Cancer Chemother Pharmacol (1998) 42 (Suppl): S54–S59
© Springer-Verlag 1998

ORIGINAL ARTICLE

**Edward A. Sausville · Richard D. Lush · Donna Headlee
Adaline C. Smith · William D. Figg · Susan G. Arbuck
Adrian M. Senderowicz · Eiichi Fuse · Hiromi Tanii
Takashi Kuwabara · Satoshi Kobayashi**

Clinical pharmacology of UCN-01: initial observations and comparison to preclinical models

Abstract UCN-01 (7-hydroxystaurosporine; NSC 638850) is a protein kinase antagonist selected for clinical trial based in part on evidence of efficacy in a preclinical renal carcinoma xenograft model. Schedule studies and in vitro studies suggested that a 72-h continuous infusion would be appropriate. In rats and dogs, maximum tolerated doses produced peak plasma concentrations of approximately 0.2–0.3 μM. However, concentrations 10-fold greater are well tolerated in humans, and the compound has a markedly prolonged $T_{1/2}$. Specific binding to human α_1-acidic glycoprotein has been demonstrated. These findings reinforce the need to consider actual clinical pharmacology data in "real time" with phase I studies.

Work presented at the 13th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "Strategic Cross Talk between Major Oncology Groups/Clinical Pharmacology in Cancer Chemotherapy," 17–18 October 1997, Nagoya, Japan

E. A. Sausville · D. Headlee · A. M. Senderowicz
DTP Clinical Trials Unit, Medicine Branch, Division of Clinical Sciences, National Cancer Institute, Bethesda, MD, USA

R. D. Lush · W. D. Figg
Developmental Therapeutics Department, Medicine Branch, Division of Clinical Sciences, National Cancer Institute, Bethesda, MD, USA

A. C. Smith
Toxicology and Pharmacology Branch, Developmental Therapeutics Program, National Cancer Institute, Bethesda, MD, USA

S. G. Arbuck
Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA

E. Fuse · H. Tanii · T. Kuwabara · S. Kobayashi
Drug Development Research Laboratories, Pharmaceutical Research Institute, Kyowa Hakko Kogyo Co., Ltd., Shizuoka, Japan

E. A. Sausville (✉)
Developmental Therapeutics Program, National Cancer Institute, Executive Plaza North, Suite 843, 6130 Executive Blvd, Rockville, MD 20852, USA
email sausville@dtpax2.ncifcrf.gov
Tel. 1 301 496 8720; Fax 1 301 402 0831

Key words Staurosporine, 7-hydroxy · Protein kinase antagonist · α_1-Acidic glycoprotein

Introduction

UCN-01 (7-hydroxystaurosporine) was first identified by Takahashi et al. [10] as a selective but nonspecific inhibitor of protein kinase C (PKC). Subsequent work by these investigators demonstrated potent inhibition of the growth of cultured cell lines and antitumor activity against human tumor xenografts in athymic mice [1, 8]. PKC isoforms α, β, and γ are most sensitive to UCN-01(IC_{50} ≈30 nM), with PKC δ and ε 12 being less affected (IC_{50} ≈550 nM) and PKC ξ not affected by the drug [9]. However, a major question is the relative importance of this anti-PKC activity as a basis for antiproliferative effect of UCN-01. Wang et al. [12] demonstrated that under conditions in which the very selective PKC antagonist GF109203X as well as UCN-01 can both affect phorbol ester-mediated transcriptional activation of c-*fos*, only UCN-01 potently affected cell growth. In addition, UCN-01 induced apoptosis in T-lymphoblasts while GF109203X did not. These results suggest that cellular targets in addition to PKC must be considered to explain the potent growth inhibitory effect of UCN-01.

