Cancer Chemother Pharmacol (1994) 33: 484–488

Cancer Chemotherapy and Pharmacology

Pharmacokinetics of the anticancer agent 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine in rats

Mingxin Qian[1]*, Xiaogen Wang[1], Kirupa Shanmuganathan[2], Chung K. Chu[2], James M. Gallo[1]***

[1] Department of Pharmaceuties, College of Pharmacy, University of Georgia, Athens, Georgia, USA
[2] Department of Medicinal Chemistry, College of Pharmacy, University of Georiga, Athens, Georgia, USA

Received: 9 June 1993/Accepted 4 October 1993

Abstract. The pharmacokinetics of a new 2-halo-2′-deoxyadenosine analogue, 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) adenine [CL-F-ara-A], was characterized in rats following the development of a new high-performance liquid chromatography (HPLC) technique. This halogenated derivative was thought to have improved gastrointestinal stability that would facilitate oral administration. The HPLC method consisted of a single ethyl acetate extraction and reverse-phase chromatographic conditions. The method resulted in approximately 83% recovery of CL-F-ara-A from plasma and a sensitivity of 20 ng/ml. At i.v. doses of 10 and 25 mg/kg, the total clearance of CL-F-ara-A decreased from 2.1 to 1.5 l h^{-1} kg^{-1}, with the reduction being attributed to saturation of metabolism. The elimination half-lives following i.v. bolus administrations were estimated to be a mean of 1.35 and 1.84 h at the two respective doses. The volume of distribution at steady state was not significantly different at the two doses, being 3.6 and 3.2 l/kg. The percentage of protein binding of CL-F-ara-A in rat plasma was only 13.3%. Administration of equivalent oral doses resulted in biovailability estimates of approximately 50%, indicating that oral treatment regimens of CL-F-ara-A are feasible.

Introduction

Antimetabolites have been widely used to treat a variety of tumors. The new antimetabolites fludarabine [9-β-D-arabinofuranosyl-2-fluoroadenine] and its 5′-monophosphate derivative and 2-chloro-2′-deoxyadenosine (CdA)are adenosine deaminase-resistant deoxyadenosine analogs that have proved useful in the treatment of human lymphoid malignancies [4]. Fludarabine monophosphate was recently approved by the FDA for the treatment of refractory lymphocytic leukemia. Although their exact mechanism of action is unclear, a number of studies suggest that it may involve intracellular metabolic conversion to active triphosphates that inhibit enzyme systems involved in DNA synthesis, such as DNA polymerase α, ribonucleotide reductase, and DNA primase and ligase 1 [1, 3–5, 22, 25, 26]. Additionally, CdA was also found to induce production and accumulation of DNA strand breaks and cause cell death [10] and was exquisitely toxic in vitro to nondividing and proliferating normal human lymphocytes and to many leukemic cell species [1].

Similar to many anticancer drugs, despite their significant antitumor activity, fludarabine and CdA have dose-related toxicities of myelosuppression and immunosuppression [5]. It has been suggested from cell culture and animal studies [23] that 2-fluoradenine, a metabolite produced by *Escherichia coli* purine nucleoside phosphorylase [11], may contribute to the clinical toxicities seen with fludarabine, although evidence that it is released from fludarabine in humans is absent at this time. CdA has been found to be unstable in acidic medium and is degraded rapidly by the bacterial nucleotides phosphorylase and trans-deoxyribosylase [1]. Gastrointestinal acid instability may limit the systemic bioavailability of CdA and prevent its oral use.

To incorporate the best properties of fludarabine and CdA into one compound, a new 2′-arabino-fluoro derivative of CdA, 2′-chloro-2′-arabino-fluoro-2′-deoxyadenosine (CL-F-ara-A), has been recently synthesized [18, 20]. In terms of in vitro cytotoxicity, CL-F-ara-A resembles CdA but is more potent than fludarabine in three human cell lines, HEp-1, CCRF-CEM, and K562, and in murine leukemia L1210 [13, 18]. Pharmacodynamics studies show that CL-F-ara-A is the most effective compound tested against P388 leukemia [18] and chronic lymphocytic leukemia in SCID mice [2]. As compared with CdA, CL-F-ara-A is much more stable at a pH of 2 and more resistant

