Phase I population pharmacokinetics of irofulven

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Our aim was to develop a population pharmacokinetic model for irofulven and to assess covariates that might affect irofulven pharmacokinetics. Irofulven was administered by 5- or 30-min i.v. infusion to cancer patients during a phase I study. Blood samples were collected over 4 h. Plasma samples were analyzed to quantitate irofulven by high-performance liquid chromatography. Population pharmacokinetic analysis was performed using a non-linear mixed effects modeling program, MP2. Fifty-nine patients were available for pharmacokinetic analysis. Irofulven plasma concentration–time profiles were best described by a two-compartment pharmacokinetic model. Clearance and central volume of distribution were not significantly influenced by individual characteristics, i.e. body weight (BW), body surface area (BSA), age and gender. Final parameter estimates of clearance and central volume of distribution were 616 l/h and 37 l, respectively, resulting in a very short terminal half-life of less than 10 min. A relatively high level of variability was observed in irofulven pharmacokinetics, which was mainly due to a significant residual variability, 39%. For a 30-min irofulven infusion, the optimal sampling schedule for clearance estimation using the Bayesian method was the three time points 0.35–0.45, 0.80 and 1–1.2 h from the beginning of a 30-min infusion. We conclude that after i.v. infusion of irofulven, plasma clearance was high and not dependent upon patient age, gender, BSA or BW. *Anti-Cancer Drugs* 14:353–358 © 2003 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2003, 14:353–358

Keywords: anticancer drugs, Bayesian method, irofulven, population pharmacokinetics

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Received 3 February 2003 **Revised form accepted** 25 February 2003

Introduction

Irofulven (6-hydroxymethylacylfulvene, MGI-114) is a novel cytotoxic agent derived from illudin S, a natural sesquiterpene of fungal origin. Among illudin S derivatives, irofulven displayed an increased preclinical therapeutic margin and was selected for clinical development [1]. In previous phase I trials, irofulven was administered for a 5 days every 4 weeks schedule [2,3]. Clinically, the toxicity profile was characterized by bone marrow suppression, and poor but manageable tolerance due to nausea and vomiting. However, evidence of clinical antitumor activity and the striking preclinical antitumor effects of irofulven support further investigations of this drug.

Pharmacokinetics of drugs have generally been shown to be variable in cancer patients due to both clinical status and concomitant multiple drug intake, leading to an increased toxicity (due to increased drug exposure) or a lower efficacy (as a result of decreased drug exposure). Pharmacokinetic evaluations of irofulven have been conducted on repeated 5- or 30-min i.v. infusion schedules in 46 and 10 patients, respectively [2,3]. In these studies, a short half-life was reported (less than 10 min) and a high level of variability in irofulven pharmacokinetics was observed, particularly with the 5-min infusion administration. However, very little information on the irofulven pharmacokinetic model and parameters has been obtained.

A phase I study using three different i.v. administration schedules (day 1, 8, day 1, 15 and day 1, 8, 15) every 3–4 weeks was designed in order to reduce the toxicity, and to find the maximum tolerated dose and the recommended dose for phase II studies, and to assess schedules that would be more amenable to combination with other chemotherapeutic agents. We conducted a population pharmacokinetic analysis of plasma concentration–time data obtained during this phase I trial. Furthermore, the influence of demographic characteristics of patients on irofulven pharmacokinetics was investigated.

Methods

Patients

Adult patients with histologically or cytologically proven malignancy refractory to standard therapy were eligible for enrollment. Other inclusion criteria were ECOG performance status ≤ 2, life expectancy > 3 months, previous anticancer treatment discontinued at least 4 weeks prior to first dose of irofulven (6 weeks for

0959-4973 © 2003 Lippincott Williams & Wilkins DOI: 10.1097/01.cad.0000070482.94284.ce

mitomycin C), absolute neutrophil count $\geq 2000/mm^3$, platelets $\geq 150\,000/mm^3$, hemoglobin ≥ 9 g/dl, bilirubin within normal range, aspartate transaminases or alanine transaminases $\leq 1.5\times$ upper limit of normal, Cockroft and Gault index of creatinine clearance ≥ 60 ml/min, and corrected serum calcium < 2.7 mmol/l. Each patient provided written informed consent. This study was approved by the local ethics committee in France (CCPPRB).

