *Results*: Plasma concentration vs time data were best described by a two-compartment model for 17AAG and a one-compartment model for 17AG. Volumes of distribution were 24.2 and 89.6 l for 17AAG. Total elimination clearances were 26.7 and 21.3 l/h for 17AAG and 17AG, respectively. Both fixed and random effects pharmacokinetic parameters were well estimated. None of the covariates explained the interindividual variability in 17AAG and 17AG pharmacokinetic parameters or improved the fit of the model based on objective function changes. *Conclusions*: A population pharmacokinetic model was developed to describe 17AAG and 17AG population pharmacokinetic parameters and interindividual variabilities. There were substantial interindividual variabilities in 17AAG and 17AG pharmacokinetic parameters despite BSA-normalized dosing.

Keywords Geldanamycin · NONMEM · Population pharmacokinetics

X. Chen (✉)
Department of Medical Oncology and Hematology,
Princess Margaret Hospital, Room 5-221A,
610 University Ave., Toronto, ON, Canada, M5G 2M9
E-mail: eric.chen@uhn.on.ca
Tel.: +1-416-9462263
Fax: +1-416-9462082

R. R. Bies
Department of Pharmaceutical Sciences,
School of Pharmacy, University of
Pittsburgh, Pittsburgh, PA 15213, USA

R. K. Ramanathan · E. G. Zuhowski · D. L. Trump · M. J. Egorin
Molecular Therapeutics/Drug Discovery Program,
University of Pittsburgh Cancer Institute,
Pittsburgh, PA 15213, USA

R. K. Ramanathan · D. L. Trump · M. J. Egorin
Division of Hematology/Oncology,
Department of Medicine, School of Medicine,
University of Pittsburgh, Pittsburgh, PA 15213, USA

M. J. Egorin
Department of Pharmacology, School of Medicine,
University of Pittsburgh, Pittsburgh, PA 15213, USA

Introduction

17-(Allylamino)-17-demethoxygeldanamycin (17AAG), an analog of geldanamycin, is an anticancer agent with a novel mechanism of action. It binds specifically to and inhibits the cytosolic chaperone protein, heat-shock protein 90 (HSP90) [17, 18]. 17AAG binding inhibits HSP90-mediated conformational folding of client proteins including oncoproteins such as $p185^{erbB2}$, raf-1 and Bcr-Abl; and promotes degradation of these oncoproteins [15, 16]. Based on this unique mechanism of action, 17AAG is currently undergoing clinical development in multiple phase I/II studies [3, 14, 23].

After intravenous administration to mice, 17AAG distributes widely, and undergoes extensive hepatic metabolism [6, 7]. One of its major metabolites, 17-(amino)-17-demethoxygeldanamycin (17AG), is as active as 17AAG in depleting cellular $p185^{erbB2}$ [19]. The metabolism of 17AAG to 17AG is mediated by CYP3A4

[7]. Preliminary data indicate that 17AAG also distributes widely after intravenous administration and is cleared rapidly in humans [3, 14, 23]. In addition, 17AAG area under the curve (AUC) increases linearly with doses from 10 to 160 mg/m^2 [3].

The population pharmacokinetic approach has been advocated as a useful tool in early development of new anticancer agents [5, 21]. In contrast to the traditional pharmacokinetic approach, the population pharmacokinetic approach allows complex pharmacokinetic modeling and simultaneous analysis of data from a wide range of doses, schedules and individuals. This is particularly useful where subjects receiving lower doses may not have as many measurable data points due to assay limitations [1, 20]. Information from all subjects can be combined under the population pharmacokinetic approach to provide reasonable estimates of pharmacokinetic parameters for subjects receiving lower doses [20]. In addition, the influence of individual patient characteristics on pharmacokinetic behavior can be investigated. For example, population pharmacokinetic analysis has shown that patients with elevated liver enzymes have a 27% decrease in docetaxel clearance and are at a higher risk of toxicity [5]. This insight resulted in recommendations of dose reduction in patients with hepatic impairment.