Initial experiments to define additional targets for the compound's action have documented that the drug can abrogate the G_2 checkpoint of cells exposed to DNA-damaging agents [3, 4, 13]. This effect is associated with relative tyrosine dephosphorylation of cyclin-dependent kinase 1 [13], and increases the susceptibility of cells to radiation or cisplatin. Seynaeve et al. initially demonstrated the capacity of UCN-01 to inhibit progression through G_1 [8], and Akinaga and colleagues have recently demonstrated that UCN-01 can cause hypophosphorylation of the retinoblastoma susceptibility protein (pRb) as cell cycle arrest develops [2]. Therefore it is clear that UCN-01 targets unique aspects of cell cycle regulation in comparison to standard antineoplastic agents, and consideration

Table 1 In vivo activity of UCN-01 in A498 renal carcinoma xenografts (*T/C* tumor/control)

Dose (mg/kg)	Schedule (day of dose)	%T/C (day)	%Growth delay
12.5	Q4 d × 3 (20, 24, 28)[a]	34 (33)	89
4.8	Qd × 3 (14–16)[b]	22 (21)	15
8	Q8 h bid (14, 16, 18)[a]	15 (21)	35
7.5	Qd × 5 (20–24)[a]	20 (26)	64

[a] Administered intravenously
[b] Administered subcutaneously

of UCN-01 as a candidate for clinical study is of interest owing to its antitumor activity and potential modulation of tumor susceptibility to DNA-damaging agents.

In this paper, we report the preclinical rationale for developing data to support initial clinical trials using a 72-h continuous intravenous infusion. However, the initial clinical studies also described here have revealed that the pharmacologic features of UCN-01 in humans differ greatly from prior observations in several animal species.

Patients and methods

Plasma UCN-01 was quantitated in patients receiving a 72-h infusion. A reverse-phase high pressure liquid chromatography (HPLC) method was developed utilizing a Hewlett Packard 1090 liquid chromatography system (Hewlett Packard, Palo Alto, Calif., USA) equipped with a photodiode array and fluorescence detectors. A Waters Nova-Pak Phenyl (3.9×150 mm) column (Waters, Milford, Mass., USA) was used and the compounds were detected using in-line ultraviolet light (292 nm) and a fluorescence detection system (excitation 290 nm, emission 400 nm). Preclinical data suggested that a sensitivity of around 10 ng/ml was necessary. A gradient mobile phase consisting of acetonitrile and 0.05 M ammonium acetate buffer, pH 4.15, was used (1 ml/min). UCN-01 was isolated from plasma using acetonitrile protein precipitation. Standard curves were prepared between the concentrations of 10 and 10 000 ng/ml, and linearity was shown at this range of concentration. UCN-01 elutes at 9.5 min whereas UCN-02 elutes at 7.8 min. The assay appears to be sensitive for quantitation of the pharmacokinetics of these agents in clinical trials.

Protein-binding characteristics of UCN-01 were evaluated by ultracentrifugation and by an equilibrium dialysis procedure first suggested by Dr Jerry Collins, US Food and Drug Administration, Rockville, MD, USA, wherein human plasma is placed in one chamber of a 2-chamber cell, with animal plasma in the opposite chamber, and distribution across a permeable membrane is assessed using the HPLC assay described above.

Preclinical evaluations of efficacy in athymic mouse xenografts were conducted according to methods outlined by Plowman et al. [7]. Preclinical toxicology evaluations in rats and beagle dogs were conducted according to methods outlined by Tomaszewski and Smith [11].

Initial phase I evaluation of UCN-01 in patients utilized a 72-h continuous infusion repeated every 14 days. Prior to entry to the study, adult patients >18 years of age without primary brain tumors or brain metastases were required to have Eastern Cooperative Oncology Group performance status 0–2, creatinine clearance >60 cc/min, serum aspartate transaminase and serum alanine transaminase levels <2.5 × upper limits of normal, total bilirubin <1.5 × upper limits of normal, <50% liver replacement by tumor, hemoglobin >9.0 g/dl, platelets >100 000/mm^3, absolute granulocyte count >1500/mm^3, and prothrombin and partial thromboplastin times within normal limits. Patients were also required to be without ileal or ureteral stomas, without prior radiation therapy to >30% of bone marrow, without evidence of active atherosclerotic vascular disease, without need for anticoagulation or need for treatment of local complications, and without evidence of >grade I neuropathy at study entry. Patients were also required to have evidence of progressive disease for which a standard therapy was of equivocal or no value. Patients were reevaluated after 2 courses of therapy. If no evidence of disease progression or nonreversible toxicity was present, the patient was eligible for additional courses of therapy, and reevaluated after every 3 courses or as indicated by clinical signs.

