

# Circadian Rhythm-varying Plasma Concentration of 5-Fluorouracil during a Five-Day Continuous Venous Infusion at a Constant Rate in Cancer Patients<sup>1</sup>

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## ABSTRACT

A circadian rhythm in the plasma concentration of 5-fluorouracil (5-FUra) is demonstrated in seven patients receiving this drug as a continuous venous infusion at a constant rate for 5 days. All patients had stage C bladder carcinoma and received *cis*-diamminedichloroplatinum(II) (45–91 mg/m<sup>2</sup>) on day 1 as a 30-min venous infusion at 5 p.m. Continuous venous infusion of 5-FUra (450–966 mg/m<sup>2</sup>/day) was started on day 2 at 8:30 a.m. via a volumetric pump and lasted for 5 days (until day 6). Blood samples were obtained on EDTA every 3 h on days 2, 4, and 6 on each patient (20 samples/patient). 5-FUra plasma concentration was determined by high performance liquid chromatography. Data were analyzed by both multiple analysis of variance and cosinor. Mean lowest and highest values ( $\pm$ SEM) were, respectively, 254  $\pm$  33 ng/ml at 1 p.m. and 584  $\pm$  160 ng/ml at 1 a.m. ( $F = 2.3$ ;  $P < 0.03$ ). Because of large intersubject differences in 24-h mean plasma concentration, data were also expressed as percentages of each patient's 24-h mean. Both analysis of variance and cosinor analysis further validated ( $P < 0.0001$ ) a circadian rhythm with a double amplitude (total extent of variation) of 50% of the 24-h mean and an acrophase located at  $\sim$ 1 a.m. (estimated time of peak). Such findings warrant a thorough scrutiny at the chronopharmacology of anticancer drugs when designing continuous infusion schedule. A circadian modulation of the infusion rate of this drug may further optimize the therapeutic index of such treatment modality.

## INTRODUCTION

CVI<sup>3</sup> of cancer chemotherapy have recently been advocated for reducing the toxic side effects of cytostatics without impairing their antitumor effectiveness (1). This applies in particular to the CVI of 5-FUra over 5 consecutive days in patients with gastrointestinal carcinoma (2, 3). This schedule has also been combined with CDDP for patients with head and neck cancers (4, 5). The dose-limiting toxicities of 5-day CVI of 5-FUra mostly include stomatitis and nausea and vomiting (3). The occurrence of such toxic side effects was correlated with high plasma concentrations of 5-FUra (6–8). On another hand, the extent of host toxicity of 5-FUra, like that of 20 anticancer agents, varies predictably as a function of dosing time in laboratory rodents (9). Optimal host tolerance for 5-FUra, as gauged by survival, resulted from administering this drug in the first half of the rest span of mice (10). The present study represents a first step towards a clinical optimization of 5-day CVI of 5-FUra. A monitoring of plasma concentrations of 5-FUra delivered at constant rate for 5 days was undertaken along the 24-h scale in seven patients suffering from bladder cancer. Such investigation was further warranted by the facts that (a) drug pharmacokinetics depend upon their dosing time in humans (11) and (b) a preliminary report suggested that 5-FUra concentrations might be higher at night than during the day despite infusion at constant rate (12).

Received 10/13/87; accepted 12/15/87.

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<sup>1</sup> Supported in part by Grant 6180 from ARC, Villejuif, France.

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<sup>3</sup> The abbreviations used are: CVI, continuous venous infusion(s); 5-FUra, 5-fluorouracil; CDDP, *cis*-diamminedichloroplatinum(II); ANOVA, analysis of variance.

## MATERIALS AND METHODS

**Patient Characteristics.** Seven patients (6 men and 1 woman) aged 58–81 years (median, 72 years) agreed to participate in this study after having been informed of its aims and nature. All had stage C transitional cell carcinoma of the bladder and received our standard chemotherapy protocol for this disease. All patients had a good performance status (<2 in the WHO classification). Times of awakening ranged from 6:30 a.m. to 7 a.m., and retiring times were from 9 p.m. to 9:30 p.m.

All had normal renal function as gauged by serum creatinine and normal liver functions as gauged by serum  $\gamma$ -glutamyltransferase, transaminases, bilirubin, prothrombin time, and liver echography (Table 1).