* *Present address:* Fox Chase Cancer Center, Department of Medical Oncology, 7701 Burholme Avenue, Philadelphia, PA 19111, USA

** *Present address:* Chongqing University of Medical Sciences, Chongqing, China

Correspondence to: James M. Gallo

to degradation by *E. coli* purine nucleotide phosphorylase [2]. This result, coupled with the potentially lower toxicity of the breakdown product 2-chlora adenine relative to 2′-fluoroadenine, indicates that CL-F-ara-A is a promising new antimetabolite.

The pharmacokinetics of CdA and fludarabine have been documented in various animals and in humans [6, 8, 9, 12, 14–17, 19]. However, pharmacokinetic information on CL-F-ara-A is lacking. In this report a new high-performance liquid chromatography (HPLC) technique for CL-F-ara-A is presented that was subsequently applied to characterize the pharmacokinetics of CL-F-ara-A in rats.

Materials and methods

Chemicals. CL-F-ara-A [2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine] and the internal standard 3′-azido-2′-3′-dideoxyuridine (AZddU) were kindly provided by Dr. David Chu, College of Pharmacy, University of Georgia. The purity of CL-F-ara-A was >98% as determined by HPLC. Stock solutions of both drugs were prepared in double-distilled, deionized water and stored at –20° C. HPLC-grade acetonitrile and ethyl acetate were purchased from J. T. Baker (Phillipsburg, N. J.). All other chemicals were reagent-grade or better and were obtained from commercial sources.

Chromatography. The HPLC system (Waters Chromatograph Division, Milford, Mass.) consisted of a model 510 pump, a model 712 WISP autoinjector, a model 484 absorbance detector, and a model 746 data module. An analytical column (Hypersil ODS, 5 μm, 150–4.6 mm inside diameter Alltech Associates, Deerfield, Ill.) preceded by a guard column filled with 30–40 μm pellicular RP-18 perisorb material (Upchurch Scientific, Inc., Oak Harbor, Wash.) was used for all analyses. The mobile phase consisted of acetonitrile: water (8:92, v/v) without a buffer. The chromatographic analyses were performed at ambient temperature at a flow rate of 2 ml/min with the detector wavelength set at 260 nm.

Sample preparation. To 100 μl of plasma sample, 10 μl of internal standard (AZddU, 20 μg/ml) solution was added to a microcentrifuge tube. In all, 1 ml of ethyl acetate was added to each tube and then shaken on a horizontal shaker for 10 min, followed by centrifugation at 10,000 *g* for 10 min. The organic layer was transferred to a clean tube and evaporated to dryness under nitrogen gas in a 50° C water bath. The resultant residue was reconstituted with 200 μl of mobile phase and a 100-μl aliquot was injected onto the HPLC system. To a 20-μl aliquot of urine, 10 μl of internal standard (AZddU, 1 mg/ml) solution was added to a microcentrifuge tube and then diluted with 970 μl of deionized water to yield a 1:50 dilution. In all, 20 μl of the final mixture was injected directly onto the HPLC system.

Standard curves for plasma or urine were prepared by adding known amounts of CL-F-ara-A and AZddU to pooled blank plasma or urine. Peak height ratios of CL-F-ara-A to AZddU in unknown plasma samples were used to calculate CL-F-ara-A plasma concentrations from linear regression equations obtained from standard curves.

Protein binding and stability of CL-F-ara-A in plasma. Binding of CL-F-ara-A to rat plasma protein was determined by filtration of plasma through a Centrifree (Amicon, Danvers, Mass.) micropartition system using a YMT membrane with a molecular-weight cutoff of 30 kDa. Prior to filtration, CL-F-ara-A was added to rat plasma at initial concentrations of 0.312, 2.5, 20, and 100 μg/ml and then incubated at 37° C for 20 min. The plasma samples were then centrifuged at 1,164 *g* for 25 min and 100 μl of each ultrafiltrate was injected onto the HPLC system. Phosphate-buffered saline solutions (pH 7.4) containing the same CL-F-ara-A concentrations as in plasma were treated in a fashion similar to plasma to determine the binding of CL-F-ara-A to the Centrifree system. Quadruplicate samples were run for each concentration. Stability studies of CL-F-ara-A in rat plasma at concentrations of 0.312, 2.5, 20, and 100 μg/ml were conducted at ambient temperature for 0, 6, and 24 h and at –20° C for 1, 3, 7, and 14 days, respectively.