Results

Schedule studies in xenograft models

Preclinical evaluation of UCN-01 in the in vitro 60 cell line screen of the National Cancer Institute Developmental Therapeutics Program revealed notable sensitivity of the renal carcinoma cell line A498 (data not shown). Therefore efforts to demonstrate in vivo activity in A498 athymic mouse xenografts were undertaken. Essentially no or equivocal activity was observed when UCN-01 was administered by the intraperitoneal route. However, as shown in Table 1, when administered by the intravenous route or by subcutaneous infusion, good evidence of growth suppression on a variety of schedules was apparent. Since the best tumor/control value was obtained with a frequent (twice daily) administration schedule and prior in vitro studies [8] were consistent with continuous exposure to the drug for as long as 72 h being necessary to convey a lasting antiproliferative effect in certain (although not all) cell types, it was decided to conduct the first phase I study with the drug as a 72-h continuous intravenous infusion. This was supported by evidence of activity when given by 72-h subcutaneous infusion to xenograft-bearing mice.

Preclinical toxicology and pharmacology of UCN-01

To support initial clinical trials with the 72-h infusion, toxicologic evaluation on the same or an analogous schedule was undertaken in rats and beagle dogs. Male and female Fischer 344 rats were given doses of UCN-01 0, 0.5, 1, and 2 mg/kg/injection (0, 1, 3, 6 mg/kg/day; 0, 6, 18 and 36 mg/m^2/day) i.v. 3 times daily every 8 h for 3 days. Doses of 2 mg/kg/injection were lethal in 5/20 animals on days 5–6. Maximum body weight loss was 17–21%. Leukopenia was dose related, and pathology revealed lymphoid tissue atrophy, bone marrow depletion, small intestinal atrophy, and inflammation at the injection site. The maximum tolerated dose (MTD) was 1 mg/kg/injection given 3 times daily for 3 days. Bone marrow toxicity appeared to be dose limiting in the rat. In pharmacokinetic studies, male rats given UCN-01 10 mg/kg iv had an elimination $t_{1/2}$ of 4 h. The mean volume of distribution (V_d) was 15.7 l/kg, which greatly exceeds total body water and indicates extensive tissue binding of UCN-01. In addition, the clearance of UCN-01 from rat plasma (Cl) was rapid.

Beagle dogs were dosed with UCN-01 0.03, 0.05, and 0.1 mg/kg/h as a 72 h continuous infusion (0.72, 1. 2 and 2.4 mg/kg/day; 14.4, 24 and 48 mg/m^2/day). Swelling

Table 2 Phase I clinical trial of UCN-01: Initial dose levels (*BSA* body surface area, Cl_t total body clearance, V_c volume of central compartment, Cl_d distributional clearance, V_p volume of peripheral compartment, $T_{1/2\alpha}$ half-life of initial phase, $T_{1/2\beta}$ half-life of terminal phase, C_{max} maximal plasma concentration)

A) Patient characteristics

Dose (mg/m²/day × 3)	No. of patients	Age (years)	Male:female	BSA (m²)	Creatinine clearance (mL/min)
1.8	3	60 (54–68)	3:0	1.94 (1.8–2.0)	101 (68–111)
3.6	1	48	0:1	1.88	64

B) Pharmacokinetic parameter estimates

Dose (mg/m²/day × 3)	Cl_t (L/h)	V_c (L)	Cl_d (L/h)	V_p (L)	$T_{1/2\alpha}$ (h)	$T_{1/2\beta}$ (h)	C_{max} (μM)
1.8	0.0135 (0.006–0.05)	3.25 (1.3–4.8)	0.189 (0.13–0.22)	7.64 (4.6–7.8)	9.13 (3.8–9.2)	488.8 (386–1342)	3.22 (2.3–3.5)
3.6	0.0058	1.24	0.1926	6.27	3.66	915	6.71