As part of a phase I program, the objective of the present study was to develop a population pharmacokinetic model to describe the time course of 17AAG and its major metabolite 17AG after intravenous infusion, to capture interindividual variability of 17AAG and 17AG after intravenous infusion, and to investigate possible influences of patient demographic variables and biochemical markers on the pharmacokinetic parameters of 17AAG in cancer patients.

Patients and methods

Patients

Patients were eligible if they had a histologically confirmed diagnosis of advanced epithelial cancer or malignant lymphoma not curable with standard therapy or for which there was no standard therapy. Additional eligibility criteria included: Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; adequate renal, hepatic and bone marrow function; age $\geq$18 years; a life expectancy of at least 3 months; and no active anticancer treatment within 4 weeks of study entry. The protocol was approved by the Institutional Review Board of the University of Pittsburgh Cancer Institute. All patients gave written, informed consent before entering the study.

Drug administration and pharmacokinetic sampling

17AAG was supplied by the National Cancer Institute in sterile vials containing 50 mg 17AAG in 2.0 ml dimethylsulfoxide. It was reconstituted with a diluent consisting of 2% egg phospholipids and 5% D5W to a final concentration of 1 mg/ml within 8 h of administration. 17AAG was given as a 1-h i.v. infusion weekly for 3 weeks, followed by a 1-week rest. The starting dose level was 10 mg/m^2, and dose levels were escalated to 20, 30, 40, 55, 75, 97, 127, 220, 295, and 395 mg/m^2. Because of the volume to be infused, the duration of infusion was increased to 2 h in three patients at the 295 mg/m^2 dose level, and two patients at the 395 mg/m^2 dose level. Serial blood samples were collected into heparinized tubes before the first dose of 17AAG, 30 min into the infusion and at the end of infusion, and at 5, 10, 15, and 30 min and 1, 2, 4, 8, 12, 16, 18, and 24 h after completion of the infusion. Plasma samples were separated by centrifuging blood samples at 1000 *g* for 10 min and stored at -70°C until analyzed. Plasma 17AAG and 17AG concentrations were quantified by high-performance liquid chromatography (HPLC) with UV detection as previously described [6, 7]. The lower limit of quantitation of the assay was 100 n*M* for both 17AAG and 17AG.

Population pharmacokinetic analyses

Plasma concentration vs time data for both 17AAG and 17AG were modeled simultaneously with NONMEM (version V 1.1; GloboMax LLC, Hanover, Md.). The structural model was based on comparison of two-compartment and one-compartment models for both 17AAG and 17AG. Models were parameterized in terms of volume of distribution and clearance (Fig. 1). To aid the identification of pharmacokinetic parameters, the volume of distribution of 17AG

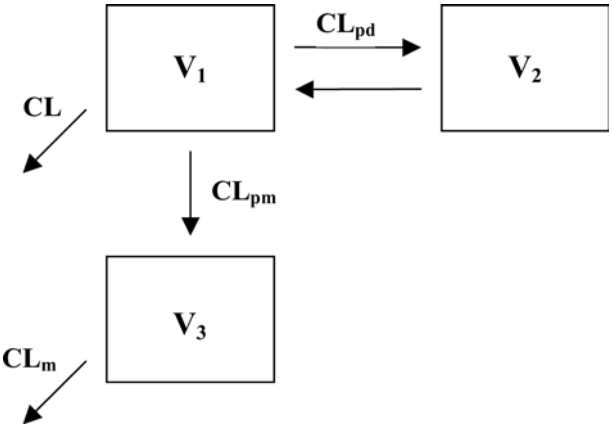

Fig. 1 Structural pharmacokinetic models of 17AAG and 17AG. *Boxes* represent central (*1*, *3*) and peripheral (*2*) compartments. *Arrows* represent first-order processes. V_1 volume of the central compartment for 17AAG, V_2 volume of the peripheral compartment for 17AAG, V_3 volume of distribution for 17AG (assumed to be equal to V_1), CL_{pd} distribution clearance between the central and peripheral compartments of 17AAG, CL_{pm} metabolic clearance of 17AAG to 17AG, CL elimination clearance of 17AAG other than conversion to 17AG, CL_m elimination clearance of 17AG

central compartment (V_3) was assumed to be equal to that of 17AAG (V_1) since these two volumes had similar values during estimation steps [9]. The final model selection was based on changes in objective function values (−2 log likelihood) provided by NONMEM as well as inspection of residual plots. Changes in objective function values approximate the chi-squared distribution. An alpha level for significance of 0.05 was used. Thus, a change in the objective function value of 3.84, representing $P = 0.05$ with df = 1, was considered to be statistically significant to discriminate between two hierarchical models.

