Pharmacokinetics of a Hematoregulatory Peptide (SK&F 107647) in Healthy Male Volunteers and in Patients with Colorectal or Pancreatic Adenocarcinoma Not Amenable to Standard Therapy

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Purpose. To describe the pharmacokinetics of SK&F 107647, a synthetic hematoregulatory peptide, in healthy volunteers and in patients with adenocarcinoma.

Methods. SK&F 107647 pharmacokinetics were evaluated in 2 dose-escalation studies. Volunteers received SK&F 107647 as single 15-minute *iv* infusion doses of 1, 10, 100, 500, and 1000 μg/kg. Cancer patients received 2-hour *iv* infusions of 0.001, 0.01, 0.1 and 1 μg/kg once daily for 10 days. Drug concentrations were quantified in plasma and urine of healthy volunteers and on days 1 and 10 in plasma of cancer patients receiving the two top dose levels.

Results. In volunteers, mean clearance (CL) ranged from 76.7 to 101 ml/hour/kg; mean volume of distribution at steady-state (V_{ss}) ranged from 175 to 268 ml/kg. Most of the administered dose was renally excreted as intact peptide within 24 hours postinfusion. In patients, mean CL was 57.6 ml/hour/kg, mean V_{ss} ranged from 128 to 150 ml/kg and terminal half-life from 2.1 to 3.4 hours. There was little accumulation of drug. In both studies, linear pharmacokinetics was observed. Clearance approached normal glomerular filtration rate (GFR) in volunteers and correlated with creatinine clearance in cancer patients.

Conclusions. SK&F 107647 exhibits linear pharmacokinetics, a small V_{ss}, and clearance, primarily renal, approaching normal GFR.

KEY WORDS: SK&F 107647; peptide; pharmacokinetics; hematoregulatory; adenocarcinoma; cytokines.

INTRODUCTION

Colony-stimulating factors have been used to stimulate hematopoietic recovery of the bone marrow following treatment with cytotoxic agents or following bone marrow transplantation (1,2). SK&F 107647 is a novel, low-molecular-weight, synthetic peptide that induces colony-stimulating activity and the release of hematopoietic mediators responsible for myeloid recovery (Fig. 1). It is a hematoregulatory agent that acts on stromal cells to induce the synthesis and release of hematopoietic (blood-cell stimulating) mediators, including macrophage colony-stimulating factor (M-CSF) and hematopoietic synergistic factor (HSF). These mediators act in concert to enhance the production of granulocytes and macrophages to optimize host defenses. SK&F 107647 has demonstrated a broad range of biological activities in immunocompromised and immunocompetent animal models and in humans (3,4) and therefore, may be useful in the treatment of potentially life-threatening neutropenia and myelotoxicity resulting from cancer chemotherapy. The multilineage activity of this peptide, together with its enhancement of stem-cell function and host defenses against bacterial fungal and viral infection, support its evaluation in cancer patients (5–7). SK&F 107647 has previously been administered at single intravenous doses of 0.01 to 100 ng/kg to cancer patients (3). This report describes the pharmacokinetics of SK&F 107647 following single and repeated intravenous (*iv*) infusions in healthy volunteers and in patients with adenocarcinoma not amenable to standard therapy.

MATERIALS AND METHODS

Subjects

SK&F 107647 was first evaluated in patients with adenocarcinoma of colorectal or pancreatic origin or other non-lymphoid solid tumors not amenable to standard therapy and then in healthy volunteers at higher dose levels than those examined in the patients. The studies were conducted according to the provisions of the Declaration of Helsinki and its amendments; appropriate local institutional review boards approved both studies and all subjects provided written informed consent.

Healthy Volunteers

Criteria for inclusion were male sex; age between 18 and 45 years, inclusive; body weight between 50 and 100 kg (within 15% of ideal weight for height, frame and age); no significant clinical, laboratory, electrocardiographic, or drug screen abnormalities; and a negative hepatitis B test within 3 months of the start of the study. Criteria for exclusion were prescription medication within 14 days or nonprescription medicine within 48 hours before the first study day; history of substance abuse; a history of gastrointestinal, hepatic, or renal disease or other condition known to interfere with the pharmacokinetics of drugs; definite or suspected smoker; exposure to more than 2 new chemical entities within 12 months or participation in a drug trial within 3 months prior to the first study day; and donation of more than 1500 ml of blood (including this study) in the previous 12 months.