Figures in parentheses are ranges

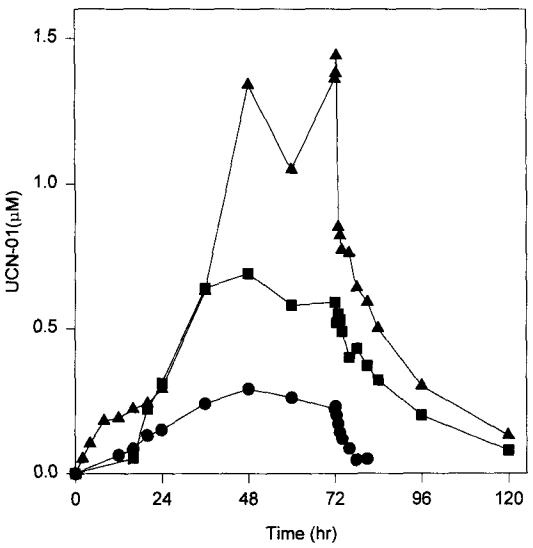

Fig. 1 UCN-01 concentration in dogs. Beagle dogs received continuous UCN-01 infusion at 0.03 (●), 0.05 (■), and 0.1 (▲) mg/kg/h for 72 h. Plasma UCN-01 concentrations were determined at the indicated times

occurred in the area around the subcutaneous port and catheter; this was believed to be due to extravasation of UCN-01. Diarrhea occurred in UCN-01-treated dogs in a dose-related fashion, occurring in 1/4 dogs in the 0.03 mg/kg/h group, 3/4 dogs in the 0.05 mg/kg/h dose group, and 4/4 dogs in the 0.1 mg/kg/h dose group. Drug-related leukopenia (neutropenia) and thrombocytopenia occurred on study days 3–7. The mean C_{max} plasma concentrations were 0.19, 0.33, and 1.37 μM for the 0.03, 0.05, and 0.1 mg/kg/h dose groups, respectively (Fig. 1). Drug-related histopathologic lesions occurred primarily in the lymph tissue/nodes and at the site of infusion. Hepatic inflammation/necrosis, adrenal gland hypertrophy, renal necrosis/hemorrhage, intestinal necrosis, and testicular hypospermia were also present. The MTD was 0.05 mg/kg/h as a 72-h infusion (1.2 mg/kg/day, 24 mg/m²/day). At the MTD, the $t_{1/2}$ was 16.3 h, with a V_d of 3.9 l/kg and a Cl of 0.17 l/h/kg. Local (site of injection) and gastrointestinal toxicity occurred in dogs treated with UCN-01 as a continuous 72-h infusion.

Initial clinical pharmacology of UCN-01

A phase I study of UCN-01 administered to humans was commenced in April 1996 at the Clinical Center, National Institutes of Health, Bethesda, MD, USA. Patient characteristics for some of the patients accrued to the first 2 dose levels are shown in Table 2A. The study is still open to accrual. In contrast to the pharmacology in rats and dogs described above, the disposition of UCN-01 in humans was markedly different. A prolonged $t_{1/2\beta}$ was noted (Fig. 2), with a range of 489–915 h (Table 2B). This behavior correlated with slow calculated clearance (0.0058–0.0135 l/h). The volume of the central compartment was small and in the case of the 1.8 mg/m²/day × 3 dose level approximated plasma volume. Peak plasma concentrations at the end of the infusion ranged from 3.22 μM at 1.8 mg/m²/day × 3 to 6.71 μM in the first patient at 3.6 mg/m²/day × 3. In contrast to dogs, in which peak plasma concentrations of approximately 0.33 μM were associated with the MTD, humans tolerated plasma concentrations of >20-fold this concentration without evident toxicity. It should be noted that the delayed and prolonged clearance of UCN-01 meant that some second (and subsequent) courses were administered prior to clearance of drug from the previous course of therapy. Despite these much higher than expected plasma drug concentrations, the 4 patients shown in Fig. 2 experienced essentially no toxicity attributable to the drug.

