Flucytosine kinetics in subjects with normal and impaired renal function

Kinetics and bioavailability of flucytosine were studied in 5 subjects with normal renal function. Kinetic parameters and absorption were compared after a 500-mg dose administered in the following manner: intravenously, aqueous solution, and capsules while fasting; capsules after meals; and capsules with antacid. Encapsulation, food, and antacid decreased the absorption rate constant but the total amount absorbed orally did not differ significantly. Bioavailability assessed by the urinary recovery or comparison of the AUC_0 to AUC_{iv} on the average showed 76% to 89% oral absorption. In 3 patients on hemodialysis, the serum concentrations in the β-phase following oral flucytosine in capsules during fasting were in the same range as those after a comparable intravenous dose. The mean steady-state distribution volume (V_{dss}) was 0.679 L/kg in normal subjects and ranged between 0.413 and 0.706 L/kg in 9 patients with renal failure. The mean t½β was 4.2 hr in normal subjects and the renal clearance was comparable to creatinine clearance. In renal failure, a linear regression analysis showed the t½β (hr) to be numerically about 5 times the steady-state serum creatinine concentration (mg/dl). Under the conditions of the study, hemodialyzer clearance of flucytosine was rapid and similar to creatinine hemodialyzer clearance. Computer simulation based on the measured pharmacokinetic parameters demonstrated that a loading dose (20 mg/kg) after dialysis should result in therapeutic plasma concentrations for susceptible organisms and avoid toxic levels.

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Flucytosine (5-fluorocytosine, Ancobon) is a fluorinated pyrimidine chemically related to fluorouracil and floxuridine. It has been shown to be effective against candidiasis, chromomycosis, and cryptococcal meningitis.[14, 15] The drug is not metabolized by man and is excreted unchanged in the urine.[9, 16] Until recently, the oral capsule was the only available dosage form. Limited kinetic studies have been done with this preparation in patients with normal renal function and renal failure.[2, 6, 8, 13] The recent availability of an intravenous preparation and a specific sensitive chemical assay with the use of high-pressure liquid chromatography have made it possible for us to investigate the bioavailability of the oral preparation more completely as well as the kinetics of the drug in man with normal and impaired renal function.

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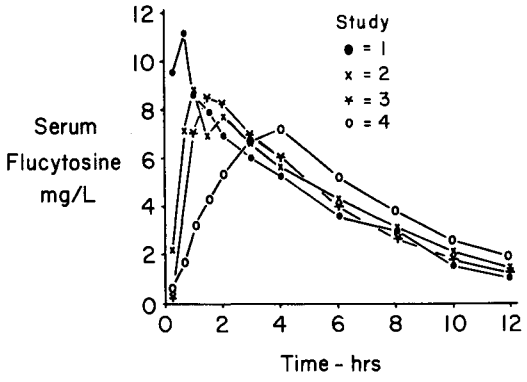

Fig. 1. The mean serum concentration of flucytosine after a 500-mg dose orally.

Methods and procedures

Subjects with normal renal function.

Oral studies. Four men and one woman volunteered for four separate oral studies about 1 wk apart. The subjects were 18 to 40 yr old (mean, 25) and weighed 53 to 73 kg (mean, 61). All subjects were shown by medical examination to be in good physical condition with normal blood and urine laboratory values. Verbal assurance was obtained from all subjects that they had taken no known enzyme-inducing agents for 1 mo and no other drugs for 1 wk preceding the study. One subject (No. 3 in Table II) was on levothyroxine (0.3 mg daily) for chronic hypothyroidism.

The subjects fasted overnight before each experiment and were not permitted to eat, apart from test meals, until 4 hr after dosing. Medication was administered between 8 and 9 A.M.; blood samples (4 to 5 ml) were collected from a forearm vein into a syringe and placed in a tube containing no anticoagulant immediately before dosing and at 20 and 40 min and 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hr after dosing. Serum was separated and frozen until assayed. Urine was collected for 48 hr after dosing and aliquots were frozen until assayed.

