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Phase I clinical trial of 1-[2-[2-(4-pyridyl)-2-imidazoline-1-yl]-ethyl]-3-(4-carboxy-phenyl)urea (CGP 15720A)

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Summary. A phase I clinical trial of the intravenous administration of a novel pyridyl imidazoline ethyl carboxy phenyl urea was carried out in 42 patients with advanced solid tumors. Five schedules were evaluated: I, daily $\times 5$; II, daily $\times 10$; III, daily $\times 15$; IV, continuous infusion for 5 days; V, continuous infusion for 7 days. Toxicity was not seen in schedule I (maximum dose 3 g/m^2/day) and was minimal in schedule IV (6 g/m^2/day). In schedule II it was seen at 2 and 3 g/m^2/day, in schedule III at 2 g/m^2/day and in schedule V at 6 g/m^2/day. Dose-limiting toxicity consisted of a syndrome of lethargy and fatigue. There were no definitely drug-related changes in hematologic or serum chemistry parameters. No responses were seen, but relief of pain in three patients with prostate cancer was noted. Pharmacokinetics indicate a short half-life, limited volume of distribution, and rapid renal clearance. The recommended dose for phase II studies is 3 g/m^2/day $\times 10$ or 2 g/m^2/day $\times 15$ days.

Introduction

The compound 1-[2-[2-(4-pyridyl)-2-imidazoline-1-yl]-ethyl]-3-(4-carboxy-phenyl)urea (CGP 15720A, PIEC) (Fig. 1) was synthesized by Schmidt-Ruppin and Marxer as part of a novel series of substituted ureas. It showed activity against diethylnitrosamine-induced epidermoid carcinoma of the larynx in hamsters, producing a maximum of 83% reduction in tumor area [6]. Against a human bronchogenic carcinoma line in nude mice, it produced a maximum decrease of 98.2% in tumor weight [4, 6].

In toxicology studies the drug proved to be remarkably non-toxic. At doses of 6, 9 and 12 g/m^2 it failed to produce lethality in mice after a single intraperitoneal injection. Weight gain in the treated and untreated groups was essentially the same. A dose of 6 g/m^2, given daily for 5 days, failed to induce lethality but did result in weight loss. At doses of 9 and 12 g/m^2, 20% of male animals and 10% of female animals died after treatment and there was considerable weight loss in the survivors. Single doses of 12 g/m^2 produced no significant alteration in serum chemistry parameters and no histopathologic lesions were seen on autopsy [3].

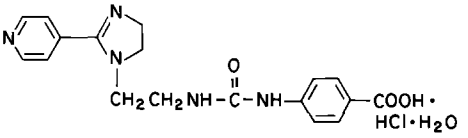

Fig. 1. Structure of PIEC (CGP 15720A)

Intravenous studies in beagle dogs were carried out at doses of 20, 40 and 80 g/m^2. These doses produced vomiting, peripheral vasodilatation, salivation, a drop in body temperature, facial edema, muscle tremors, sedation and diarrhea. At 40 g/m^2, convulsions occurred and one dog died at this dose. At autopsy, thymic enlargement and adrenal atrophy were noted. Doses of 15 and 20 g/m^2/day for 5 days produced, in addition, a fall in hematocrit and an increase in LDH with no change in other chemistry parameters. Fibrosis and atrophy of the prostate was also noted in the treated dogs [3].

On the basis of its preclinical activity, its complete lack of myelosuppression and the absence of any toxicity at doses which produced antitumor effect, the compound was entered into a phase I clinical trial at RPMI. The study was performed under an IND from the FDA, after approval of the clinical protocol by the Institutional Review Board of Roswell Park Memorial Institute. A preliminary report of these data has been published [2].

Methods

Patients with advanced cancer not amenable to other treatments, or for whom other treatments had proven ineffective, were entered onto the study, after giving written informed consent to the study and after the experimental nature of the treatment, the possible hazards, the alternatives and the freedom to withdraw at any time from the study had been carefully explained to them, both orally and in writing. The requirements for entry into the study were an expected survival of at least 2 months duration, at least a 2-week interval since the last dose of potentially myelosuppressive therapy (6 weeks for a nitrosourea and mitomycin C) and recovery from reversible toxicity, a 3-week interval since surgery, except for minor procedures, and the absence of acute intercurrent complications or pregnancy. The minimal hematologic parameters required were a white count of at least 4000/mm^3 and a platelet count of at least 100000/mm^3. The minimum biochemical parameters

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required were serum glutamic oxaloacetic transaminase (SGOT) of less than 100 IU/L and serum creatinine of 1.5 mg/dl or less. Patients were not allowed to have radiation, except small-port radiation, during the course of the study, and were excluded if they had a history of asthma or other acute allergic conditions. The observations made and their frequency are listed in Table 1.