Cancer Patients

Criteria for inclusion were age ≥18 years; documented advanced adenocarcinoma of colorectal or pancreatic origin or

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ABBREVIATIONS: AUC, area under curve; CL, clearance; CL_{cr}, creatinine clearance; C_{max}, maximum plasma concentration; iv, intravenous; GFR, glomerular filtration rate; $t_{1/2}$ elimination half-life; V_{ss}, volume of distribution at steady state.

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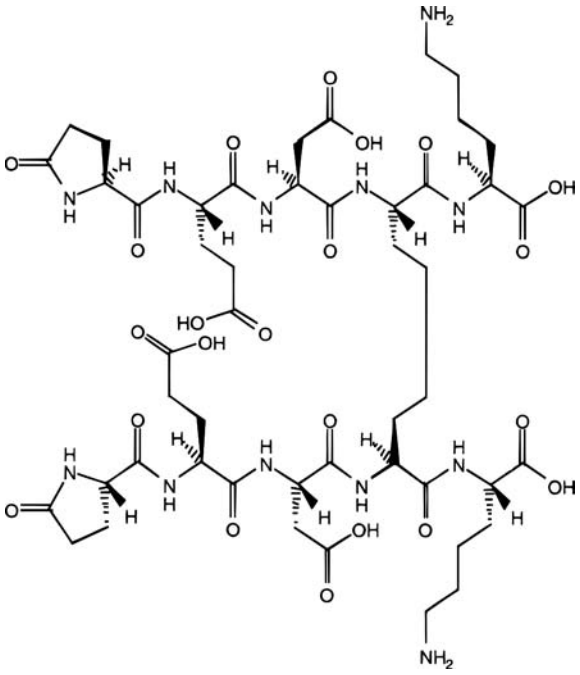

Fig. 1. Chemical structure of SK&F 107647, (S)-5-*oxo*-L-prolyl-L-α-glutamyl-L-α-aspartyl-N^8(5-amino-1-carboxypentyl)-8-*oxo*-N^7-[*N*-[*N*-(5-*oxo*-L-prolyl)-L-α-glutamyl]-L-α-aspartyl]-L-*threo*-2,7,8 tri-amino-octanoyl-lysine (molecular weight = 1171.17 Da).

other non-lymphoid solid tumor not amenable to standard therapy at the time of the study; presence of measurable primary tumor or metastasis; female patients of childbearing potential who had a negative urine pregnancy test at screening; European Cooperative Oncology Group (ECOG) performance status of ≤2 and a life expectancy of ≥3 months; and willingness and ability to comply with the protocol and specified assessment schedule. Criteria for exclusion were history, signs, or symptoms of brain or leptomeningeal disease; more than 1 previous chemotherapy protocol; current or planned chemotherapy treatment within 8 weeks prior to screening or before completion of initial follow-up visit; known or suspected infection; pregnancy, breast feeding, planning a pregnancy, or not using an acceptable method of birth control; treatment with cytokine or other immunomodulatory therapy within the 21 days prior to screening; previous or concomitant extended field radiotherapy; severe allergic or autoimmune disease; recent treatment with an investigational drug or investigational vaccine; concomitant or prior myeloproliferative disorder; severe allergic or autoimmune disease; history of substance abuse within 6 months prior.

Within 7 days of the start of the study, cancer patients were required to meet minimum clinical laboratory requirements, including hemoglobin ≥10.0 g/dl, white blood count ≥2.5×10^9/L, platelet count ≥80×10^9/L, total neutrophil count ≥1.5×10^9/L, prothrombin time (PT) ≤14 seconds, partial thromboplastin time (PTT) ≤35 seconds, serum creatinine and serum bilirubin ≤2 times upper reference limit, and AST ≤2 times upper reference limit if liver metastases were absent or ≤4 times upper reference limit if liver metastases were present.