Subjects received a single 500-mg dose of flucytosine as a capsule or aqueous solution. A standard hospital breakfast was given when indicated in the study protocol as follows: study 1—500 mg as an aqueous solution with 100 ml of water on an empty stomach; study 2—500 mg as a single capsule with 100 ml of water on an empty stomach; study 3—500 mg as a single capsule with 100 ml of water immediately after a standard breakfast; study 4—500 mg as a single capsule with 100 ml of water immediately after 30 ml of aluminum hydroxide: magnesium hydroxide, 4:1 (Aludrox); repeated similar doses of the antacid were given at 30-min intervals thereafter for 4 hr.

Intravenous studies. Three of the subjects who had participated in the oral studies and one additional subject participated. After an overnight fast, 500 mg of a commercial intravenous solution of flucytosine (10 gm/L) was given rapidly (1 to 2 min) into a forearm vein. Blood and urine collections were similar to that described for the oral studies.

Patients with renal insufficiency.

Oral studies. Two women and one man on chronic, thrice-weekly hemodialysis were studied. Because of her small size (36.2 kg), one patient received a single 500-mg capsule orally, whereas the other 2 patients each took 1,000 mg (2 capsules). The drug was taken after at least 6 hr of fasting and within 2 hr after completion of routine hemodialysis.

Blood samples were obtained during the initial 2 hr after drug ingestion as previously described for normal subjects. After 2 hr, however, blood was then obtained every 6 to 8 hr up to 48 hr after dosing.

Two patients also received the same oral dose after each of three subsequent dialysis treatment periods to study drug cumulation and removal during dialysis. Blood samples were obtained at the beginning, midpoint, and end of each hemodialysis treatment. In both cases, a Gambro Lundia (17μ) dialyzer was used for about 6 hr with blood flow from 150 to 200 ml/min and dialysate flow from 450 to 500 ml/min.

Intravenous studies. Six patients with severe renal insufficiency (glomerular filtration rate [GFR], <10 ml/min) in addition to 3 patients who participated in the oral studies received either 500 or 1,000 mg of flucytosine intravenously in a forearm vein over a 3- to 5-min period. Frequent blood samples were obtained in a manner similar to that in the oral study. The renal clearance of a single injection of ^{169}Yb-DTPA or endogenous creatinine was used to estimate the glomerular filtration rate (GFR) at the time of study.[12]

Assays. Flucytosine was assayed by high-

Table I. *Kinetic parameters with oral* flucytosine in normal subjects*

Parameter	Study 1	2	3	4	IV*	Paired t test
k_a (hr^{-1})	5.08 ± 0.58†	1.54 ± 0.38	0.291 ± 0.459	1.45 ± 0.06		1 > 2-4
k_{el} (hr^{-1})	0.226 ± 0.019	0.179 ± 0.073	0.263 ± 0.110	0.198 ± 0.202		NSD‡
t½ (hr)	3.1 ± 0.3	3.9 ± 1.1	2.6 ± 1.9	3.5 ± 1.2		NSD
$AUC_0^{0-\infty}$(mg) (L^{-1})(hr)	54.3 ± 4.1	60.3 ± 7.4	62.3 ± 29.9	56.3 ± 2.7		NSD
V_{dext}(L/kg)	0.621 ± 0.089	0.697 ± 0.251	0.459 ± 0.075	0.676 ± 0.208		NSD
Urinary recovery						
0-24 hr (mg) (L^{-1})	239 ± 154	232 ± 176	213 ± 142	169 ± 99	400 ± 108	NSD
24-48 hr (mg) (L^{-1})	16.7 ± 13.3	12.8 ± 9.5	16.2 ± 19.8	43.7 ± 62.5	7.1—§	NSD
48 hr recovery (%)	88 ± 11	81 ± 23	76 ± 18	82 ± 15	99 ± 7	NSD

*Intravenous urinary concentrations in 4 subjects but only 3 participated in oral studies (see text).
†±1 SD.
‡No significant difference.
§Only two values.