**Chemotherapy Protocol.** Patients received CDDP on day 1 (Cisplatin; Roger Bellon Laboratories, France) at a dose of 41–91 mg/m<sup>2</sup>. CDDP was diluted in 250 ml of 0.9% NaCl solution and infused i.v. at a rate of 1 mg/min, starting at 5 p.m. This time was selected because it is that of the least renal and gastrointestinal toxicity of this drug (13, 14). Intravenous hydration consisted of a 3-h infusion of 1 liter of 5% dextrose containing 6 g of NaCl, 3 g of KCl, and 500 ml of 20% mannitol given both before and after CDDP infusion.

On days 2, 3, 4, 5, and 6, 5-FUra (Roche Laboratories, Paris, France) was infused i.v. at a constant rate with a volumetric pump (VMM; Vial Medical, France). The dose of 5-FUra to be delivered over 24 h (450–966 mg/m<sup>2</sup>/day) was diluted in 1 liter of 5% dextrose. 5-FUra infusion was initiated at 8:30 a.m. on day 2 (15.5 h after the onset of CDDP infusion). The arm vein in which the infusion was performed was shielded from light.

**Pharmacokinetic Study.** Blood sampling (5 ml) was performed every 3 h on day 2 (first day of infusion), day 4, and day 6 (last day of infusion) at 10 a.m., 1 p.m., 4 p.m., 7 p.m., 11 p.m., 1 a.m., 4 a.m., and 7 a.m. A small heparinized catheter was introduced into an arm vein opposite to the infusion arm in order to allow repeated blood samplings. After 3 ml of blood were removed, 5 ml were collected into EDTA-containing tubes and quickly centrifuged by nurses at the hospitalization level. Plasma was kept at  $-20^{\circ}\text{C}$  until 5-FUra determinations by high performance liquid chromatography which were performed within the 10 days following sampling (15). The sensitivity limit was 5 ng/ml. The day-to-day variation coefficient evaluated for 14 different determinations of a plasma spiked with 1000 ng/ml was 4% (SD/mean  $\times$  100).

**Statistical Analysis.** Raw data were plotted as a function of sampling time for each patient to visually estimate inter- and intraindividual variability. Because of interpatient differences in actual 5-FUra doses delivered, data on plasma concentrations were also expressed as percentages of each individual's 24-h mean separately on each sampling day. Data were analyzed by multiple analysis of variance, plexograms, and cosinor (16).

Plexograms consist of plots of mean values ( $\pm$ SEM) as a function of sampling time.

Time series were also analyzed by the cosinor method with a period ( $\tau$ ) of 24 h. The rhythm characteristics estimated by this linear least squares method include the mesor ( $M$ , rhythm-adjusted mean), the double amplitude ( $2A$ , difference between minimum and maximum of fitted cosine function), and the acrophase ( $\phi$ , time of maximum in fitted cosine function, with local midnight as  $\phi$  reference). They are given with their 95% confidence limits. A rhythm is detected (with regard to the considered  $\tau$ ) when  $A$  differs from zero (non-null amplitude test) with  $P < 0.05$ . The cosinor method was applied both to individual and to pooled time series.

## RESULTS

The plasma concentration of 5-FUra (ng/ml) varied largely over the 5-day treatment course for each patient. Minimal and maximal values, respectively, ranged from 70 to 333 ng/ml in patient 1, from 75 to 708 (patient 2), from 103 to 324 (patient 3), from 44 to 637 (patient 4), from 190 to 724 (patient 5), from 129 to 3330 (patient 6), and from 117 to 563 (patient 7).

Large intersubject differences characterized the 24-h mean plasma concentration of 5-FUra, with statistical significance ( $F$  from ANOVA = 8.5,  $P < 0.0001$ ) (Table 2). Conversely no difference in 24-h mean plasma 5-FUra concentrations was noticed between day 2 ( $324 \pm 72$  ng/ml), day 4 ( $310 \pm 26$ ), and day 6 ( $373 \pm 32$ ) ( $F$  from ANOVA = 0.5,  $P = 0.60$ ).

In order to investigate whether intraindividual temporal variations of 5-FUra concentrations were synchronized, subsequent analyses were performed on data transformed as percentages of each individuals 24-h mean on each study day.