The distribution of individual pharmacokinetic parameters was assumed to be log-normal constraining parameter values to be positive. For example, V_1 was modeled as $V_{1i} = \mathrm{TVV}_1 \times e^{\eta i}$, where V_{1i} is the V_1 of the ith individual, TVV_1 is the typical value of V_1 for the whole population, and η_i is the interindividual random effect term for the ith individual (η was assumed to be normally distributed with mean of 0 and variance of ω^2). Residual variability, which included intraindividual variability, was evaluated with additive, proportional and combined additive and proportional models. A fourth model, $Y_{\mathrm{obs},i} = Y_{\mathrm{pred},i} + \varepsilon \times e^{\eta i}$, was also evaluated ($\epsilon$ is the typical residual variability in the study population, η_i s the interindividual random effect term which was assumed to be normally distributed with mean of 0 and variance of ω^2) [12]. The first-order conditional estimation method with interaction was used throughout this analysis. NONMEM implemented with Wings for NONMEM (version 302, N. Holford, http://wfn.sourceforge.net) was used.

Individual Bayesian estimates of pharmacokinetic parameters were obtained using the POSTHOC option in NONMEM. A stepwise, generalized additive modeling (GAM) procedure was then used to select covariates that could further explain the interindividual variability. Xpose (version 3), an S-PLUS-based model building software [10], was used to implement GAM. Covariates investigated included demographic variables (age, sex, performance status, weight, height, BSA) and biochemical markers (AST, bilirubin, serum creatinine). Covariates that correlated significantly with pharmacokinetic parameters, as indicated by the Akaike information criterion [2], were selected for further testing in NONMEM. For example, the relationship between CL and BSA was modeled as $\mathrm{TVCL} = \theta_1 + \theta_2 \times \mathrm{BSA}$, where θ_1 is the typical population value and θ_2 is the constant associated with changes in BSA. In addition, covariates were centered on their medians as well: for example, $\mathrm{TVCL} = \theta_1 + \theta_2 \times (\mathrm{BSA}/1.85)$, where 1.85 m^2 was the median value of BSA for subjects in this study. As in the structural model building process, a covariate was entered into the model only if the resulting objective function value decreased by ≥3.84 ($P = 0.05$, df = 1). A backward elimination was subsequently performed, and variables remained in the final model only when the elimination of a variable caused an increase in the objective function value of ≥6.6 ($P = 0.01$, df = 1).

Results

A total of 43 patients participated in this study. Patient characteristics and baseline biochemical markers are listed in Table 1. At the time of study entry, the average age was 62 years (range 24–83 years), and the median ECOG performance status was 1 (range 0–2). The 17AAG dose was escalated 11 dose levels from a starting dose of 10 to 395 mg/m^2.

Complete pharmacokinetic profiles were available for all 43 patients. Typical plasma concentration vs time profiles of 17AAG and 17AG are shown in Fig. 2 for two patients, one treated at the 40 mg/m^2 dose level and one treated at the 395 mg/m^2 dose level. The final pharmacokinetic model consisted of a two-compartment model for 17AAG and a one-compartment model for 17AG (Fig. 1). This model provided similar objective function values and fitting to the model with two-compartments for both 17AAG and 17AG, but with two fewer parameters. It was used for developing the covariate model.