Table II. *Kinetic parameters with intravenous flucytosine in normal subjects*

Parameter	Subject 1	2	3	4	Mean (±1 SD)
Weight (kg)	65.4	54.6	69.1	73.3	
V_1 (L/kg)	0.266	0.258	0.165	0.234	0.231 ± 0.046
V_{dss} (L/kg)	0.651	0.626	0.798	0.641	0.679 ± 0.080
k_{12} (hr^{-1})	3.07	1.84	7.90	2.02	3.71 ± 2.85
k_{21} (hr^{-1})	2.12	1.25	2.06	1.17	1.65 ± 0.51
k_{el} (hr^{-1})	0.475	0.527	0.732	0.476	0.553 ± 0.122
$AUC_{iv}^{0-\infty}$ (mg) (L^{-1}) (hr)	54.0	68.8	63.2	64.8	62.7 ± 6.3
t½β (hr)	3.8	3.6	4.8	4.4	4.2 ± 0.6
Cl_p (ml) (min^{-1})*	154	121	132	129	134 ± 14
Cl_r (ml) (min^{-1})†	144	129	142	117	133 ± 13
Cl_{cr} (ml) (min^{-1})‡	127	126	113	112	120 ± 8
$\frac{\beta}{k_{el}}\left(1+\frac{k_{12}}{k_{21}}\right)$	0.948	0.899	0.748	0.573	0.792 ± 0 169

*Cl_p: Plasma clearance.
†Cl_r: Renal clearance.
‡Cl_{cr}: Creatinine clearance.

pressure liquid chromatography.[1] Creatinine determinations were made by an Auto-analyzer technique.[3] Radionuclide counting was done in an automatic gamma well counting system. Plasma protein binding was measured by ultrafiltration with the use of Amicon Centriflo cones. Drug in plasma (5 ml) was ultrafiltered (0.5 ml obtained) and both samples were analyzed for flucytosine. These concentrations were compared with those obtained with drug in binding buffer (138 mM NaCl, 1.5 mM $MgCl_2$, 1.6 mM $NaHCO_3$, 1 mM NaH_2PO_4, 2.5 mM $CaCl_2$, and 4 mM KCl) to check for binding of drug to the cone membrane during ultrafiltration. Binding to the cone membrane did not occur.

Pharmacokinetic analysis. The times when samples were obtained and serum concentrations of the drug were fitted with equal weighting to a two-compartment (IV studies) or a one-compartment (oral studies) model by a nonlinear least-squares computer program written by us. Apparent volumes of distribution and

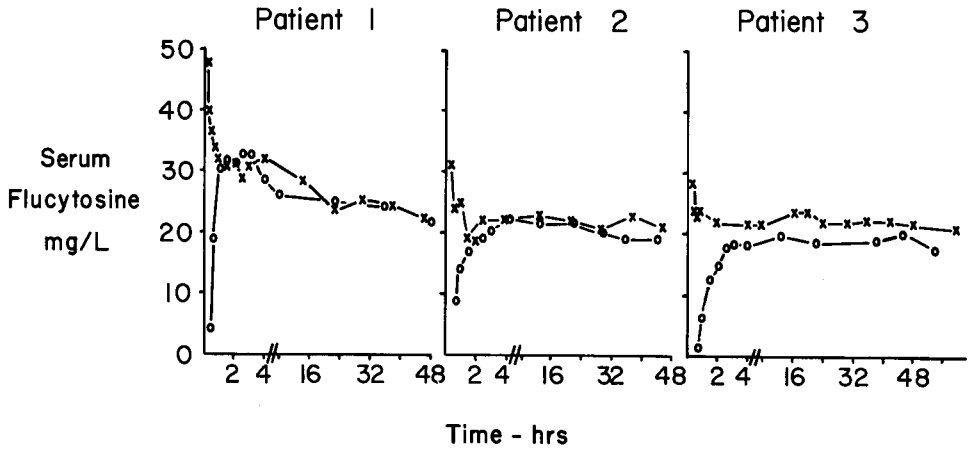

Fig. 2. The serum concentration of flucytosine in each of 3 patients with end-stage renal failure. Flucytosine (500 mg) was given orally (o-o) or intravenously (x-x).