Study design

Irofulven was supplied as 10-ml glass vials containing 10 mg of sterile, vacuum-dried product (MGI Pharma, Bloomington, MN). Nine dose levels, 13.3–28 mg/m^2, given as a 5- or 30-min i.v. infusion depending on the administration schedule (day 1, 8 from 15 to 24 mg/m^2, day 1, 15 from 20 to 28 mg/m^2 and day 1, 8, 15 from 13.3 to 18.6 mg/m^2) were investigated. Blood samples were typically collected 4, 15, 25, 35, 45, 60, 120, 240 and 360 min and 25, 35, 40, 50, 60, 70, 90 and 150 min after the beginning of drug administration for 5- and 30-min i.v. infusion, respectively. Samples were collected in tubes containing lithium heparinate, immediately placed on ice and centrifuged at 4°C. Plasma was then discarded and frozen at –80°C pending analysis, but for no more than 2 weeks.

Analytical method

Plasma irofulven concentrations were determined by high-performance liquid chromatography. The system consisted of a Waters 515 pump with a Waters 717 injector. An Alltech Altima C_{18} analytic column ($4.6\times$ 250 mm; particle size 5 μm) and a Brownlee RP_{18}, 7 μm (15×3.2 mm) prefilter were used. The mobile phase included acetonitrile:methanol:water (25:15:60, v/v/v) and the flow rate was 1 ml/min. Irofulven was detected by ultraviolet (UV) absorbance at 330 nm with a Waters 484 UV detector. In brief, immediately after thawing, 1.5 ml of plasma was acidified with 0.5 ml 0.01 M sodium acetate at pH 5, then 50 μl of internal standard, illudin S, was added. Solid NaCl, 0.7 g, was then added to the mixture. Irofulven was extracted from plasma by addition of 5 ml dichloromethane:pentane (1:1, v/v). The organic phase was evaporated to dryness under a stream of nitrogen. The residue was solved by 150 μl of mobile phase and 40 μl of this mixture was injected. The lower limit of quantification was 0.5 ng/ml. The calibration curve was linear over the range 0.5–1000 ng/ml.

Population pharmacokinetic modeling

Concentration–time data were analyzed using a non-linear mixed effects modeling approach, implemented in the program MP2 (Micropharm Population, INSERM, Paris, France) [4]. Data were fitted to one- and two-compartment pharmacokinetic models with first-order elimination. Random effects were modeled according to the following equations:

- Residual errors (ε), e.g. for a proportional error model:

$$C_{OBS} = C_{PRED}\times(1+\varepsilon)$$

  where C_{OBS} and C_{PRED} are the observed and model-predicted concentrations, respectively.
- Inter-individual errors (η), e.g. for a proportional error model:

$$CL = TV(CL)\times(1+\eta)$$

  where TV(CL) is the typical clearance of the population.

We investigated several error models (i.e. proportional error model with constant coefficient of variation and additive random effect models) to describe inter-patient and residual variability. A graphical analysis of predicted versus observed (PRED versus OBS) concentrations was performed to test the value of each model. Also, comparison between the mean of the individual Bayesian parameter estimates and the population mean estimates served to discriminate between the error models.

The influence of each patient covariate on CL, V_1, V_2 and Q was systematically tested via a generalized additive modeling. Such covariates included gender, age, body weight (BW), body surface area (BSA) and body mass index (BMI), as well as dose and infusion rate. Full and reduced models (one parameter less) were compared by the χ^2-test of the difference between their respective objective function values. A change of at least 7 points ($p < 0.01$, 1 d.f.) was required for the addition of a single parameter in the model. The effect of a covariate was considered to have improved the fit if there was a significant decrease in the objective function value of at least 7 points compared to the base pharmacokinetic model (with no covariate). An intermediate multivariate model was then obtained including all significant covariates. In order to keep only those covariates with the largest contribution to predict irofulven pharmacokinetics in a final multivariate model, a change of 11 points ($p < 0.001$, 1 d.f.) of the objective function was required for the retention of a single parameter during backward stepwise multiple regression analysis.