Population pharmacokinetic parameters are listed in Table 2. All structural (fixed effects) pharmacokinetic parameters were well estimated. Volumes of distribution of 17AAG were 24.2 and 89.6 l for the central (V_1) and peripheral (V_2) compartments, respectively, and approximately 24 l for 17-AG (V_3). The total body clearance was 26.7 and 21.3 l/h for 17AAG and 17AG, respectively. The metabolic clearance of 17AAG to 17AG was 12.4 l/h, indicating that 46.4% of 17AAG is metabolized to 17AG. When individual post hoc model-predicted 17AAG and 17AG concentrations were plotted against observed concentrations (Fig. 3), model-predicted concentrations were symmetrically distributed around the line of unity. Outliers for the observed vs predicted 17AAG concentrations did not correlate with outliers for the observed vs predicted 17AG concentrations.

The interindividual variability was determined for all structural pharmacokinetic parameters with the coefficient of variation ranging from 24.9% for V_2 to 125% for CL. Thus, there was substantial interindividual variability despite the fact that the 17AAG dose was normalized according to BSA. The fourth residual error

Table 1 Patient characteristics and baseline parameters

	Mean (±SD)	Range
Patient characteristics		
Age (years)	62 ± 12	24–83
Sex (male/female)	25/18	
Weight (kg)	77 ± 17	44–117
Height (cm)	168.8 ± 10.2	147–189
BSA (m^2)	1.9 ± 0.2	1.4–2.4
Baseline parameters		
ECOG performance status	1 (median)	0–2
AST (U/l)	28.8 ± 17.7	12–94
Bilirubin (μmol/l)	8.7 ± 4.9	3.4–25.7
Serum creatinine (μmol/l)	83.0 ± 21.6	53–141

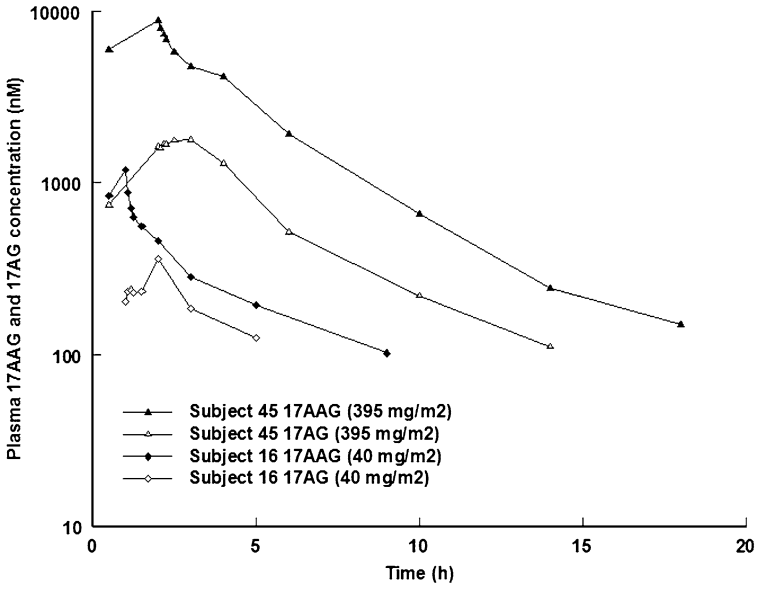

Fig. 2 Plasma concentrations of 17AAG and 17AG in two patients at two different dose levels

model yielded the lowest objective function value and best residual plots. Therefore, this model was used in all subsequent analyses. The residual variability was 182 n*M* for 17AAG and 80 n*M* for 17AG, each of which were similar to the 100 n*M* limit of quantitation of the HPLC method.

The GAM analyses suggested that several covariates could potentially further explain the interindividual variability in pharmacokinetic parameters. These covariates were age and baseline serum creatinine for V_2 ($P < 0.001$ for both age and serum creatinine), BSA for CL ($P < 0.001$), age for CL_{pm} ($P < 0.001$), and BSA for CL_{pd} ($P < 0.001$). As a result, these covariates were tested separately in NONMEM. However, inclusion of covariates did not result in a significant reduction in the objective function value or improvement in goodness-of-fit plots. Therefore, the final model did not include any of these covariates.

Discussion

The novel anticancer agent, 17AAG, is currently undergoing clinical development [3, 14, 23]. Although its metabolism and pharmacokinetics have been characterized in preclinical studies [6, 7], this report is the first description of its pharmacokinetics in humans. After intravenous infusion, 17AAG had a large volume of distribution and high clearance, similar to the findings in animal studies. In addition, a high percentage of 17AAG was converted to its active metabolite, 17AG, in humans.