Table III. *Bioavailability measured by comparing oral to intravenous AUC*

	3 normal subjects				
Parameter	*Study 1*	*Study 2*	*Study 3*	*Study 4*	*Study IV*
$AUC_0^{0-\infty}$ (mg) (L^{-1}) (hr)	54.1 ± 5.1*	56.8 ± 7.8	51.5 ± 5.8	58.1 ± 12.9	
$AUC_{iv}^{0-\infty}$ (mg) (L^{-1}) (hr)					65.6 ± 2.9
$AUC_0/AUC_{iv} \times 100$	82.7 ± 10.5	86.8 ± 14.1	78.4 ± 5.3	89.1 ± 23.0	

appropriate model rate constants were derived from the fitted coefficients and exponents for each set of data as described by Wagner.[17]

Bioavailability was estimated by comparing the area under the curve (AUC) of the serum concentration vs time plot following oral drug ingestion (AUC_0) with that determined after intravenous injection (AUC_{iv}). Bioavailability was also assessed by comparing the total urinary recovery following both routes of administration in normal subjects. In 3 patients on chronic hemodialysis, the peak drug concentration after oral ingestion was compared with the peak concentration in the β-phase after intravenous injection as a measure of bioavailability.

Statistics. Serum concentrations at each sampling time, urine data, and pharmacokinetic parameters were examined by analysis of variance. If significant differences due to treatments were obtained ($p < 0.05$), results from individual studies were compared by a paired t test.

Results

Subjects with normal renal function.

Oral studies. Mean serum concentrations are summarized in Fig. 1. Table I contains kinetic data and a summary of recoveries in urine.

The data demonstrate that an aqueous solution of flucytosine is more rapidly absorbed than the capsular form in the fasting state and that ingestion of the drug with a meal or antacid decreases the rate of absorption during the first hour. The mean peak serum concentration during fasting with the solution was 11.2 mg/L at 40 min and 8.7 mg/L with capsules at 1 hr. Furthermore, large deviations about the mean serum concentration in the initial 2 hr indicate a marked intersubject variation in the absorption rate constant, particularly with capsules. After 6 hr, the mean serum concentration of flucytosine was greatest when taken with a meal.

Although the rate constant for gut absorption varied between studies, the AUC data and urinary recoveries (Table I) showed no significant difference in total absorption.

Intravenous studies. The studies done in 4 subjects are summarized in Table II. The serum concentration curve/time plot was fitted to a two-compartment open model. The apparent steady-state volume of distribution was 45 ±

Table IV. *Kinetic parameters of oral and intravenous flucytosine in three hemodialysis patients*

Parameter	Patients		
	1	*2*	*3*
Oral			
Weight (kg)	78.0	62.2	36.2
k_a (hr^{-1})	1.49	0.778	0.767
$V_{d\ ext}$ (L/kg)	0.396	0.694	0.691
k_{el} (hr^{-1})	0.01	0.005	0.0001
t½ (hr)	68.1	135.1	542.9
$AUC_0^{0-\infty}$ (mg) (L^{-1}) (hr)	3,190	4,550	15,200
Cl_p (ml) (min^{-1})	5.2	3.7	0.6
Peak concentration (mg) (L^{-1})	31.7*	22.6*	20.0†
Intravenous			
V_1 (L/kg)	0.214	0.312	0.276
V_{dss} (L/kg)	0.413	0.706	0.602
k_{12} (hr^{-1})	1.50	2.03	5.10
k_{21} (hr^{-1})	1.62	1.61	4.26
k_{el} (hr^{-1})	0.014	0.005	0.0001
t½β (hr)	93.1	340	1160
Cl_p (ml) (min^{-1})	4.0	1.5	0.2
Cl_{cr} (ml) (min^{-1})	2.0	—	0
$AUC_{iv}^{0-\infty}$ (mg) (L^{-1}) (hr)	4,170	11,300	38,200
Peak concentration (mg) (L^{-1})	31.2*	22.2*	22.3†

*Dose, 1.0 gm.
†Dose, 0.5 gm.

12L or 0.679 L/kg which probably represents a value close to total body water in these subjects. Elimination of the drug was rapid with a mean k_{el} of 0.553 ± 0.122 hr^{-1} and a t½β of 4.2 ± 0.6 hr. The similar mean plasma and renal clearance rates suggest little biotransformation of the drug and renal excretion only.

As noted by Wagner,[17] the use of a one-compartment model for kinetic predictions of drug dosage regimens is satisfactory when $\frac{\beta}{k_{el}}\left(1 + \frac{k_{12}}{k_{21}}\right)$ approaches unity. This was only true for Subject 1 (Table II), with a mean for the group of 0.792. Thus, for subjects with normal renal function, better predictions of steady-state plasma concentrations would be obtained if a two-compartment open model were used for calculations.