The drug was supplied by the Pharmaceutical Research Department of Ciba-Geigy Ltd. (Basel, Switzerland) in ampules containing 500 and 1500 mg. The starting dose of the phase I study was 500 mg/m^2/day for 5 days. The planned dose escalation was by 100% increments until some sign of effect was seen, then by 50% increments to mildly toxic dose levels and 33% increments to moderate reversible toxicity. The drug was given reconstituted in 1.4% sodium bicarbonate at a maximum concentration of 7.5 mg/ml, initially as a 1-h infusion. Since the volume of the infusate increased with increasing dose, it became necessary to give the drug over a period of several hours (approximately 5 h for the highest dose of 3 g/m^2). Subsequently, a continuous infusion at a starting dose of 6 g/m^2/day, was explored.

Pharmacokinetic studies. A high-performance liquid chromatography method was developed for the assay of PIEC in body fluids and is described in detail elsewhere [5]. Data were analysed and pharmacokinetic parameters calculated using the computer programs BMDPAR [1] on a Univac 90/80 computer as previously described [5].

Results

Five schedules of administration of PIEC were evaluated: I, daily ×5; II, daily ×10; III, daily ×15; IV, continuous infusion (CI) for 5 days; V, CI for 7 days. The doses explored were as follows: schedule I 0.5, 1.0, 2.0 and 3.0 g/m^2/day; schedule II 1.0, 2.0 and 3.0 g/m^2/day; schedule III 2.0 g/m^2/day; schedules IV and V 6.0 g/m^2/day. The patients' characteristics and doses received are listed in Table 2. Some suitable patients, who had been entered on a dose which proved to be non-toxic, were subsequently readmitted to the study at a higher dose. Forty-two patients received a total of 60 complete and five incomplete courses of the drug.

Table 1. Serial observations on patients entering the phase I study of PIEC

Parameter	Frequency of observations			
	Twice weekly	Weekly	Every 3 weeks	Every 6 weeks
Body weight		X		
WBC, platelet count	X(1)			
Hemoglobin, hematocrit		X		
Differential count		X		
Reticulocyte count		X		
Serum chemistry[a]		X		
Serum cortisol (a. m.)			X	
Thyroxine			X	
Clotting studies[b]			X	
Serum protein electrophoresis			X	
Urinalysis		X		
Stool guaiac			X	
Chest X-ray				X
ECG				X
EEG				X

[a] Serum chloride, total CO_2, potassium, sodium, blood urea nitrogen, glucose, calcium, phosphorus, creatinine, uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, lactic dehydrogenase, serum glutamic oxalpacetic transaminase

[b] Prothrombin time, activated partial thromboplastin time, fibrinogen, fibrin degradation products, fibrin monomer

Schedule I

Doses of 0.5, 1, 2, and 3 g/m^2/day ×5 days were explored. Although no toxicity was seen at 2.0 g/m^2, a dose of 4.0 g/m^2 would have involved an unduly large infusion volume. The dose was, therefore, escalated to 3.0 g/m^2. No drug-related side effects were seen. Since no hint of toxicity was seen, and because of the logistics of giving a larger single dose, it was decided to increase the dose by going over to a daily ×10 administration.

Schedule II

Three dose levels were explored, 1.0, 2.0, and 3.0 g/m^2/day ×10. Above 1.0 g/m^2, most patients received only a single course of treatment before evaluation for toxicity and response. No toxicity was seen at 1.0 g/m^2/day ×10. Three patients were treated at 2.0 g/m^2/day ×10. All developed toxicity, consisting of fatigue and lethargy, lasting up to 1 week post drug infusion.