Plasma protein binding of UCN-01

The prolonged $t_{1/2\beta}$ and toleration of higher than expected concentrations of UCN-01 suggested that the plasma protein-binding properties of UCN-01 in humans might

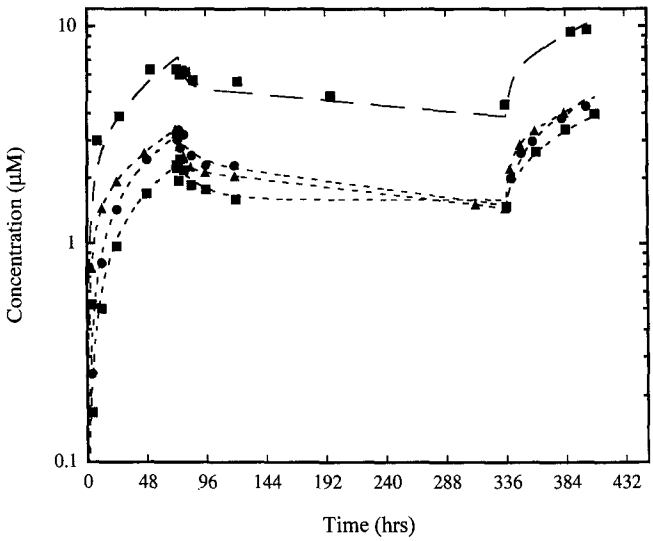

Fig. 2 UCN-01 concentration in humans. Patients were enrolled in the UCN-01 72-h continuous infusion phase I trial and received UCN-01 at dose level 1 (1.8 mg/m²/24 h×3; patients 1, ■; 2, ●; and 3, ▲;- - - -) or dose level 2 (3.6 mg/m²/24 h×3; Patient 4, ■; ——)

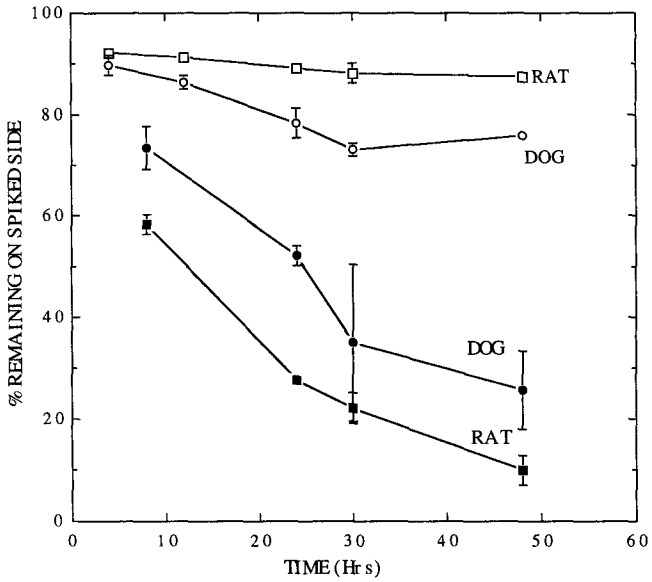

Fig. 3 Distribution of UCN-01 between human and animal plasma in a 2-chamber dialysis cell. UCN-01 (8000 ng, approximately 16 μM) was spiked into a chamber containing human plasma, and the concentration of drug in an adjoining chamber containing plasma of the indicated species was determined at the indicated time (open symbols). In a separate series, UCN-01 (8000 ng, approximately 16 μM) was spiked into the chamber containing the indicated animal species plasma, and the concentration of drug in the adjoining chamber containing human plasma was determined at the indicated time (closed symbols)

Table 3 In vitro unbound plasma fractions

	Added UCN-01 concentration (μM)	
Species	2.07	20.7
Human	<0.02%	0.22±0.04
Dog	0.42±0.07	0.49±0.11
Rat	1.75±0.22	1.88±0.09
Mouse	1.17±0.09	1.65±0.04*