Bioavailability studies. The urinary recovery data (Table I) indicate incomplete and variable drug absorption following oral dosing. Statistical analysis did not show significant bioavailability differences between studies. The comparison of the AUC_0 to AUC_{iv} (Table III) gave similar results with 78% to 89% of the ingested flucytosine being absorbed in this small group of subjects. The similarity of these two evaluations suggests also that little biotransformation of the drug occurs.

Patients with renal insufficiency.

Oral and intravenous studies. The serum concentrations are graphically displayed in Fig. 2 and the kinetic values summarized in Table IV for the 3 patients who participated in both studies. Comparing the oral peak drug concentration to that obtained after intravenous injection of the same dose suggests that the mean fraction of flucytosine absorbed in this group was 98% of the dose, but comparison of the AUC_0 to AUC_{iv} (Table IV) suggests mean oral absorption of only 50%. In this case the AUC calculations are suspect. The very slow elimination of flucytosine in severe renal failure makes accurate calculations of the AUC difficult and, as noted here, may be incompatible with other measurements.

In addition to the 3 patients receiving the drug by two routes, 6 patients with renal failure received a single intravenous dose of flucytosine. All but one (No. 4, Table V) of these patients were on dialysis. Because this is a heterogenous group with varying degrees of re-

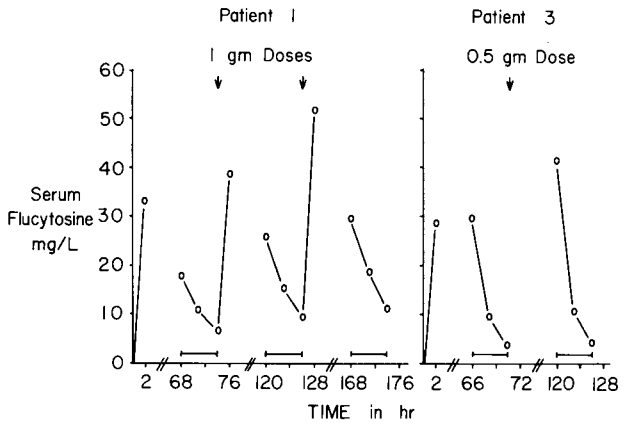

Fig. 3. The serum concentration of flucytosine in 2 patients (Nos. 1 and 3) who were receiving hemodialysis for end-stage renal failure. The period of hemodialysis (I—I) was approximately 6 hr. In vivo hemodialyzer clearance was calculated to be 128 ml/min. The initial and subsequent doses were 1 gm orally in Patient 1 and 0.5 gm orally in Patient 3. Patient 1 had residual renal function, whereas Patient 3 was anephric.

Table V. *Kinetic parameters with intravenous flucytosine in patients with renal failure*

Parameters	*Patients*					
	4	*5*	*6*	*7*	*8*	*9*
Weight (kg)	78.2	67.1	65.5	50.9	78.1	61.9
V_1 (L/kg)	0.334	0.217	0.270	0.250	0.233	0.323
V_{dss} (L/kg)	0.581	0.506	0.598	0.502	0.607	0.520
k_{12} (hr^{-1})	0.916	1.32	1.42	2.18	2.29	0.822
k_{21} (hr^{-1})	1.39	1.32	1.16	2.17	1.42	1.34
k_{el} (hr^{-1})	0.043	0.012	0.013	0.025	0.004	0.010
$t_{1/2\beta}$ (hr)	28.5	147	119	55.9	430	114
Cl_p (ml) (min^{-1})	12.1	3.1	3.9	6.8	1.3	3.3
Cl_r (ml) (min^{-1})	6.7	—	2.3	4.4	0	3.6
$Cl_{^{169}Yb\text{-}DTPA}$ (ml) (min^{-1})	8.2	—	2.3	4.8	0	0.5
$\frac{\beta}{k_{el}}\left(1+\frac{k_{12}}{k_{21}}\right)$	0.985	0.997	1.09	0.992	1.0	0.998

sidual renal function, individual kinetic parameters are summarized in Table V.