Pharmacokinetics study. Adult male Sprague-Dawley rats (256–316 g) were obtained from Charles River Breeding Laboratory (Wilmington, Mass.). At 1 day before experimentation, the rats were anesthetized with a 0.75 ml/kg dose of a 3:2:1 (by vol.) mixture of ketamine HCl (100 mg/ml): acepromazine maleate (10 mg/ml): xylazine HCl (20 mg/ml) and then had a right jugular vein cannula (silicone tubing, 0.047 in outside diameter) inserted. The animals were housed in metabolic cages and were fasted overnight and during the first 4 h of the study yet were provided with water ad libitum. The disposition of CL-F-ara-A was determined following i.v. bolus doses of 10 and 25 mg/kg given via the jugular vein cannula and oral doses of 10 and 25 mg/kg given via gastric intubation. Five rats were studied at each dose level for both i.v. and oral administration. CL-F-ara-A was formulated in PEG 400:0.9% NaCl (50:50, v:v, at concentrations ranging between 5 and 10 mg/ml). Blood samples of 0.25 ml were collected at 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, and 24 h from the cannula into heparinized microcentrifuge tubes and then centrifuged to yield plasma. The blood volume was maintained by injecting an equal volume of 0.9% NaCl following each blood sample. The total urine volume was measured over 24 h following the dose and aliquots were stored for analysis. Both plasma and urine samples were frozen at –20° C until analysis.

Data analysis. Noncompartmental analysis was used to calculate the pharmacokinetic parameters of CL-F-ara-A. For each animal and CL-F-ara-A administration, areas under the plasma concentration-time curve (AUC) and first nonnormalized moment (AUMC) were determined by Lagrange polynomial interpolation and integration from time zero to the last measured sample time with extrapolation to time infinity using the least-squares terminal slopes [22]. The following pharmacokinetic parameters were estimated for CL-F-ara-A:

$$Cl_t = \frac{Dose_{iv}}{AUC_{iv}}, V_{ss} = \frac{Dose_{iv} \times AUMC_{iv}}{(AUC_{iv})^2}, Cl_r = \frac{(X_u)_{iv}}{AUC_{iv}},$$

$$Cl_{nr} = Cl_t - Cl_r, t_{1/2} = \frac{0.693}{K}, f_e = X_u/Dose, \text{and } F = \frac{(f_e)_{ig}}{(f_e)_{iv}},$$

where Cl_t is the total systemic clearance, V_{ss} is the volume of distribution at steady state, $t_{1/2}$ is the elimination half-life, K is the terminal disposition rate constant, F, is the systemic bioavailability, f_e is the fraction of dose excreted unchanged in the urine, Cl_r is the renal clearance, and X_u is the amount of drug excreted in the urine from time zero to 24 h.

The observed time of the maximal concentration (t_{max}) and the maximal concentration (C_{max}) were recorded for CL-F-ara-A following the oral administrations. The harmonic mean and pseudo-standard deviation of half-lives for CL-F-ara-A was calculated by the jackknife method [13]. A *t*-test was used to determine significant differences in the measured parameter in the low- and high-dose group of each administration. A P value of less than 0.05 was considered statistically significant.