Six patients were entered on a dosage level of 3.0 g/m^2/day ×10, of whom three completed one course and one completed two courses. Of the patients who completed at least one course (n = 4), toxicity was seen in three. Two developed lethargy and fatigue and one developed thrombocytopenia after course number 2, with a drop in platelet count to 91000/mm^3 (see Table 3). This patient had prostatic carcinoma and was extensively pretreated with chemotherapy. Of the two patients who did not complete a 10-day course, in one the dose was discontinued after 7 days of treatment because of disease-related deterioration in the patient's condition, with development of oliguria. In the other patient, the drug was discontinued after eight doses because the patient developed tremors and heart palpitations. No drug-related arrhythmia could be discerned on ECG. This was considered drug-related toxicity, so that toxicity was seen in four of five patients evaluable for toxicity at this dose.

Schedule III

Because the major drug-related toxicity on schedule II was lethargy and fatigue, without significant myelosuppression or organ related toxicity, it was elected to evaluate a daily ×15 days schedule at a dose of 2.0 g/m^2/day ×15.

Five patients were entered at this dose. Three completed one course and one completed two courses.

One patient had an ischemic cardiac episode on day 7 of the treatment and the treatment was discontinued. Of the remaining four patients, toxicity was seen in two (see Table 3). One patient complained of fatigue and lethargy, had hypertension during the drug infusion and displayed thrombocytopenia to a platelet count of 42000/mm^3 5 days after the last dose. In addition, this patient had he-

Table 2. Phase I study of PIEC: patient characteristics

No.	Age (years)	Sex	Diagnosis	Prior therapy	Performance status[a]	PIEC (g/m² × day/no.)	Dose courses
1	42	F	Adeno ca rectum	5-FU, MeCCNU, MitC	1	0.5 × 5/2	3 × 5/1
2	69	F	Adeno ca rectum	RT, DAMP	0	0.5 × 5/2	3 × 5/3
3	36	M	Mesothelioma pleura	RT, ADR	3	0.5 × 5/1	
4	53	M	Adeno ca lung	BLEO, 5-FU, MTX	1	0.5 × 5/2	
5	67	M	Squamous ca lung	BLEO, 5-FU, MTX, ADR DDP, VCR, CTX, VBL, MitC	0	0.5 × 5/2	
6	67	F	Adeno ca colon	5-FU	1	0.5 × 5/2	
7	60	M	Adeno ca colon	5-FU, DAMP	0	1 × 5/2	3 × 5/2
8	60	M	Adeno ca colon	DAMP	0	1 × 5/2	
9	69	M	Adeno ca colon	MeCCNU, VCR, 5-FU, STREPT	0	1 × 5/2	
10	45	M	Adeno ca colon	RT, 5-FU	0	2 × 5/2	
11	66	M	Squamous cell ca of unknown origin	RT	3	2 × 5/2	
12	57	M	Adeno ca of unknown origin	5-FU, ADR, MitC	3	2 × 5/1	
13	73	F	Adeno ca colon	None	1	2 × 5/2	
14	57	M	Large cell ca lung	BLEO, DDP, VBL, MitC	3	3 × 5/inc.	
15	43	M	Pseudomyxoma peritonei	5-FU, hydroxyurea	1	3 × 5/2	
16	43	M	Squamous cell ca lung	RT, CTX, ADR, MTX, PROC	1	3 × 5/1	
17	71	M	Adeno ca lung	DDP, ADR, MTX, 5-FU, VCR	1	3 × 5/2	1 × 10/2
18	66	M	Small cell ca lung	RT, BLEO, DDP	1	3 × 5/2	
19	61	F	Adeno ca colon	None	0	3 × 5/2	
20	68	M	Squamous cell ca lung	DAMP, CHIP	3	3 × 5/2	
21	58	M	Malignant melanoma	DDP, DTIC, BCNU, VCR, ActD	3–4	1 × 10/1	
22	51	M	Small cell ca lung	5-FU, MTX, BLEO, ADR DDP, MTX, VCR, CTX, MitC	3	1 × 10/1	
23	61	F	Adeno ca colon	DAMP, 5-FU, CF	2	2 × 10/1	
24	69	M	Adeno ca prostate	DDP, Estracyt, 5-FU, CTX, MTX	3–4	2 × 10/5	6 × 7/1 CI
25	61	F	Adeno ca lung	CTX, ADR, MTX, PROC, BLEO, DDP, VBL, MitC	0	2 × 10/1	3 × 10/1
26	52	M	Renal cell ca	Megace, immunotherapy	1	3 × 10/1	
27	67	M	Adeno ca prostate	RT, DES, DDP, 5-FU, CTX, MTX	2	3 × 10/inc.	2 × 15/1
28	74	F	Transitional cell ca, kidney	RT, 5-FU, CTX, ADR	3	3 × 10/inc.	
29	55	F	Transitional cell ca bladder	MTX, CHIP	2	3 × 10/1	
30	74	M	Adeno ca prostate	RT, 5-FU, CT, DDP, Estracyt, MTX, ADR, 5-FU	1	3 × 10/2	
31	55	M	Adeno ca prostate	5-FU, DES	1	2 × 15/2	
32	57	F	Small cell ca lung	RT, CTX, CCNU, VP-16, VCR, ADR, 5-FU	1	2 × 15/1	
33	74	M	Adeno ca prostate	5-FU, MTX, Megace, DES	3	2 × 15/inc. (discontinued on day 7)	
34	44	M	Squamous cell ca head and neck	RT, photoradiation	3	2 × 15/inc.	
35	56	M	Adeno ca, unknown primary	RT		6 × 5/1 CI	6 × 7/1
36	60	F	Adeno ca colon	Sodium cyanate, photoradiation	1	6 × 5/1	6 × 7/1
37	54	M	Adeno ca colon	5-FU	1	6 × 5/1	
38	57	M	Adeno ca lung	VCR, MTX, MitC	1	6 × 5/1	
39	66	M	Adeno ca lung	5-FU, VCR, ADR, MTX	1	6 × 5/1	
40	64	M	Adeno ca prostate	TACE, MTX, CTX, 5-FU DDP, Estracyt, Anandron	2	6 × 5/1 inc. drug discontinued on day 2	
41	49	M	Squamous cell ca lung	BLEO, DDP, VBL, MitC	2	6 × 7/2	
42	44	M	Extragonadal seminoma	DDP, VCR, BLEO, VP-16, ActD, CTX, CHIP	1	6 × 7/1 inc. drug discontinued on day 6	