Study Design

Healthy Volunteers

The pharmacokinetics of SK&F 107647 was evaluated in a phase I single-blind, placebo-controlled, dose-escalation, four-way crossover study in 8 healthy male volunteers following an 8 hour fast. SK&F 107647 was administered as a single iv infusion at doses of 1, 10, 100, 500 and 1000 μg/kg. Each subject received 3 rising doses of SK&F 107647 and a randomized placebo (a total of 4 treatments) separated at 6-day intervals. Subjects were divided into 2 groups who received the following treatments: Group 1 (n = 4): 1, 10, 100 μg/kg SK&F 107647 and randomized placebo, or Group 2 (n = 4): 100, 500, 1000 μg/kg SK&F 107647 and randomized placebo. Study medication (SK&F 107647 or placebo) was diluted in a total of 50 ml 5% dextrose in water and administered intravenously via syringe pump over 15 minutes.

Cancer Patients

SK&F 107647 was given as part of an open-label, dose-escalation study to 24 patients with adenocarcinoma of colorectal or pancreatic origin or other nonlymphoid solid tumor not amenable to standard therapy. Four groups of 6 patients each received SK&F 107647 at doses of 0.001, 0.01, 0.1, or 1 μg/kg daily for 10 consecutive days. Study medication (50 ml) was administered as a daily 2-hour iv infusion at a constant rate of 25 ml/h for 10 consecutive days via an indwelling iv central line using a CADD Plus® pump (Deltec, Smith Industries; St. Paul, MN). Pharmacokinetic assessments were performed in the 0.1- and 1-μg/kg dose groups as the drug concentration would have been below the limit of quantification of the assay for the lower dose levels. Dosing began at the lowest dose level and progressed to the next higher dose level when at least 3 patients completed the study at the lower dose with acceptable tolerability.

Sample Collection

After the start of the SK&F 107647 infusion, serial blood samples (2 ml) were collected from healthy volunteers and cancer patients into lithium-heparin polypropylene tubes and promptly chilled. Plasma was obtained by centrifugation at approximately 4°C at approximately 3000 rpm for 20 minutes. Samples were stored at approximately −20°C until time of analysis.

Healthy Volunteers

Blood samples for pharmacokinetic analyses were drawn at the following times: predose, 15 minutes (just prior to ending the infusion), 20 minutes (5 minutes after the infusion end), 30 minutes, 45 minutes, then 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, and 72 hours from the start of the infusion. Serial urine samples were collected from a subset of subjects prior to treatment and over the approximate time intervals of 0 to 24, 24 to 48, and 48 to 72 hours postinfusion. The volume of urine collected during each interval was recorded and a 10-ml homogeneous aliquot was frozen prior to analysis.

Cancer Patients

On study days 1 and 10, blood samples were drawn at the following times for the 0.1- and 1-μg/kg dose groups: predose, 0.5, 1, 2 (just prior to ending the infusion), 2.08, 2.25, 2.5, 3, 4, 5, 6, 8, 10, and 14 hours after the start of infusion. For study day 1 only, an additional blood sample was drawn at 24 hours after the start of infusion.

Assay Methods

SK&F 107647 plasma concentrations were determined using a sensitive radioimmunoassay (RIA). The linear range of the assay was 0.0149 ng/ml to 0.7067 ng/ml; the lower limit of quantification was 0.0149 ng/ml. Precision and accuracy of the assay were verified using a 3-run validation; the within-run precision ranged from 2.9%–8.2% and between-run precision ranged from 1.7%–7.5% for concentrations between 0.0151 ng/ml and 0.7024 ng/ml. Mean accuracy ranged between 96.8% and 103.1%. SK&F 107647 was isolated from urine samples by cation-exchange solid-phase extraction; drug concentrations in urine were quantified using a high-performance liquid chromatography (HPLC) assay with fluorescence detection. The linear range for this assay was 50 to 1000 ng/ml; samples with concentrations above this range were diluted prior to final analysis. The recovery from urine was approximately 90%. The average within-run precision varied between 1.9% and 12.3% and the average between-run precision varied between 4.5% and 7.9%. The average accuracy of the method ranged between 97.1% and 101.7.

Pharmacokinetic Analysis

SK&F 107647 plasma concentration–time data were analyzed by noncompartmental methods. The following parameters were calculated: maximum observed plasma concentration (C_{max}), area under the plasma concentration–time curve from zero to the last measurable time point ($AUC_{0\text{-}t}$), area under the plasma concentration–time curve extrapolated to infinity ($AUC_{0\text{-}\infty}$), plasma clearance (CL), terminal elimination rate constant (λ_z), elimination half-life ($t_{1/2}$), and volume of distribution at steady state (V_{ss}).