Two-way ANOVA revealed a highly statistically significant effect of sampling time ( $F = 5.5$ ,  $P < 0.00002$ ), with a significant interaction between subject and sampling time ( $F = 1.7$ ,  $P = 0.01$ ). No interaction was validated between study day and sampling time ( $F = 1.4$ ,  $P = 0.16$ ). Cosinor analysis was performed on the time series from each patient and validated a circadian rhythm in plasma 5-FUra concentration for 4 of 7 patients, with acrophases occurring at night between 10 p.m. and 3 a.m. (Table 3). The double amplitude ranged from 46 to

Table 1 Patient characteristics

Patient	Sex	Age (yr)	Wt (kg)	Body area (m <sup>2</sup> )	No. of cycle studied	Total dose (mg/24 h)	
						CDDP	5-FUra
L. A. (1)	M	67	62	1.76	6	100	1700
A. A. (2)	M	76	65	1.77	2	80	800
N. B. (3)	M	78	55	1.59	2	100	800
B. A. (4)	M	72	47	1.44	2	100	1000
L. J. (5)	F	58	30	1.10	3	100	1000
B. K. (6)	M	81	65	1.74	3	100	1000
R. A. (7)	M	72	65	1.70	1	120	1200

Table 2 Twenty-four-h mean plasma concentration of each patient over the 5-day treatment course

Patient	24-h mean $\pm$ SEM <sup>a</sup> (ng/ml)
1	206 $\pm$ 17
2	441 $\pm$ 39
3	193 $\pm$ 11
4	225 $\pm$ 30
5	359 $\pm$ 26
6	650 $\pm$ 147
7	420 $\pm$ 50
All	340 $\pm$ 26

<sup>a</sup> $F$  from ANOVA = 8.5;  $P < 0.0001$ .

Table 3 Circadian variation in plasma concentrations of 5-FUra results from cosinor analysis, with a period ( $\tau$ ) of 24 h

Patient	$P^a$	Double-amplitude $\pm$ SD <sup>b</sup>	Acrophase $\pm$ SD <sup>c</sup>
1	0.17	34	1.10
2	0.05	54	3.10
3	0.01	46 $\pm$ 44	22.20 $\pm$ 270
4	0.67	21	5.00
5	0.0008	84 $\pm$ 48	0.20 $\pm$ 155
6	0.07	106	1.40
7	0.19	110	18.00
1-7	<0.0001	43 $\pm$ 23	1.00 $\pm$ 130

<sup>a</sup> From an  $F$  test of the rejection of the null-amplitude hypothesis.

<sup>b</sup> Estimated total extent of variation  $\pm$  SD, as percentage of the mesor.

<sup>c</sup> Time of maximum (h and min)  $\pm$  SD (min).

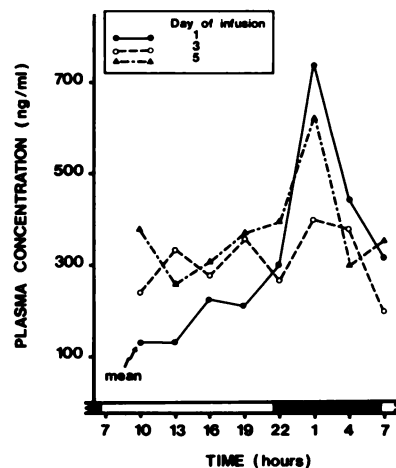


Fig. 1. Circadian rhythm in plasma concentrations of 5-FUra in 7 patients with bladder carcinoma receiving continuous venous infusion of 5-FUra at a constant rate for 5 days (with CDDP at 17 h on day 0). Mean plasma concentration of 5-FUra as a function of sampling time on first, third, and fifth days of continuous venous infusion of 5-FUra at constant rate. Each value represents the mean of seven patients. Two-way ANOVA revealed a statistically significant effect of sampling time on raw values ( $F = 2.3$ ;  $P < 0.03$ ). The reproducibility of the circadian pattern from day to day was indicated by the lack of any statistically significant effect of sampling day ( $F = 0.6$ ;  $P = 0.52$ ) and by the absence of any significant interaction between the effects of sampling time and that of sampling day ( $F = 0.60$ ;  $P = 0.85$ ).