Bias and variability in concentration prediction were evaluated according to

$$\text{Bias}\,(\%) = \sum(\text{OBS}-\text{PRED})/\text{PRED}\times 100$$

$$\text{Variability}\,(\%) = \sum|\text{OBS}-\text{PRED}|/\text{PRED}\times 100$$

where PRED and OBS represented the predicted and observed concentrations using the final population model.

Limited-sampling model

Given the population pharmacokinetic parameters, the theoretical optimal sampling times were determined by mean of the program OSP-Fit, based on random search and stochastic gradient algorithms [5].

Results

Demographic data

Most patients were treated for digestive cancer, sarcoma or lung cancer. Fifty-nine patients (36 men and 23 women, ranging in age from 20 to 79 years) were available for population pharmacokinetic evaluation. Main demographic characteristics are listed in Table 1.

Population pharmacokinetics

A total of 337 plasma concentration–time values were included in the analysis. Plasma irofulven concentrations ranged from 0.5 to 691 ng/ml. Twenty-three and 36 patients received 5- and 30-min infusions, respectively. Two or three courses were available for 13 and six patients, respectively. The range of dose administered per course was from 19 to 61 mg. Individual plasma irofulven concentration–time data are depicted in Figure 1.

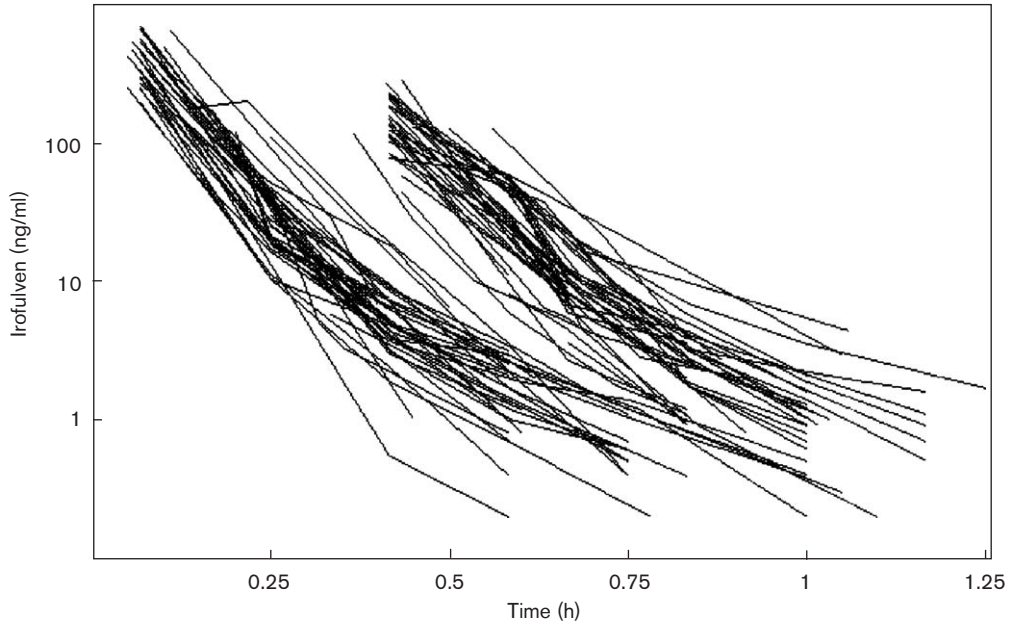
Table 1 Demographic data of the 59 cancer patients

Item	Mean	Range	SD
Male/female		36/23	
Age (years)	54	20–79	14
Weight (kg)	70	36–117	18
BSA (m^2)	1.8	1.25–2.45	0.25
Body mass index (kg/m^2)	24	16–48	5.0

A two-compartment model with first-order elimination described the data. The parameters of the structural model were systemic clearance (CL), central and peripheral compartment volumes (V_1, V_2), and intercompartmental clearance (Q). Inter-patient and residual variability were best described by proportional error models. This modeling was found to fit the data reasonably well. However, the inter-individual variabilities for V_1 and Q were estimated to be nearly zero, and could be removed from the model with no detriment to the fit (no significant increase in the objective function).