Abbreviations: RT, Radiation therapy; 5-FU, 5-fluorouracil; MeCCNU, 1-(2-chloroethyl)-3(4-methylcyclohexyl)-1-nitrosurea; DAMP, 2,4-diamino-5-adamantyl-6-methyl pyrimidine; BLEO, bleomycin; MTX, methotrexate; ADR, doxorubicin; DDP, cisplatin; VCR, vincristine; CTX, cyclophosphamide; VBL, vinblastine; MitC, mitomycin C; STREPT, streptozotocin; PROC, procarbazine; BCNU, 1,3-bis-chloro(2-chloroethyl)-1-nitrosourea; CHIP, iproplatin; DTIC, dacarbazine; ActD, actinomycin D; CF, citrovorum factor; DES, diethylstilbestrol; VP-16, etoposide; inc., incomplete course

[a] ECOG, Eastern Cooperate Oncology Group

Table 3. Phase I study of PIEC: results

Dose (g/m^2/day)	*n*	Toxicity		Remarks
		Hematologic	Other	
0.5 × 5	6	None	None	Two patients had arrhythmia, one atrial flutter 1 h after first dose, one tachycardia atrial premature contractions after first dose. Felt not to be drug-related
1.0 × 5	3	None	None	–
2.0 × 5	4	None	None	–
3.0 × 5	10	None	None	Patient no. 14 received only two doses
1.0 × 10	3	None	None	–
2.0 × 10	3	None	Lethargy, fatigue (3)	One patient (no. 24) had marked improvement in performance status lasting 6 months with continued drug administration
3.0 × 10	6	Thrombocytopenia (platelet count 91 000/mm^3 on day 16 of second course) in one patient	Lethargy, fatigue (2); tremors after dose 8 (1)	One patient received only seven doses because of disease progression, one received only eight doses because of possibly drug-related side effects (tremors and palpitations). One patient had relief of pain for 6 weeks.
2.0 × 15	5	Thrombocytopenia associated with DIC, probably not drug-related, in one patient (platelet count 42 000/mm^3)	Lethargy, fatigue (2); hypertension (1)	One patient received only seven doses because of myocardial ischemia on day 7. One patient had transient improvement in pain lasting 3 weeks
6.0 × 5	6	None	Nausea, vomiting and diarrhea (1); hypertension (1)	One patient received only 2 days of drug because of severe emotional problems
6.0 × 7	5	Thrombocytopenia (platelet count 49 000/mm^3) in one patient	Lethargy, weakness (3); confusion (1); seizure (1)	One patient had only 6 days of drug because of grand mal seizure