Results and discussion

A new HPLC method was developed for the quantitation of CL-F-ara-A. Under isocratic conditions, the retention times of the internal standard and CL-F-ara-A were 4.6 and 6.2 min, respectively. The extraction recoveries obtained using the ethyl acetate procedure were 88.8% ± 1.1% for AZddU and 83.9% ± 2.7% for CL-F-ara-A. The complete sample preparation time was less than 30 min. The assay was linear over a plasma concentration range of 0.02–20 μg/ml (y = 0.0028+0.419 x, r^2 = 0.999), with a lower

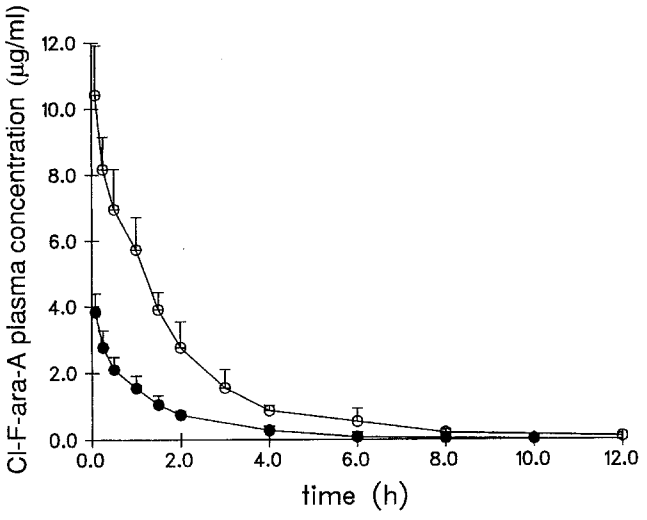

Fig. 1. CL-F-ara-A plasma concentration profile in rats following i.v. doses of 10 (•) and 25 mg/kg (○). Each point represents the mean value +1 SD, $n = 5$

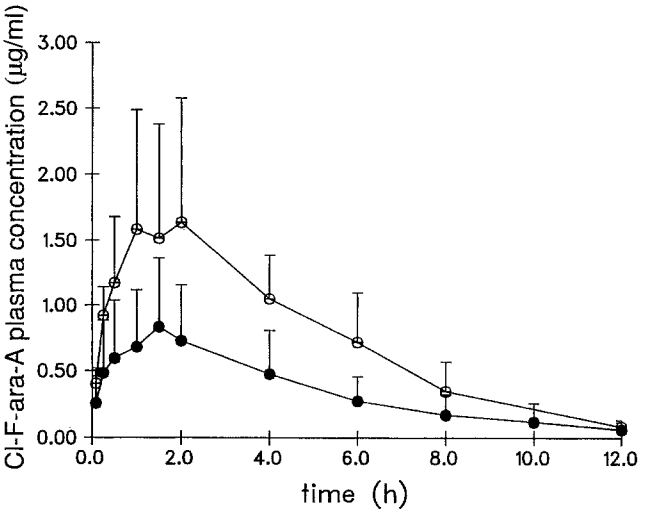

Fig. 2. CL-F-ara-A plasma concentration profile in rats following intragastric doses of 10 (•) and 25 mg/kg) (○). Each point represents the mean value +1 SD, $n = 5$

limit of quantitation of 0.02 µg/ml. As Table 1 shows, the intraday and interday percentage coefficients of variation (%CV) and percentage biases were under 11% except for a % CV of 16.5% found for CL-F-ara-A at 0.04 µg/ml. Overall, this method is simple and rapid and requires a small sample volume.

CL-F-ara-A binding to plasma protein was characterized over the plasma concentration range studied. The mean percentage bound to plasma protein was only 13.3% ± 1.3% ($n = 16$), suggesting that a large fraction of CL-F-ara-A is available for cellular uptake. It was also found that CL-F-ara-A was stable in rat plasma both at room temperature and at –20° C for over 2 weeks. This result is consistent with the observation by Carson et al. [2] in which CL-F-ara-A was shown to have increased stability in acid and against *E. coli* phosphorylases as compared with CdA.

Figures 1 and 2 show the plasma concentration-time profiles of CL-F-ara-A in the rat following i.v. and intragastric administrations, respectively. Pharmacokinetic parameters characterizing the disposition of CL-F-ara-A are listed in Table 2. Although the dose range was small, a significant difference was found in total and nonrenal clearances between the two i.v. dose groups. About 45% of the CL-F-ara-A dose was excreted in urine as the parent drug, which suggests that a substantial fraction of the compound is metabolized. El Dareer et al. [8] observed a similar fraction of renal excretion of 2-F-ara-A in mice. The observation that nonrenal clearance of CL-F-ara-A decreases at the higher dose level indicates a saturable metabolic process, which did result in a slightly longer half-life being seen at the higher dose level. However, since metabolic identification was not considered in the present study, the implicated enzymes(s) is unknown. Therefore, the consequence of this nonlinearity with respect to toxicity or dose regimen design in patients cannot be assessed at this early stage in drug development.