Each value represents the mean ± SD of 3 samples
* P <0.01 vs 2.07 μM

Table 4 Binding parameters of UCN-01 to plasma and AGP

Sample	K_a (×10⁶ l/mol)	*n*	k (×10⁶ l/mol)
Human plasma	799±244	–[a]	2.39±0.10
hAGP	803±144	0.721±0.034	1.04±0.06
Human serum albumin	–[b]	–	1.24±0.04
Dog AGP	13.2±8.3	0.344±0.093	1.05±0.09
Rat AGP	–	–	1.58±0.03

Each value represents the mean ± SD calculated by the nonlinear least-squares method
[a] Binding capacity in plasma was 16.4±0.7 μM
[b] Specific binding was not observed

differ from those in other species. Table 3 demonstrates the species difference of plasma protein binding in vitro. The unbound fraction (fu) in humans was <0.02% at 2.07 μM, while that in dogs, rats, and mice was 0.42%, 1.75%, and 1.17%, respectively. At 20.7 μM the fu values in humans increased to 0.22%, which may be due to partial saturation of binding.

To determine the plasma protein fraction to which UCN-01 might have the greatest affinity, 1 μg/ml UCN-01 was incubated with 1% human globulin, 4% human serum albumin, and 0.1% human α_1-acidic glycoprotein (hAGP), with 37.1%, 6.2%, and <0.02% of added drug appearing in the unbound fraction, respectively. These data indicate that UCN-01 might bind tightly to hAGP. Table 4 demonstrates that while UCN-01 showed no evidence of specific binding to rat AGP or human serum albumin, the association constant of UCN-01 for hAGP was 8.03±1.44 × 10⁸ l/mol and 7.99±2.44 × 10⁸ l/mol for human plasma, indicating species-specific high-affinity AGP binding by UCN-01.

To demonstrate the functional consequences of the differential affinity for UCN-01 of human as compared to rat or dog plasma, a 2-chamber dialysis cell containing animal plasma on one side and human on the other was utilized (Fig. 3). When UCN-01 was added to dog or rat plasma, UCN-01 distributed to the human plasma-containing cell so that by 48 h of incubation approximately 20–30% remained in the dog plasma-containing cell and <10% in the rat plasma-containing cell. In contrast, when added to the human plasma-containing cell, <10% of the added drug appeared to be able to associate with the dog or the rat plasma-containing cell.

To estimate the plasma concentration that might allow free UCN-01 to become available for distribution to tissue sites, 2-chamber equilibrium dialysis cells were used, with plasma spiked with various concentrations of UCN-01 on one side and phosphate-buffered saline on the other. Table 5 demonstrates that at approximately 16 μM, free drug to the extent of approximately 226 nM might become available, increasing to approximately 1.95 μM at a total concentra-

Table 5 Estimation of free UCN-01 in relation to total plasma drug concentrations

Chamber no.	UCN-01 (μM)	% accountable	% free
1	4.14	226	0.96
2	8.28	87.9	0.76
3	16.56	86.8	1.37
4	24.84	74.9	1.96
5	41.4	50.9	4.72

Dialysis chambers were preincubated with a stock of UCN-01 solutions (28.98 μM) prior to introduction of plasma containing UCN-01 of the indicated concentration, and separated from 0.015 M Na phosphate, pH 7.4, 0.15 M NaCl (phosphate-buffered saline). After a 4-h incubation, the UCN-01 concentration in the PBS-containing compartment was determined (% free) as was the apparent UCN-01 concentration in the plasma-containing compartment. The total amount of UCN-01 observed at 4 h allowed estimation of the amount of drug that apparently adsorbed to the apparatus (% accountable)

tion of approximately 41 μM. Such estimates should be viewed as approximate because extensive preequilibration of the apparatus was necessary to obtain meaningful data owing to the tendency of UCN-01 to adsorb to the apparatus and membrane. Nonetheless, they estimate the plasma concentrations at which significant "free," i.e., not bound to a high-affinity site, drug might become apparent.