maturia. Coagulogram in this patient showed a low fibrinogen level and increased concentration of fibrin degradation products, which, together, were indicative of disseminated intravascular coagulation (DIC) and were considered to be disease-related rather than drug-related. Thrombocytopenia, in this patient, is, thus, likely due to DIC and not to drug induced myelosuppression.

Continuous infusion: Schedules IV, V

Because of the logistic problems associated with a daily × 15 drug administration, CI at a dose of 6.0 g/m^2/day × 5 was evaluated. Nine patients were entered on CI and eight completed at least one course of 5 days; three patients had two courses. One of the nine patients (patient no. 24, Table 2) had had prior exposure to PIEC.

Schedule IV. In the 5-day administration, six patients were entered. One was discontinued after 2 days because of poor psychological and emotional status. Four patients had no symptoms and no hematological or chemical changes and were deemed non-toxic. One patient had gradually increasing blood pressure during the drug infusion from 130/70 mm Hg before treatment to 194/100 mm Hg on day 5. The patient was treated with Aldomet, 250 mg bid, with fall of blood pressure to 160/80. He subsequently received 7 days CI of PIEC without hypertension (Aldomet was continued). One patient had nausea, vomiting and diarrhea on day 5 which subsided within 24 h of stopping the drug.

Schedule V. Four patients received five courses of 7 days CI. Three of these developed toxicity. All three had lethargy and weakness. In addition, one had generalized pruritis on days 3–5, one had slight confusion and one had anorexia. One patient had thrombocytopenia with a platelet nadir of 49 000/mm^3. A fifth patient had 6 days of drug infusion but this was discontinued when the patient had a grand mal seizure. CAT scan with contrast was negative for brain metastases. A drug effect of PIEC must be assumed, as at autopsy this patient showed essentially normal cerebral cortices.

The possibility of cardiac effect from this drug deserves comment. Early in the study two patients developed arrythmia after the first dose of 0.5 g/m^2. In both cases, the patient had thoracic disease and it was felt that these episodes were not drug-related. Two patients have shown hypertension which could be drug-related, but in both cases the drug was continued without incident. Of more concern are four cases of myocardial ischemia in some temporal relationship to drug administration. Patient no. 15 (Table 2) had a history of myocardial infarction 5 years before entry into the study. Four weeks after completion of his second course of 3 g/m^2/day × 5, he developed acute chest pain

and collapsed and died the following day. Autopsy showed myocardial infarction. Patient no. 26 had a complete right bundle branch block on ECG. She received 3 g/m^2/day for 8 days. On readmission 4 weeks later, an ECG showed, in addition to the previously noted right bundle branch block, marked T wave inversion. Patient no. 33 had a pretreatment ECG which showed intermittent minor T wave changes. He commenced daily administration of 2 g/m^2/day but on day 7 developed severe substernal chest pain. ECG showed ischemic changes and the drug was discontinued. ECG was normal the following day. Patient no. 40 had a pretreatment ECG which showed minor changes (he had no history of cardiac disease). He started continuous infusion of PIEC (6 g/m^2/day) but on day 6, the drug was discontinued because he had a grand mal seizure. Five days later he developed tachypnea and chest pain and died the same day. Autopsy showed the cause of death to be myocardial infarction.

Pharmacokinetics of PIEC

The principal pharmacokinetic parameters for 17 patients, analyzed according to a two-compartment open model, are shown in Table 4. The beta-phase half-life ($t_{1/2}$beta) ranged from 1.66 to 12.34 h. However, 14 of 17 values lay in the range 3.16–8.00 h; the median value was 4.44 h. The steady state volume of distribution (Vss) was, in general, a little more than half that of the total body water, suggesting limited intracellular penetration of the drug. Renal clearance (Clr) accounted for a median of 64% of total plasma clearance (Cl) (range 46%–72%, n = 11) and excretion at 24 h was up to 90% of the administered dose.