Renal and nonrenal clearance values were lower than the typical values for glomerular filtration rate (GFR) and liver blood flow, respectively, indicating that CL-F-ara-A is not a highly cleared compound. The steady-state volumes of distribution were 3.64 and 3.2 l/kg at the 10- and 25-mg/kg dose level, respectively. This suggests extensive binding of CL-F-ara-A to tissue components since the values are greater than those for the vascular space (–15 ml) and the body weight of the animals. It was noted that the elimination half-lives of CL-F-ara-A were longer following intragastric administration as compared with i.v. administration. The higher values obtained following intragastric treatments may have been due to a prolonged absorption phase (i.e., t_{max} values of ~2 h) and its resultant effect on

Table 1. Intra- and interday variation of the CL-F-ara-A HPLC assay in rat plasma

Prepared concentration (µg/ml)	Intraday			Interday		
	Measured concentration (µg/ml)	CV%	% Bias[a]	Measured concentration (µg/ml)	CV%	% Bias[a]
0.04	0.036	16.5	–8.8	0.041	11.1	2.6
0.312	0.307 ± 0.005	1.6	–1.5	0.317 ± 0.034	10.7	1.6
2.50	2.47 ± 0.09	3.8	–1.2	2.66 ± 0.15	5.7	6.4
20	19.48 ± 0.21	1.1	–2.6	19.86 ± 1.12	5.6	–0.7

$n = 5$ for each concentration

[a] $\%\ \text{Bias} = \dfrac{[\text{measured concentration} - \text{prepared concentration}]}{\text{prepared concentration}} \times 100$

Table 2. Pharmacokinetic parameters of CL-F-ara-A following the administration of i.v. and intragastric doses of 10 and 25 mg/kg to rats

Dose	Intravenous administration					
	Cl_t (l h^{-1} kg^{-1})	Cl_r (l h^{-1} kg^{-1})	Cl_{nr} (l h^{-1} kg^{-1})	f_e (%)	V_{ss} (l/kg)	$t_{1/2}$ (h)[d]
10 mg/kg	2.1 ±0.3[a, b]	0.89±0.19	1.21±0.30[b]	42.8± 9.7[c]	3.64± 9.7	1.35±0.18[b]
25 mg/kg	1.5 ±0.2	0.68±0.27	0.82±0.18	45.5±14.0	3.21±0.73	1.84±0.41
Dose	Intragastric administration					
	C_{max}(μg/ml)	t_{max} (h)	f_e (%)	F (%)	$t_{1/2}$ (h)	
10 mg/kg	0.9 ±0.45	1.9 ±1.7	22.1 ±8.4	51.6	2.28±0.50[e]	
25 mg/kg	1.81±0.79	1.7 ±0.5	20.6 ±4.9	45.2	2.13±0.69[e]	

[a] All data are expressed as mean values ±SD with $n = 5$ unless otherwise noted, except F, which is given as the mean
[b] Significantly different from the corresponding value at 25 mg/kg
[c] $n = 4$, urine in 1 animal was contaminated with blood and not included in the mean
[d] Harmonic mean and pseudo-standard deviation
[e] Significantly different from the corresponding half-life following i.v. administration (see Discussion)

defining the terminal elimination phase. Ideally, blood samples should have been obtained beyond 12 h for the oral studies to ensure definition of the terminal phase. However, as based on the sensitivity limit (20 ng/ml) and the measured 12-h concentrations, post-12-h samples may have been difficult to quantitate. The half-lives determined following i.v. administration are the more reliable values.