Accumulation ratio was determined as the ratio of $AUC_{0\text{-}t}$ on study day 10 to $AUC_{0\text{-}t}$ on study day 1. Creatinine clearance (CL_{Cr}) was calculated from serum creatinine measurements by the Cockcroft-Gault equation (8). CL_{Cr} values determined on study days 1, 2, and 10 of dosing were averaged to determine an overall CL_{Cr} value for each patient. Amount of drug excreted in the urine as intact SK&F 107647 during each time period was determined from the urine concentrations and collection volumes. The percent of dose recovered in the urine as intact peptide was calculated.

Statistical Analysis

Due to the exploratory nature of these studies, statistical power computations were not made and sample size was based on feasibility. Linear regression was performed to assess dose proportionality and potential correlation with weight and renal function (creatinine clearance). Percent coefficient of variation was computed as (mean/standard deviation) ×100.

Table I. Demographics in Healthy Volunteers and Cancer Patients[a]

	SK&F 107647 dose groups			
Healthy volunteers	1- and 10-μg/kg/day (n = 4)	100-μg/kg/day (n = 8)	500- and 1000-μg/kg/day (n = 4)	Overall (n = 8)
Gender				
Male	4	8	4	8
Race				
Caucasian	4	8	4	8
Mean (SD) age in years	30.0 (9.4)	30.6 (6.6)	32.0 (3.3)	30.6 (6.6)
Mean (SD) weight in kg	79.6 (7.1)	81.4 (6.7)	83.3 (6.7)	81.4 (6.7)
Mean (SD) height in cm	176.0 (5.3)	181.1 (7.2)	187.0 (4.2)	181.1 (7.2)

	SK&F 107647 dose groups				
Cancer patients	0.001 μg/kg/day (n = 6)	0.01 μg/kg/day (n = 6)	0.1 μg/kg/day (n = 6)	1 μg/kg/day (n = 6)	Overall (n = 24)
Gender					
Male	5	3	4	2	14 (58%)
Female	1	3	2	4	10 (42%)
Race					
African American	1	0	0	0	1 (4%)
Asian	1	0	0	0	1 (4%)
Caucasian	4	6	6	6	22 (92%)
Mean (SD) age in years	58.0 (13.5)	58.5 (9.0)	53.5 (10.2)	65.8 (11.1)	59.0 (11.3)
Mean (SD) weight in kg	74.8 (15.5)	74.1 (19.2)	66.7 (7.4)	69.5 (13.2)	71.2 (13.9)
Mean (SD) height in cm	169.5 (13.1)	170.9 (16.8)	166.1 (9.8)	163.7 (14.6)	168.0 (13.2)

[a] SD = standard deviation.

Clinical Monitoring

All healthy volunteers and cancer patients underwent a physical examination before administration of SK&F 107647 and before discharge from the research institution. Safety evaluations including vital signs, 12-lead electrocardiograms (ECGs), complete blood count with differential, blood chemistry, and urinalysis were obtained before dosing and at specified intervals up to 24 hours postinfusion. Adverse event reports were elicited by spontaneous reporting by subjects, nursing observation, and direct questioning of subjects, and documented appropriately. Follow-up assessments were performed 7 to 15 days after the final dosing day in healthy volunteers and at study days 14 to 16 in cancer patients.

RESULTS

A total of 32 subjects (8 healthy volunteers, 24 cancer patients) received treatment with SK&F 107647. Pharmacokinetic analyses were conducted in all of the healthy male volunteers and in 11/24 cancer patients. Subject demographics are summarized in Table I. In the cancer patients, most (17/24, 71%) of the tumors were classified as adenocarcinomas, one patient had cholangiocarcinoma, and the tumor histology was unknown in 6 cases. The tumor diagnosis varied widely between patients. The most common diagnosis was carcinoma of the pancreas, which was present in 6 patients. The most common prior and concomitant medications were chlorhexidine (100%), lidocaine (92%), acetaminophen (67%), midazolam (42%), propoxyphene (29%), aluminum hydroxide (25%), lactulose (25%), dantron (21%), ciprofloxacin (21%), and dihydrocodeine bitartrate (21%). Prior chemotherapy regimens included 1 (n = 4) or 2 (n = 5) courses of single agent fluorouracil, 1 course of fluorouracil/cisplatin/epirubicin (n = 5), and 1 course of single-agent fluorouracil plus a subsequent course of an investigational agent.