Discussion

PIEC is a compound of novel structure which has been studied in an initial clinical tiral. It was remarkably non-toxic in preclinical toxicology and this characteristic was also seen in the clinical trial.

Administration of 3 g/m^2/day for 5 days failed to produce any side effects or any evidence of hematological or biochemical abnormalities. A dose of 1 g/m^2/day for 10 days was also nontoxic. The major toxicity seen was a syndrome of weakness and lethargy which was not associated with any biochemical or electrolyte abnormalities, no fall in blood pressure or any other detectable side effects. Four patients developed evidence of cardiac ischemia during, or at some time after, PIEC treatment. Though it is difficult to indict the drug in each of these cases because of the prior history, the occurrence of four instances suggests that considerable circumspection is called for in the use of this agent in patients with a prior history of myocardial ischemia or ECG abnormalities.

The pharmacokinetics of PIEC show a short-half life, rapid renal excretion and limited distribution intracellularly, all of which are in line with the low toxicity of the drug. Studies with ^{14}C-labeled PIEC, previously reported [5], indicate that the drug is neither metabolized nor bound to plasma protein. It is therefore likely that impairment in renal function, but not impairment in hepatic function, will increase the toxicity of the agent.

There were no complete or partial responses with the agent. Three patients with prostatic carcinoma experienced decrease in bone pain and one of these showed an improvement in performance status from 3 to 0–1 which lasted for 6 months with continued administration of the drug, at which time his disease progressed. Since the drug produced prostatic atrophy in dogs, these observations are of some interest.

The recommended dose for phase II studies is 3 g/m^2/day × 10 or 2 g/m^2/day for 15 days. However, because of the logistic problems posed by this schedule, we are currently evaluating oral administration of the drug.

Table 4. Pharmacokinetics of PIEC

Patient no.	Dose (g/m^2)	Pharmacokinetic parameter (mean ± SD)								
		AUC (μg/ml · h)	$t^1/_2$ alpha (h)	$t^1/_2$ beta (h)	Vc (l)	Vss (l)	Kd (l/kg)	Cl (l/h)	%Ur. Excr (at 24 h)	CLr (l/h)
2	0.50	114.82	0.73	4.49	14.37	28.23	0.52	6.10	71.40	3.67
3	0.50	33.95	0.31	1.66	22.65	43.02	0.46	29.45	–	–
5	0.50	124.40	0.31	3.33	11.09	25.81	0.42	6.43	42.00	4.20
6	0.50	200.70	0.22	4.44	8.29	27.44	0.25	4.98	69.20	2.96
7	1.00	240.15	0.19	2.62	10.20	26.61	0.26	8.33	69.80	5.31
10	2.00	855.50	1.42	5.01	15.36	22.29	0.26	4.68	69.50	2.15
11	2.00	526.91	0.94	4.19	14.51	24.15	0.35	6.83	–	–
12	2.00	627.36	1.71	12.34	17.49	33.53	0.48	5.74	–	–
24	2.00	859.68	0.61	4.35	14.09	24.77	0.30	4.65	–	–
24	2.00	803.85	1.17	5.06	14.10	23.03	0.26	4.98	64.00	3.56
2	3.00	1101.50	1.56	5.16	11.82	16.34	0.29	3.81	48.40	1.91
13	3.00	821.38	0.50	3.40	7.73	16.41	0.21	4.75	90.20	3.31
14	3.00	1005.43	0.92	4.77	10.91	20.06	0.29	5.07	–	–
16	3.00	764.87	0.87	3.79	9.97	15.10	0.25	6.28	70.00	4.54
17	3.00	701.98	0.83	3.16	15.83	24.05	0.25	8.55	64.80	4.34
20	3.00	1026.17	1.87	7.48	17.25	24.33	0.35	5.26	64.00	3.37
26[a]	3.00	1786.89	2.34	8.00	17.83	25.47	0.31	3.36	–	–

A dash indicates that data were not available

Abbreviations: AUC, area under curve; $t^1/_2$ alpha, alpha-phase half-life; $t^1/_2$ beta, beta-phase half-life; Vc, volume of the central compartment; Vss, steady state volume of distribution; Kd, mass average distribution coefficient; Cl, plasma clearance; %Ur. excr., percent of dose excreted in urine; Clr, renal clearance

[a] Fifth day pharmacokinetics

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