In the present study, the oral bioavailability of CL-F-ara-A was 52% and 45%, respectively, at the 10- and 25 mg/kg doses. Fludarabine monophosphate, a water-soluble derivative of fludarabine, has been shown to have an oral bioavailability of between 75% and 100% in dogs and 70% in humans [12, 17, 19]. The oral absorption of CdA was reported to be approximately 50% in leukemia patients [15]. Recently, Carson et al. [2] observed that CL-F-ara-A has a 10-fold higher blood level than CdA in SCID mice, which results in a significantly greater efficacy of CL-F-ara-A against chronic lymphoid leukemia as compared with CdA. Unfortunately, other pharmacokinetic parameters were not reported. Thus, it would be premature to extrapolate the bioavailability values of CL-F-ara-A in animals to humans; however, one could project that oral bioavailability would not significantly limit the development of this compound.

Finally, it should be appreciated that the noncompartmental data analysis methods, which assume linear kinetics, will provide concentration- or time-averaged values for the kinetic parameters when in fact the drug undergoes nonlinear processes [7]. A nonlinear model for CL-F-ara-A would best be developed in conjunction with metabolite data since administration over a larger range of doses, which would also facilitate development of a nonlinear model, is not possible due to its acute toxicity. In the present study, at 10-mg/kg (1 of 6 rats) and 25-mg/kg (2 of 7 rats) i.v. doses of CL-F-ara-A, some rats died within 15 min of the injection, whereas no animal died following oral treatment. Similar observations were noted for fludarabine in mice [19].

In summary, a simple and rapid HPLC assay was developed for characterizing the pharmacokinetics of CL-F-ara-A in rats. At i.v. doses of 10 and 25 mg/kg, the total clearance of CL-F-ara-A decreases from 2.1 to 1.5 l h^{-1} kg^{-1}, suggesting the involvement of a saturable elimination pathway. The volume of distribution at steady state was essentially constant and ranged from 3.2 to 3.6 l/kg at the two doses. Administration of equivalent oral doses resulted in bioavailability estimates of approximately 50%, indicating that oral treatment regimens of CL-F-ara-A are feasible.

References

1. Carson DA, Wasson DB, Beutler E (1984) Antileukemic and immunosuppressive activity of 2-chloro-2-deoxyadenosine. Proc Natl Acad Sci USA 81: 2232
2. Carson DA, Wasson DB, Esparza LM, Carreara JC, Kipps TJ, Cottam HB (1992) Oral antilymphocyte activity and induction of apoptosis by 2-chloro-2-arabinofluoro-deoxyadenosine. Proc Natl Acad Sci USA 89: 2970
3. Catapano CV, Chandlerman KB, Fernandes DJ (1990) Effect of anticancer agents on primer RNA formation in human leukemia cells. Proc Am Assoc Cancer Res 31: 2496
4. Cheson BD (1992) New antimetabolites in the treatment of human malignancies. Semin Oncol 19: 695
5. Cheson BD (1992) The purine analogs – a therapeutic beauty contest. J Clin Oncol 10: 868
6. Danharser L, Plunkett W, Keating M, Cabanilas F (1986) 9-B-D-Arabinofuranosyl-2-fluoroadenine-5′-monophosphate pharmacokinetics in plasma and tumor cells of patients with relapsed leukemia and lymphomas. Cancer Chemother Pharmacol 18: 145
7. Doshi KJ, Gallo JM, Boudinot FD, Schinazi RF, Chu CK (1989) Comparative pharmacokinetics of 3-azido-3-deoxythymidine (AZT) and 3′-azido-2-′, 3′-dideoxyuridine (AZddU) in mice. Drug Metab Dispos 17: 590–594
8. El Dareer SM, Struck RF, Trillery KF, Rose LM, Brockman RW, Montgomery JA, Hill DL (1980) Disposition of 9-beta-D-arabinofuranosyl-2-fluoroadenine in mice, dogs, and monkeys. Drug Metab Dispos 8: 63
9. Hersh MR, Kuhn JG, Phillips JL, Clark G, Ludden TM, Von Hoff, DD (1986) Pharmacokinetic study of fludarabine phosphate. NSC 312887 17: 277
10. Hirota Y, Yoshioka A, Tanaka S, Watanabe K, Otani T, Minowada J, Matsuda A, Ueda T, Wataya Y (1989) Imbalance of deoxynucleoside triphosphate, DNA double-strand breaks, and cell death caused by 2-chlorodeoxyadenosine in mouse FM3A cells. Cancer Res 49: 915
11. Huang P, Plunkett W (1987) Phosphorolytic cleavage of 2-fluoroadenine from 9-B-D-arabinofurosyl-2-fluoroadenine by *Escherichia coli* (Biochem Pharmacol 36: 2945