Discussion

The results presented here demonstrate that despite the toxicologic and pharmacologic parameters observed in dogs and rats, humans have relative refractoriness to the adverse effects of similar UCN-01 concentrations, despite elevated plasma concentrations and prolonged $T_{1/2}$. This appears at least in part to be caused by species-specific high-affinity binding to hAGP. However, additional substances that bind UCN-01 may be present in human plasma.

hAGP is a heterogeneous collection of molecules with potentially differing degrees of sialylation and aggregation, the levels of which can change rapidly as an acute-phase reactant in response to various physiologic stresses [6]. Thus more precise definition of the actual component(s) of this class of plasma proteins which most avidly binds UCN-01 is needed, with careful attention to the influence of the endogenous turnover of these molecules on the observed pharmacology of UCN-01.

Despite these caveats, it is clear that hAGP represents at least one class of high-affinity plasma binding molecule for UCN-01. That human molecules should have binding characteristics so different from those of the animals tested calls into question the ability of preclinical toxicology studies to predict confidently the expected initial human profile of adverse events and dose-limiting toxicity, and the degree of reversibility expected for these occurrences. The data in Table 5 support the idea that as the dose is increased, a fraction of "free" drug can be expected which will approximate the concentration that was well tolerated in animals (approximately 0.2–0.3 μM). This is reassuring because the animal experience would suggest that such "free" drug concentrations are associated with reversible toxicity.

The implications of these findings for the eventual utility of UCN-01 are uncertain. Consideration of the concentration vs time curves shown in Fig. 2 indicates that a substantial fraction of the drug is still present at the time of subsequent courses of therapy. Even when evaluated in species which do not possess high affinity-binding sites on hAGP, such as mice whose clearance of UCN-01 is very rapid ($t_{1/2}$ 85 min) [5], frequent dosing is associated with the optimal antineoplastic effect (Table 1). Thus if the hAGP-bound fraction can serve as a sink or reservoir from which UCN-01 can become available to tissue sites, the observed pharmacologic features would be analogous to a continuing infusion of UCN-01. Alternatively, if the "off-rate" from such binding sites is very low, then the bound molecules are essentially unavailable for ultimate distribution to the tissues. Further studies must measure "free" UCN-01 as a function of infusion time to clarify this issue.

A related concern is whether UCN-01 needs to be given as a continuous infusion, given that the clinical pharmacology in humans is now known to be different from that determined in prior animal studies. One point of view might be that a simple "loading dose," perhaps administered over short periods of time, might achieve the same saturation of hAGP as is ultimately achieved by the slower infusion. If permitted by the absence of serious toxicity related to the more rapid infusion, more time- and cost-efficient means of delivering the drug would utilize the shorter infusion schedule. While this reasoning is attractive from the strictly pharmacologic perspective, from the standpoint of maximizing eventual efficacy one must consider that in certain cell types [8] exposure to active drug concentrations for as long as 72 h is necessary to achieve maximal growth suppression. Considering the shape of the concentration vs time curves for the first 4 patients treated on this protocol (see Fig. 2), there appears to be a distribution phase immediately following completion of the 72-h infusion. This behavior raises the possibility that equilibration with very high affinity-binding sites may not be instantaneous, but rather that drug distribution to tissue sites might potentially occur during a 72-h infusion and diminish once the period of drug administration is completed. This matter will be clarified with definition of the "free" drug concentration as a function of time during and after a variety of infusion schedules.

After consideration of these data and consultations with the US Food and Drug Administration, the initial phase I protocol was altered to account for concerns related to prolonged residence time. Since the observed $t_{1/2}$ was so long, patients within a particular dose cohort receiving differing numbers of courses, depending on the rate of progression of their underlying disease, could have greatly differing cumulative drug concentrations. Thus toxicity could be more reflective of cumulative rather than of acute drug effects and the definition of MTD could potentially be compromised. Therefore in the revised protocol now being completed the period between drug administra-

tions was lengthened to one month, and one-half of the originally administered dose was administered on second and subsequent courses, but over a 36-h interval. It was anticipated from the early pharmacologic results that this dosing scheme would allow an MTD to be established based on an initial acute exposure to a given dose over 72 h, with the amount of drug that had been cleared over the preceding month being approximately replaced on subsequent administrations. Thus information should be acquired about the degree of tolerance to a sustained level over a number of courses, with little tendency to accumulate drug.