Although the population pharmacokinetics approach has been mostly restricted to sparse sampling with a large number of subjects in cancer pharmacology, this approach is being applied more frequently in early drug development [13, 21]. The detailed pharmacokinetic sampling in phase I studies allows better characterization of the structural pharmacokinetic model and interindividual and intraindividual variabilities [1, 22]. This approach was used to analyze plasma concentration vs time data for 17AAG and 17AG simultaneously in this study.

In modeling parent and its metabolites simultaneously, it is known that several parameters could not be globally identified under the conditions used in this study [9]. Specifically, the following parameters in our model were not identifiable: CL, CL_{pm} and V_3. However, combinations of these parameters are identifiable: $CL_{pm}/(V_1 \times V_3)$ and $(CL + CL_{pm})/V_1$ [9]. Various approaches have been proposed in the literature. Evans et al. [9] pointed out that if the metabolite volume of distribution is known a priori, then all parameters in our model would be identifiable; alternatively, one could assume that the parent drug is totally converted to the metabolite of interest. Another approach is to model a composite parameter of the metabolite volume of distribution and the fraction of parent drug converted to the metabolite [13]. Finally, it has been suggested that the metabolite volume of distribution could be set to 1 during modeling [4]. From animal studies, it is known that 17AG is a major metabolite of 17AAG, but not the only metabolite [6, 7, 24]. We postulated that the volume of distribution of 17AG was similar to the volume of the central compartment of 17AAG since the only structural difference between 17AAG and 17AG is the substitution of the allylamino ($–CH_2=CH–CH_2–NH_2$) group at the C-17 position in 17AAG with an amino ($–NH_2$) group at the same position in 17AG. In animal studies, the permeability surface-area products of the vascular wall and the transport rate constants have been shown to be similar for 17AAG and 17AG (0.23 vs 0.26 ml/h, and 0.062 and 0.057 h^{-1}, respectively, for 17AAG and 17AG), indicating that 17AG might have similar physiochemical properties to 17AAG [24]. Furthermore, V_3 was estimated to be 24 l in our modeling runs. Therefore, the