The very low elimination rate and plasma clearance values establish the absence of significant nonrenal excretion. As in subjects with normal renal function, the only route of elimination is renal with renal and plasma clearance being almost equal in most patients. The slowest elimination rates were in the surgically anephric patients (Nos. 3 and 8). Although we were unable to measure renal clearance in 2 patients (No. 2 and 5) during this study because of urine collection problems, they do generate a small amount of urine and have some residual function.

In contrast to normal subjects, the kinetic data in patients with renal failure (Table V) suggest a one-compartment open model to be an excellent predictor of steady-state plasma concentrations. Because flucytosine is eliminated so slowly in renal insufficiency $\frac{\beta}{k_{el}}\left(1+\frac{k_{12}}{k_{21}}\right)$ approaches unity and, therefore, $V_{dss} \simeq V_{d\,area}$.

Multiple dosing and dialysis studies. The data are graphically summarized in Fig. 3. Both patients demonstrated drug accumulation at the dose given, although substantial amounts were removed during each dialysis. Because the exchange of flucytosine between central and peripheral compartments is much more rapid

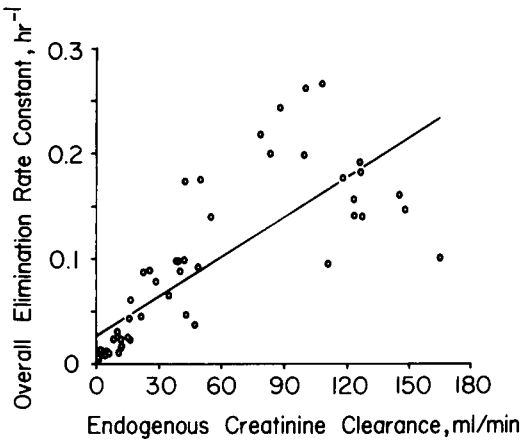

Fig. 4. The linear regression of the overall elimination rate constant (k_{el}) versus endogenous creatinine clearance in our studies plus those previously reported (Table VI) is represented by the equation: $k_{el} = 0.03 + 0.0012 * Cl_{cr}$. The correlation coefficient is 0.79.

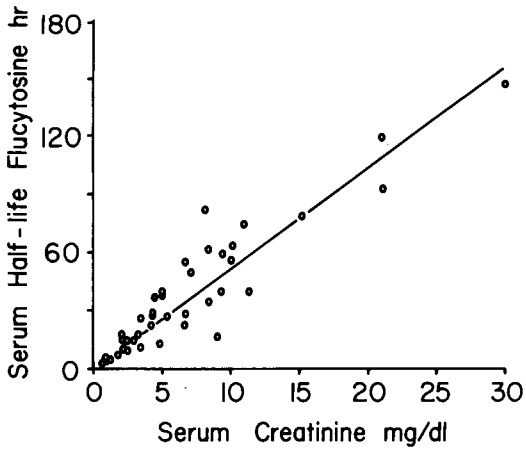

Fig. 5. The linear regression of flucytosine plasma against the serum creatinine concentration (Cr_{serum}) is represented by the equation $t½ = 0.4 + 5.2 * Cr_{serum}$. The correlation coefficient is 0.95.

than removal during dialysis, kinetics were calculated as a one-compartment open model by means of the steady-state volume of distribution (V_{dss}) from the prior intravenous study to calculated plasma clearance of drug. Because the plasma clearance during dialysis represents both endogenous and hemodialysis removal, the former was subtracted to obtain an estimate of the in vivo hemodialyzer clearance noted in Fig. 3. The in vivo dialyzer clearances were slightly higher than the 113 ± 0.9 ml/min value noted in a prior in vitro study.[4]

Discussion

Using a single 2-gm oral dose of radionuclide-labeled flucytosine in capsules, Koechlin and associates[9] found 89% and 93% of the administered radioactivity in the urine of 2 hospitalized patients. Only 0.5% of the dose appeared in the feces. The peak serum concentration of 30 to 40 mg/L occurred within 2 hr. Similar peak serum concentrations and absorption rates for oral capsules have been noted by others.[6, 13] Unfortunately, none of these earlier reports state whether or not the dose was administered in the fasting state. Our study demonstrates that the capsular form delays absorption in the fasting state in normal subjects and that ingestion of capsules with solid food decreases rate but not total absorption. This probably means that flucytosine is absorbed in the small intestines and absorption is slow when given with meals due to delayed gastric emptying.