In summary, UCN-01 provides a valuable example of how preclinical models do not accurately predict important features of human pharmacology and emphasizes further the need to acquire pharmacologic information in "real time" with the conduct of a phase I trial. UCN-01 will also be an example of how an accurate assessment of "free" and bound drug is instrumental in assessing rational phase II dosing schemes.

References

1. Akinaga S, Gomi K, Morimoto M, Tamaoki T, Okabe M (1991) Antitumor activity of UCN-01, a selective inhibitor of protein kinase C, in murine and tumor models. Cancer Res 51:4888
2. Akiyama T, Yoshida T, Tetsuya T, Shimizu M, Mizukami T, Okabe M, Akinaga S (1997) G_1 phase accumulation induced by UCN-01 is associated with dephosphorylation of Rb and CDK2 proteins as well as induction of CDK inhibitor p21/Cip1/WAF1/Sdi1 in p53-mutated human epidermoid carcinoma A431 cells. Cancer Res 57:1495
3. Bunch RT, Eastman A (1996) Enhancement of cisplatin-induced cytotoxicity by 7-hydroxystaurosporine (UCN-01), a new G_2-checkpoint inhibitor. Clin Cancer Res 2:791
4. Bunch RT, Eastman A (1997) 7-hydroxystaurosporine (UCN-01) causes redistribution of proliferating cell nuclear antigen and abrogates cisplatin-induced S-phase arrest in Chinese hamster ovary cells. Cell Growth Differ 7:779
5. Hill DL, Tillery KF, Rose LM, Posey CF (1994) Disposition in mice of 7-hydroxystaurosporine, a protein kinase inhibitor with antitumor activity. Cancer Chemother Pharmacol 35:89
6. Kremer JMH, Wilting J, Janssen LHM (1988) Drug binding to human alpha-1-acid glycoprotein in health and disease. Pharmacol Rev 40:1
7. Plowman J, Dykes DJ, Hollingshead M, Simpson-Herren L, Alley MC (1997) Human tumor xenograft models in NCI drug development. In Teicher B (ed) Anticancer drug development guide. Humana, Totowa, NJ, p 101
8. Seynaeve CM, Stetler-Stevenson M, Sebers S, Kaur G, Sausville EA, Worland PJ (1993) Cell cycle arrest and growth inhibition by the protein kinase antagonist UCN-01 in human breast carcinoma cells. Cancer Res 53:2081
9. Seynaeve CM, Kazanietz MG, Blumberg PM, Sausville E, Worland P (1994) Differential inhibition of protein kinase C isozymes by UCN-01, a staurosporine analogue. Mol Pharmacol 45:1207
10. Takahashi I, Kobayashi E, Nakano H, Murakata C, Saitoh H, Suzuki K, Tamaoki T (1990) Potent selective inhibition of 7-O-methyl-UCN-01 against protein kinase C. J Pharmacol Exp Ther 255:1218
11. Tomaszewski JE, Smith AC (1997) Safety testing of antitumor agents. In Sipes IG, Gandolf AJ, McQueen CA (eds) Comprehensive toxicology, vol 2. Pergamon, New York, p 299
12. Wang Q, Worland PJ, Clark JL, Carlson, BA, Sausville EA (1995) Apoptosis in 7-hydroxy-staurosporine-treated T lymphoblasts correlates with activation of cyclin-dependent kinases 1 and 2. Cell Growth Differ 6:927
13. Wang Q, Fan S, Eastman A, Worland PJ, Sausville EA, O'Connor PM (1996) UCN-01: a potent abrogator of G_2 checkpoint function in cancer cells with disrupted p53. J Natl Cancer Inst 88:956