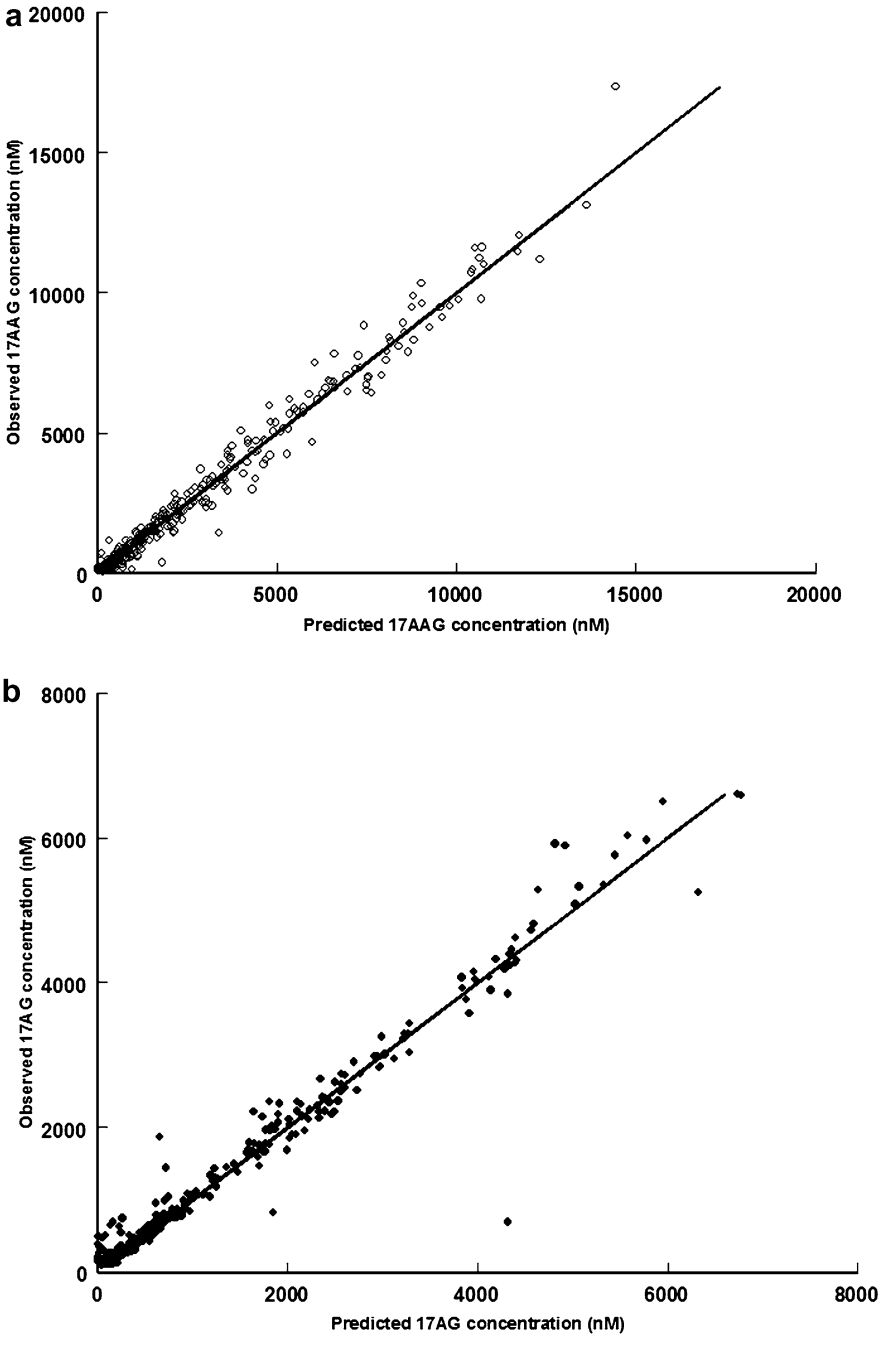

Fig. 3a, b Observed vs individual post hoc predicted plasma concentrations for (**a**) 17AAG and (**b**) 17AG. *Solid lines* represent the lines of unity

volume of distribution of 17AG was set equal to the volume of the central compartment of 17AAG so that the model could be run in a more stable fashion.

Plasma concentrations of 17AAG and 17AG predicted by the model corresponded well to observed concentrations of 17AAG and 17AG (Fig. 3), indicating that the population pharmacokinetic model adequately described the pharmacokinetic profiles of 17AAG and 17AG in this study. Both fixed and random effect parameters were well estimated with acceptable coefficients of variation.

One of the main sources of residual error in pharmacokinetic data analysis is the analytical error, the magnitude of which is, to some extent, dependent on the underlying concentration [11]. In this study, the 17AAG dose was escalated from a starting dose of 10 to 395 mg/m^2, and 17AAG and 17AG concentrations in the plasma of patients treated at the highest dose level were up to 20 times those in the plasma of patients treated at the starting dose level. The residual variability was evaluated with four models. The fourth residual error model, where the residual error magnitude could vary from subject to subject, performed significantly better than other three models with the lowest objective function value and best residual plots. This residual variability model would be applicable to other phase I

Table 2 Population pharmacokinetic parameters

Parameter	Estimate	CV (%)
Structural model		
V_1(l)	24.2	8.9
V_2(l)	89.6	8.0
CL (l/h)	14.3	27.9
CL_{pm} (l/h)	12.4	12.7
CL_{pd} (l/h)	84.4	9.4
CL_m (l/h)	21.3	12.5
interindividual variability		
ηV_1 (%)	25.0	48.6
ηV_2 (%)	24.9	52.1
ηCL (%)	125	61.0
ηCL_{pm} (%)	44.8	30.9
ηCL_{pd} (%)	46.2	41.0
ηCL_m (%)	49.4	50.0
$\eta\epsilon$17AAG (%)	94.4	31.2
$\eta\epsilon$17AG (%)	96.9	18.4
Residual variability		
ϵ17AAG (n*M*)	182	18.4
ϵ17AG (n*M*)	80	19.5

studies which generally have multiple dose levels over a wide range [8].