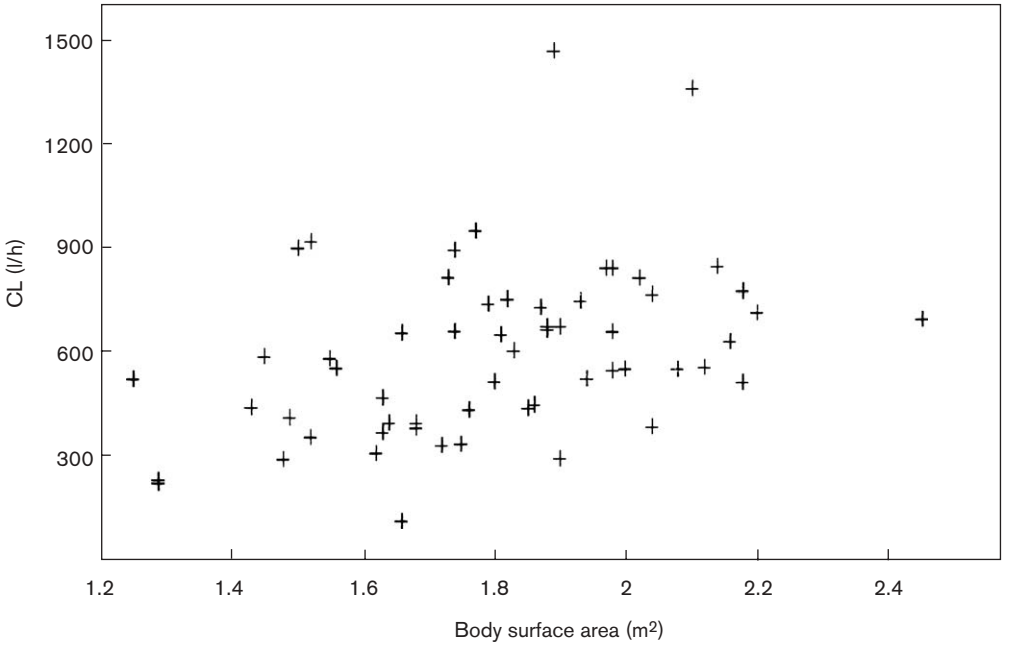
In the preliminary screening phase, the only covariate that individually reduced the objective function by more than 7 points was gender (effect on CL and V_1). Inclusion of BSA in CL and V_1 decreased the objective function value by 4.8 points. Thus, no covariate demonstrated significant influence on irofulven pharmacokinetics (since the deletion of gender in CL submodeling did not improve the objective function by at least a 11 points value, as described in Methods). Figure 2 shows the lack of any significant relationship between individual irofulven CL and BSA. Table 2 summarizes the population pharmacokinetic parameter estimates with their 95% confidence intervals.

Fig. 1



Observed irofulven plasma concentrations on a semi-log scale.

Fig. 2



Irofulven clearance versus BSA.

Table 2 Summary of irofulven parameter estimates for the population pharmacokinetic model (95% confidence interval in parentheses)

Parameter	Mean estimate	Inter-individual variability estimates (η) in %
V_1 (l)	37.3 (35–39)	NE
CL, (l/h)	616 (601–631)	14.1 (10–18)
Q (l/h)	30.3 (26–35)	NE
V_2 (l)	7.1 (6.3–8.1)	46 (33–64)
Residual error (ε) in % proportional component	39 (35–42)	NA
Derived parameters		
$T_{1/2}$ (distribution) (min)	2.4	NA
$T_{1/2}$ (terminal) (min)	10	NA

Model performance was evaluated by comparing predicted and observed irofulven plasma concentrations. As shown in Figure 3, the observed concentration versus population model-predicted concentrations were randomly distributed around the line of identity, with a correlation coefficient of 0.963 and a regression slope estimate of 1.05 ± 0.0001. There was no significant bias in concentration predictions ($2.2 \pm 61\%$, 95% confidence interval ranging from -4.3 to 8.7%), with a relatively high level of variability ($44 \pm 42\%$).