12. Kemena A, Keating MJ, Plunkett W (1990) Bioavailability of plasman fludarabine and fludarabine triphosphate (F-ara-ATP) in circulating CLL cells. Blood 76: 288 A
13. Lam FC, Hung CT, Perrier DG (1985) Estimation of variance for harmonic mean half life. J Pharm Sci 74: 229
14. Juliusson G, Liliemark J (1990) 2-Chlorodeoxyadenosine (CdA) in lymphoproliferative diseases: clinical and pharmacokinetic studies. Blood 76: 354 A
15. Liliemark J, Albertioni F, Hassan M, Juliusson G (1992) On the bioavailability of oral and subcutaneous 2-chloro-2′-deoxyadenosine in humans: alternative route of administration. J Clin Oncol 10: 1514
16. Liliemark J, Juliusson G (1991) On the pharmacokinetics of 2-chloro-2′-deoxyadenosine in humans. Cancer Res 51: 5570
17. Malspeis L, Grever MR, Staubus AE, Young D (1990) Pharmacokinetics of 2-F-ara-A (9-B-D-arabinosyl-2-fluoroadenine) in cancer patients during the phase I clinical investigation of fludarabine phosphate. Semin Oncol 17: 18
18. Montgomery JA, Shortnacy-Fowler AT, Clayton SD, Riordan JM, Secrist JA III (1992) Synthesis and biologic activity of 2′-fluoro-1-halo derivatives of 9-B-D-arabinofuranosyladenine. J Med Chem 35: 397
19. Noker PE, Duncan GF, El Dareer SM, Hill DL (1983) Disposition of 9-B-D-arabinofuranosyl-2-fluoroadenine-5′-phosphate in mice and dog. Cancer Treat Rep 67: 445
20. Parker WB, Shaddix SC, Chang CH, White EL, Rose LM, Brochman W, Shortnacy AT, Montgomery JA, Secrist JA III, Bennett LL Jr (1991) Effect of 2-chloro-9-(2-deoxy-2-fluoro-B-D-arabinofuranosyl) adenine on K562 cellular metabolism and the inhibition of human ribonucleotide reductase and DNA polymerases by its 5′-triphosphate. Cancer Res 51: 2386
21. Plunkett WP, Huang P, Gandhi V (1990) Metabolism and action of fludarabine phosphate. Semin Oncol 17: 3
22. Rocci ML, Jusko WJ (1983) Langran program for area and moments in pharmacokinetic analysis. Comp Prog Biomed 16: 203
23. Struck RF, Shortnacy AT, Kirk MC, Thorpe MC, Brockman RW, Hill DL, El Dareer SM, Montgomery JA (1982) Identification of metabolites of 9-B-D-arabinofuranosyl-2-fluoroadenine, an antitumor and antiviral agent. Biochem Pharmacol 31: 1975
24. Tseng W-C, Derse D, Cheng Y-C, Brockman RW, Bennett LL Jr (1982) In vitro biological activity of 9-B-D-arabinofuranosyl-2-fluoroadenine and the biochemical action of its triphosphate on DNA polymerases and ribonucleotide reductase from HeLa cells. Mol Pharmacol 21: 474
25. White EL, Shaddis SC, Brockman RW, Bennett LL Jr (1982) Comparison of the action of 9-B-D-arabinofuranosyl-2-fluoroadenine and 9-B-D-arabinofuranosyladenine on target enzymes from mouse tumor cells. Cancer Res 42: 2260
26. Yang S-W, Huang P, Plunkett W, Becker FF, Chan JY (1992) Dual mode of inhibition of purified DNA ligase I from human cells by 9-B-D-arabinofuranosyladenine triphosphate. J Biol Chem 267: 2345