It is important that sources of interindividual variability on drug disposition be understood early in new drug development so that rational dosing regimens can be developed. Nine readily available covariates were investigated for their potential influence on interindividual variability in 17AAG pharmacokinetics. However, inclusion of these covariates neither reduced interindividual variability in any of the six pharmacokinetic parameters included in the structural model for 17AAG and 17AG nor improved the fit of the model based on objective function changes. Specifically, there were no relationships between liver enzyme tests (AST and serum bilirubin) and pharmacokinetic parameters even though a high percentage of 17AAG was converted to 17AG presumably via CYP3A4 [7]. However, this analysis was limited by the small sample size and narrow ranges of covariates. Similar to other phase I studies, there were strict eligibility criteria in terms of organ function. For example, patients had to have AST not more than two times the upper limit of normal, and bilirubin ≤ 26 μmol/l to be eligible for this study. In addition, 17AAG doses were normalized to BSA in this study, which might have confounded the analysis of BSA and variabilities in pharmacokinetic parameters.

In conclusion, a population pharmacokinetic model was developed for describing plasma concentrations of the novel anticancer agent, 17AAG, and its major metabolite, 17AG. There were substantial interindividual variabilities in pharmacokinetic parameters despite BSA-normalized dosing. This model adequately described observed 17AAG and 17AG concentrations, and would be useful in designing future clinical studies of 17AAG.

Acknowledgements We thank Drs. S. Percy Ivy and Louise Grochow for encouragement as this work was pursued. Supported, in part, by grants NCI 2P30 CA47904, NCI U01-CA69855, NIH/NCRR/GCRC/5M01RR00056, MH64173, MH65416, MH52247, MH30915, MH65376, and P41 EB-001975 to the University of Pittsburgh Medical Center and University of Pittsburgh Cancer Institute.

References

1. Aarons L, Karlsson MO, Mentre F, Rombout F, Steimer JL, van Peer A (2001) Role of modelling and simulation in phase I drug development. Eur J Pharm Sci 13:115
2. Akaike H (1979) A Bayesian extension of the minimal AIC procedures for autoregressive model fitting. Biometrika 66:237
3. Banerji U, O'Donnell A, Scurr M, Benson C, Hanwell J, Clark S, Raynaud F, Turner A, Walton M, Workman P, Judson I (2001) Phase I trial of heat shock protein 90 (HSP90) inhibitor 17-allylamino-17-demethoxygeldanamycin (17AAG): pharmacokinetic profile and pharmacodynamic endpoints (abstract). Proc Am Soc Clin Oncol 20:326
4. Bruno R (1999) http://www.cognigencorp.com/nonmem/nm/98jul021999.html, Accessed 13 March 2004
5. Bruno R, Hille D, Riva A, Vivier N, Bokkel Huinnink WW, van Oosterom AT, Kaye SB, Verweij J, Fossella FV, Valero V, Rigas JR, Seidman AD, Chevallier B, Fumoleau P, Burris HA, Ravdin PM, Sheiner LB (1998) Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. J Clin Oncol 16:187
6. Egorin MJ, Zuhowski EG, Rosen DM, Sentz DL, Covey JM, Eiseman JL (2001) Plasma pharmacokinetics and tissue distribution of 17-(allylamino)-17-demethoxygeldanamycin (NSC 330507) in CD2F1 mice1. Cancer Chemother Pharmacol 47:291
7. Egorin MJ, Lagattuta TF, Hamburger DR, Covey JM, White KD, Musser SM, Eiseman JL (2002) Pharmacokinetics, tissue distribution, and metabolism of 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin (NSC 707545) in CD2F1 mice and Fischer 344 rats. Cancer Chemother Pharmacol 49:7
8. Eisenhauer EA, OÆDwyer PJ, Christian M, Humphrey JS (2000) Phase I clinical trial design in cancer drug development. J Clin Oncol 18:684
9. Evans ND, Godfrey KR, Chapman MJ, Chappell MJ, Aarons L, Duffull SB (2001) An identifiability analysis of a parent-metabolite pharmacokinetic model for ivabradine. J Pharmacokinet Biopharm 28:93
10. Jonsson EN, Karlsson MO (1999) Xpose—an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Comput Methods Programs Biomed 58:51
11. Karlsson MO, Beal SL, Sheiner LB (1995) Three new residual error models for population PK/PD analyses. J Pharmacokinet Biopharm 23:651
12. Karlsson MO, Jonsson EN, Wiltse CG, Wade JR (1998) Assumption testing in population pharmacokinetic models: illustrated with an analysis of moxonidine data from congestive heart failure patients. J Pharmacokinet Biopharm 26:207
13. Klein CE, Gupta E, Reid JM, Atherton PJ, Sloan JA, Pitot HC, Ratain MJ, Kastrissios H (2002) Population pharmacokinetic model for irinotecan and two of its metabolites, SN-38 and SN-38 glucuronide. Clin Pharmacol Ther 72:638
14. Munster PN, Tong W, Schwartz L, Kenneson K, Cruz A, Rosen N, Scher H (2001) Phase I trial of 17-(allylamino)-17-demethoxygeldanamycin (17-AAG) in patients with advanced solid malignancies (abstract). Proc Am Soc Clin Oncol 20:327
15. Munster PN, Marchion DC, Basso AD, Rosen N (2002) Degradation of HER2 by ansamycins induces growth arrest and apoptosis in cells with HER2 overexpression via a HER3, phosphatidylinositol 3′-kinase-AKT-dependent pathway. Cancer Res 62:3132
16. Nimmanapalli R, O'Bryan E, Bhalla K (2001) Geldanamycin and its analog 17-allylamino-17-demethoxygeldanamycin lowers Bcr-Abl levels and induces apoptosis and differentiation of Bcr-Abl-positive human leukemic blasts. Cancer Res 61:1799