The elimination rate constant, terminal half-time, apparent volume of distribution, and clearance from plasma and kidneys in subjects with normal renal function are summarized in Table VI from four reports in the literature. The mean values for kinetic parameters in normal subjects in the current study are similar to those estimated from data reported, except for that of Koechlin and colleagues.[9] The slow elimination in their 2 hospitalized patients was probably related to renal impairment; one patient had hypertension and the other had diabetes mellitus and atherosclerosis. The low renal clearance of drug in their study supports this concept. In practice, the renal clearance of flucytosine may be a reasonable estimate of GFR. We noted a close similarity of the renal clearance of creatinine and ^{169}Yb-DTPA to that of flucytosine in renal failure and normal subjects while, Wade and Sudlow[16] found its renal clearance to be close to that of inulin in a few normal subjects.

In patients with renal failure, the absorption of flucytosine is excellent and similar to that in normal subjects. Because flucytosine undergoes little nonrenal elimination, its plasma clearance closely reflects renal clearance so that anephric patients (Nos. 3 and 6) with no renal function

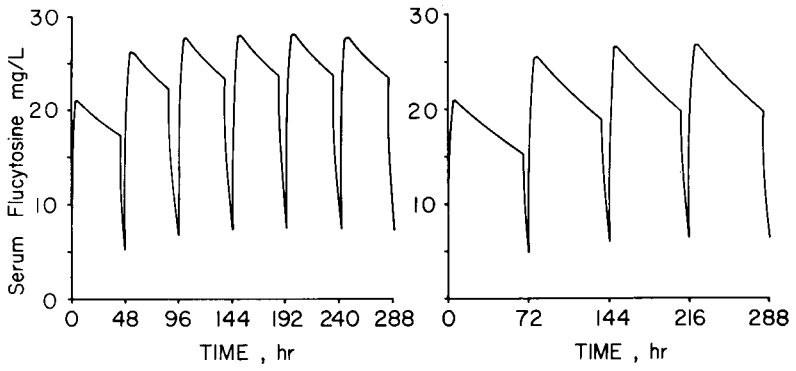

Fig. 6. A computer simulation of serum flucytosine concentration in a 70-kg patient on chronic hemodialysis who was given 1.5 gm (20 mg/kg) orally immediately after dialysis. In the *left panel*, dialysis occurs every 48 hr and in the *right panel* every 72 hr. The following assumptions were made: k_a = 1.01 hr^{-1}, k_{el} = 0.0051 hr^{-1}, A = B = 2.79, Cl_{cr} = 3 ml/min, Cl_{dial} = 113 ml/min, dialysis period = 5 hr.

Table VI. *Comparison of mean values of pharmacokinetic parameters in previous reported studies in subjects with normal renal function**

Parameters	*Study*			
	1†	*2*‡	*3*§	*4*‖
V_d (L/kg)	0.605	0.777	0.600	0.881
k_{el} (hr^{-1})	0.113	0.178	0.124	0.245
t½ (hr)	6.6	3.9	5.6	2.9
Cl_p (ml) (min^{-1})	70	167	93	227
Cl_r (ml) (min^{-1})	64	149	106	—
Cl_{cr} (ml) (min^{-1})	—	—	139	—

*Estimated from reported data based on a one-compartment, open model.
†Koechlin and associates[9]: Both patients probably had mild renal impairment; single oral dose.
‡Wade and Sudlow[16]: Single intravenous dose; $V_d = V_{d\ ext}$.
§Dawborn and associates[6]: Single oral dose.
‖Schonebeck and associates[13]: Single oral dose.

had the slowest rates of elimination. This decisive role of renal function is graphically displayed in Fig. 4 as a linear regression analysis of the overall elimination rate (k_{el}) against the creatinine clearance using previously reported values (Table VI) and data from our study.