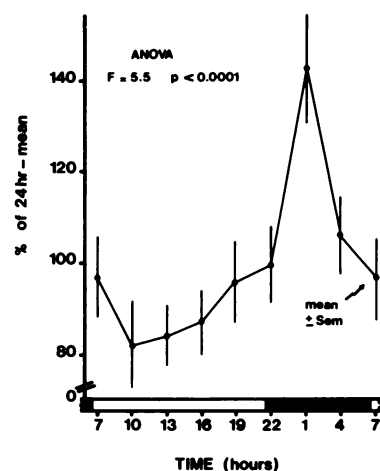


Fig. 2. Circadian rhythm in plasma concentration of 5-FUra in 7 patients with bladder carcinoma receiving continuous venous infusion of 5-FUra at a constant rate for 5 days (with CDDP at 17 h, 15 h before onset of 5-FUra infusion). Data are expressed as percentages of each subject's 24-h mean on each study day (days 1, 4, and 6). The statistical significance of such rhythm was validated both by ANOVA (see figure) and by cosinor ( $P < 0.001$ ).

54% of the 24-h mean. After pooling transformed data from all patients, a highly statistically significant circadian rhythm was documented (Table 3). Figs. 1 and 2 depict the mean variation in plasma concentration of 5-FUra for all seven patients. Maximal values were localized in the first half of the night.

## DISCUSSION

Despite the fact that 5-FUra was continuously infused at a constant rate over 5 consecutive days, no constant plasma concentrations of this drug were achieved on either infusion day.

Large inter- and intraindividual variations were observed and statistically validated. Fluctuations in circulating levels of 5-FUra have been reported previously by several authors (17-19).

The present study demonstrates that such fluctuations do not

occur at random but indeed follow a circadian rhythmic pattern, with maximal values occurring in the first half of the night. Moreover, such a rhythm was also statistically validated or suggested at an individual level in 4 of 7 patients. The predictable total extent of variation was large, *e.g.*, ~50% of the 24-h mean level. A previous report had suggested the occurrence of nocturnal high values of 5-FUra concentrations (12). The present study validates for the first time a circadian rhythm in the pharmacokinetics of this drug given as CVI at constant rate, with an appropriate experimental and statistical methodology.

None of the patients had received any radiation therapy or any chemotherapy other than 5-FUra-CDDP. All patients had a good performance status. This clinical criterion was associated with adequate circadian rhythmicity of hematological and hormonal variables. Conversely, patients with poor performance status tend to lose their 24-h rhythms (20).

Pharmacokinetic interactions between CDDP and 5-FUra have been described. Thus, a single dose of CDDP increased subsequent plasma levels of 5-FUra despite the CVI of this drug. This effect, however, lasted less than 36 h (21) and cannot account for the reproducibility of the circadian rhythm in 5-FUra plasma concentrations from day 2 to day 6.

With regard to the mechanisms involved in such circadian rhythm of 5-FUra pharmacokinetics, variations in the infusion rate and total body clearance could control the so-called "steady-state" plasma concentrations (22). Mechanically related fluctuations of the infusion rate did not exceed 2% with this device. 5-FUra clearance mainly results from liver metabolism (24), although extrahepatic clearance may also be involved (25). The high extraction rate of 5-FUra administered into the hepatic artery has been demonstrated repeatedly (24, 26, 27). 5-FUra is initially transformed into 5-FUraH2 by dehydrouracil dehydrogenase (25). Many reports have established that circadian rhythms govern the activity of numerous liver enzymes involved in drug metabolism (28). This may be the case for this and other enzymes involved in 5-FUra metabolism.

Since 5-FUra plasma levels appear to relate to the occurrence of drug-associated side effects (6–8), the knowledge of such circadian variability may help to devise schedules allowing to further optimize CVI of 5-FUra.

Thus, the dosing times of chemotherapy indeed influenced host tolerance and treatment effectiveness in cancer patients (13, 14, 29, 30). Moreover, venous infusions at constant rate of heparin (31), ketoprofen (32), or doxorubicin (33) were associated with circadian time-varying plasma drug concentrations and/or effects.

Programmable infusion pumps are now available which allow modulation of the infusion rate of 5-FUra in the 24-h scale according to circadian rhythms. Since the circadian time associated with optimal hematological tolerance for 5-FUra (early rest span) corresponded to that of optimal antitumor effect in C57BL/6 mice bearing transplantable colon 36 adenocarcinoma (34, 35), such chronotherapy may prove beneficial for optimizing the therapeutic index of 5-FUra CVI.

## ACKNOWLEDGMENTS

We thank M. Mechkouri for his help in the statistical analyses and Nicole Vríz and Elisabeth Couvé for their excellent editorial assistance.

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*Cancer Res* 1988;48:1676-1679.

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