17. Ochel HJ, Eichhorn K, Gademann G (2001) Geldanamycin: the prototype of a class of antitumor drugs targeting the heat shock protein 90 family of molecular chaperones. Cell Stress Chaperones 6:105
18. Scheibel T, Buchner J (1998) The Hsp90 complex—a super-chaperone machine as a novel drug target. Biochem Pharmacol 56:675
19. Schnur RC, Corman ML, Gallaschun RJ, Cooper BA, Dee MF, Doty JL, Muzzi ML, Moyer JD, DiOrio CI, Barbacci EG (1995) Inhibition of the oncogene product p185erbB-2 in vitro and in vivo by geldanamycin and dihydrogeldanamycin derivatives. J Med Chem 38:3806
20. Schoemaker RC, Cohen AF (1996) Estimating impossible curves using NONMEM. Br J Clin Pharmacol 42:283
21. Van Kesteren C, Mathot RA, Raymond E, Armand JP, Dittrich C, Dumez H, Roche H, Droz JP, Punt C, Ravic M, Wanders J, Beijnen JH, Fumoleau P, Schellens JH (2002) Population pharmacokinetics of the novel anticancer agent E7070 during four phase I studies: model building and validation. J Clin Oncol 20:4065
22. Williams PJ, Ette EI (2000) The role of population pharmacokinetics in drug development in light of the Food and Drug Administration's 'Guidance for Industry: population pharmacokinetics'. Clin Pharmacokinet 39:385
23. Wilson RH, Takimoto CH, Agnew EB, Morrison G, Grollman F, Thomas RR, Wasif Saif M, Hopkins J, Allegra C, Grochow LB, Szabo E, Hamilton JM, Monahan BP, Neckers L, Grem JL (2001) Phase I pharmacologic study of 17-(allylamino)-17-demethoxygeldanamycin (AAG) in adult patients with advanced solid tumors (abstract). Proc Am Soc Clin Oncol 20:325
24. Xu L, Eiseman JL, Egorin MJ, D'Argenio DZ (2003) Physiologically-based pharmacokinetics and molecular pharmacodynamics of 17-(allylamino)-17-demethoxygeldanamycin and its active metabolite in tumor-bearing mice. J Pharmacokinet Pharmacodyn 30:185