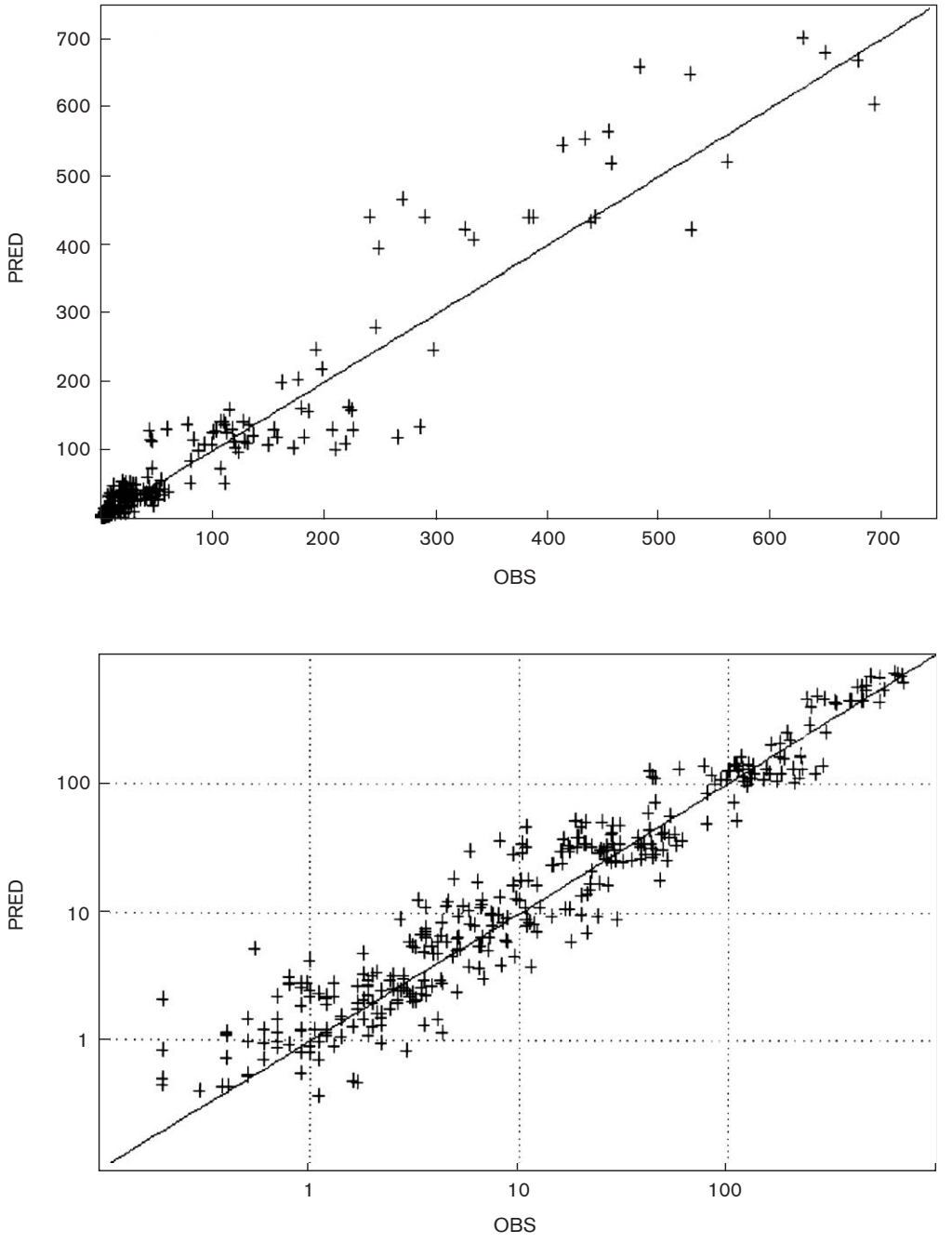
Limited-sampling model

Given the population parameters summarized in Table 2, optimization of the sampling schedule in the range 0.01–1. 5 h yielded four distinct theoretical times (this was the minimum number of time points required for the estimation process) for a 30-min infusion. The 1.5-h upper bound represents no measurable plasma concentration after the start of infusion, consistent with the short elimination half-life of irofulven. Since no inter-individual variabilities could be estimated for V_1 and Q, the following rule was applied [6]: 50 and 25% coefficient of variations were assumed for volumes and clearance terms, respectively. Then, the 'Uncertainty Option', which means that the population parameters are not assumed to be known exactly, was chosen in the optimization program. The four optimized sampling times were then 0.05, 0.37, 0.86 and 1.36 h after the start of infusion.