How can these data be used to modify flucytosine dosage in patients with renal failure? Characteristic relationships between the elimination rate of several antibiotics and the endogenous creatinine clearance in patients with renal disease were first described in the pioneer work of Kunin and associates.[11] As they noted, a plot of drug t½ against creatinine clearance is curvilinear for drugs eliminated by the kidneys. Kunin[10] clearly recognized that "exact dosage schedules are difficult to formulate in these patients because of the nature of the curve relating half-life to renal function." As noted by Dettli,[7] however, the relationship of the drug plasma elimination rate constant and the creatinine clearance is linear. As a consequence the individual value of the elimination rate constant of a drug in any patient with renal disease can be estimated by linear interpolation or extrapolation procedures. Dettli has shown that this technique can be used for estimation of drug dosage in renal failure.

Although the endogenous creatinine clearance is well suited for purposes of drug dosage adjustment, urine collections are sometimes hard to obtain in practice and we have proposed using the steady-state serum creatinine concentration as the estimating parameter of kidney

function for drugs exhibiting little nonrenal elimination.[5] Most clinicians are familiar with the concept of plasma t½ but do not commonly think in terms of elimination rate constants for drugs so that correlations between the plasma t½ of a drug and the serum creatinine concentrations may be more easily understood and applied by physicians.

As shown by Dettli, a linear relationship of these two parameters is not to be expected unless the drug is virtually entirely eliminated by renal function and nonrenal routes of elimination are negligible. Because flucytosine satisfies these criteria, a reasonable linear relationship can be demonstrated between the plasma t½ and the serum creatinine concentration (Fig. 5). Because the flucytosine distribution volume is larger than that for aminoglycoside antimicrobials (0.25 L/kg), the plasma t½ in hours for flucytosine is approximately 5 times the numerical value for the serum creatinine concentration in contrast to the aminoglycosides in which the constant is 3 times the numerical value for the serum creatinine concentration.[5]

According to Dettli,[7] it is difficult to modify the dosage regimen of a drug in renal failure in such a way that the plasma elimination profile mimics that of patients with normal renal function. The dosage regimen can be modified in such a way that the peak plasma concentration at the beginning of the dosage interval, the concentration nadir at the end of the dosage interval, or the area below the time-plasma concentration curve are identical in all patients, but it is theoretically impossible to fulfill all of these requirements simultaneously.

Usual clinical practice is to administer flucytosine in doses of 50 to 250 mg/kg/day. The dose is divided and given every 6 hr. Flexibility is somewhat limited due to a commercially fixed capsular size of 500 mg. In subjects with normal renal function and a t½ of about 4 hr, this means that drug cumulation will occur with 6 hr maintenance doses until a steady-state is achieved in about 5 t½s. With the use of the kinetic data obtained in our study and a dosage schedule of 1,000 mg every 6 hr in a 70-kg normal subject, the mean steady-state concentration will be approximately 20 mg/L with a peak plasma concentration of 27 mg/L and a minimal level of 14 mg/L. A similar mean plasma concentration could be achieved with this drug in patients with renal failure by administering an initial loading dose of approximately 20 mg/kg to achieve a plasma concentration in the range of 20 to 30 mg/L and followed by a maintenance dose which is half the loading dose at an interval equal to the individual t½ of the drug estimated in that patient from a measured creatinine clearance and Fig. 4 ($t½ = 0.7 / k_{el}$) or by the approximation obtained from 5 times the steady-state serum creatinine (Fig. 5). Although the actual t½ in a particular patient may vary severalfold from the mean in our data, there is little risk of toxicity because of flucytosine's wide therapeutic index. The prudent physician is well advised to use such data for initial estimates only and then to monitor plasma concentrations and make appropriate adjustments as therapy proceeds.

In patients with end-stage renal disease on dialysis, little drug is excreted between dialyses. Substantial amounts are removed during a typical 5- to 6-hr run (Fig. 3) and reloading must be done after dialysis. A computer simulation based on the kinetic data derived from our study (Fig. 6) suggests that safe and effective dosing for most susceptible organisms can be obtained by a 20 mg/kg dose immediately after dialysis whether dialysis occurs as frequently as every 48 hr or as infrequently as every 72 hr. Because lower or higher dialyzer clearances may occur due to unforseen changes in dialyzer performance, it is always wise, as already noted, to monitor plasma concentrations.

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