Discussion

The population pharmacokinetic approach used here for irofulven had particular relevance since a limited number of blood samples were available for some patients, i.e. due to the short half-life, late-time samples fell rapidly below assay limit of quantitation. Actually, five or less sets concentration–time data were available for 36 patients. Accordingly, analysis of the data from those patients using a conventional approach would be difficult due to a lack of information about the terminal elimination phase. Because the population approach utilizes all of the data simultaneously, all patients can be described using the same model, as missing information in some patients is borrowed from other patients. Additionally, the

Fig. 3



Top: predicted (PRED) and observed (OBS) plasma irofulven concentrations. Bottom: log-scale representation for visualization purposes in 59 patients (solid line, identity line).

population analysis from the large number of patients allows one to characterize inter- and intra-patient variability in pharmacokinetics as well as patient-specific covariates such as demographics, underlying disease and concomitant medications that can be evaluated [7].

Irofulven pharmacokinetics was best described by a two-compartment open model with first-order elimination. The mean population clearance estimate, 616 l/h or 10.2 l/min, is high, close to previously reported values in 10 and 46 patients, 4.57 l/min/m^2 and 9.7 l/min [2,3]. This close agreement between mean clearance values in different studies may explain the low inter-individual variability estimated for this parameter, 14%. The wide variability in irofulven pharmacokinetics was mainly due to the residual component of variability, 39%. This

relatively high level of residual variability may be explained by the very short half-lives for irofulven plasma decay, which add a non-negligible amount of uncertainty to the sampling times.

The very short irofulven half-life is consistent with either a rapid intracellular diffusion, or a rapid metabolism in blood or in well-perfused tissues, or both. The steady-state volume of distribution, 441 ($V_1 + V_2$), indicates a moderate tissue distribution.

As already demonstrated for other anticancer drugs, including carboplatin [8], doxorubicin, etoposide and ifosfamide [9], no significant relationship was observed between irofulven clearance and BSA (similar findings were obtained when BSA was replaced by BW). This result increases the doubts on the systematic use of BSA as a normalization factor for dose administration in chemotherapy [10,11]. For the present study, this means that irofulven AUC will probably increase or decrease as a result of dose increase or decrease based on BSA. In this study, no other covariate significantly influenced irofulven pharmacokinetics, in accordance with our criterion ($p < 0.001$) to finally retain a covariate in the model.

Given the population pharmacokinetic parameters, four optimal sampling times, after the start of infusion, were determined. The 0.05-h time is needed for a precise determination of V_1, the 0.37-h time corresponds to the plateau for a 0.5-h infusion and is useful for the CL estimation, the 0.86-h time corresponds to the inflection point between the rapid and slow elimination phases, and the 1.36-h time is in the late elimination phase. The last time point, however, corresponds to concentrations near the limit of quantification, 0.5 ng/ml. Practically, if accuracy in CL estimation is the most important issue, three optimal sampling times could include a plateau time near the steady state (0.35–0.45 h), a rapid distribution time around 0.80 h, and a late time between 1 and 1.20 h.

In conclusion, this study including 59 patients confirms previous results showing a high clearance with a very short elimination half-life. The source of variability in irofulven pharmacokinetics mainly originates from intraindividual factors. If further investigations demonstrate a relationship between exposure and a clinical, biological or toxicity endpoint, the dose adjustment could then be achieved by individual clearance estimation using a Bayesian approach and optimized sampling times.

Acknowledgments

We are indebted to the technicians of the Pharmacology Department of the Rene Huguenin Center for technical assistance.

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