Pharmacokinetics

Healthy Volunteers

Mean plasma SK&F 107647 concentration-time profiles are presented in Fig. 2 and mean pharmacokinetic data in Table II. C_{max} and AUC for SK&F 107647 correlated well with dose (r^2 = 0.96 and 0.98 respectively) within the dose range of 1 μg/kg to 1000 μg/kg indicating dose-linearity for these data. Although, a trend was observed toward slightly higher clearance values at higher dose levels. Mean clearance values were 74% to 100% of normal glomerular filtration rate (GFR) (103 ml/hour/kg). Except for the 1-μg/kg dose group, mean volume of distribution values were similar among the groups and slightly less than the extracellular body fluid volume (260 ml/kg). In the 1-μg/kg dose group, 2 subjects had volumes of distribution that were approximately 2- to 3-fold higher than those observed in the other subjects but less than total body water (600 ml/kg).

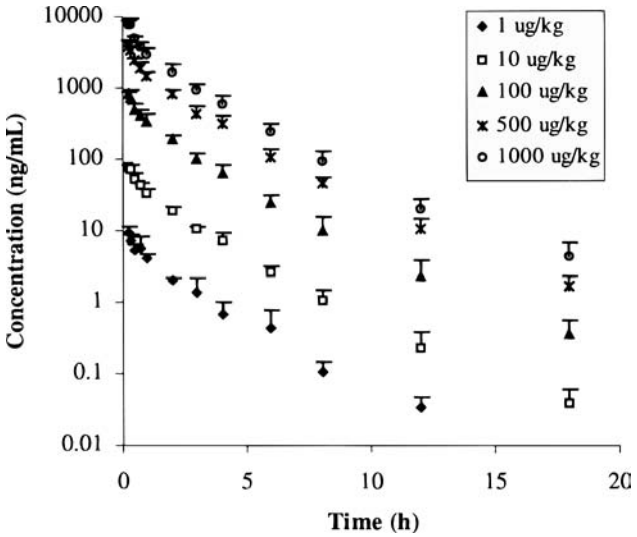

Fig. 2. Mean (+ S.E.) concentration-time profiles following administration of SK&F 107467 at 5 dose levels to healthy male volunteers.

The overall mean (SD) terminal half-life was 1.95 (0.33) hours. The percentage of extrapolated AUC was less than 15% for all subjects. The overall variability (including intra-, inter-subject and assay variability) in C_{max}, AUC, and CL of SK&F 107647 was low with coefficients of variation (CV%) <25%. The majority of the administered dose of SK&F 107647 was recovered in the urine as intact peptide within the first 24 hours postinfusion (Table III).

Cancer Patients

Mean SK&F 107647 plasma concentration-time profiles in patients are presented in Fig. 3. Mean clearance was 57.6 (21.2) and 57.6 (12.6) ml/hour/kg for the 0.1- and 1-μg/kg doses (Table IV). In general, the CL of SK&F 107647 was lower in individuals with lower creatinine clearance (Fig. 4), suggesting that decreased renal function resulted in lower SK&F 107647 clearance. The coefficient of variation for creatinine

Table II. Mean Pharmacokinetic Parameters of SK&F 107647 in Healthy Male Volunteers

	SK&F 107647 dose group				
Parameter[a]	1 μg/kg (n = 4)	10 μg/kg (n = 4)	100 μg/kg (n = 8)	500 μg/kg (n = 4)	1000 μg/kg (n = 4)
$AUC_{(0\text{-}t)}$ (ng·h/ml)	13.4 (2.40)	111 (9.50)	1084 (179)	4973 (811)	10242 (1816)
C_{max} (ng/ml)	9.40 (1.75)	78.3 (8.05)	859 (139)	3886 (715)	8046 (809)
CL (ml/h/kg)	76.7 (14.8)	90.6 (7.70)	94.9 (18.2)	103 (19.6)	101 (21.3)
V_{ss} (ml/kg)	268 (150)	186 (47.9)	75 (22.3)	189 (21.3)	185 (23.7)
$t_{1/2}$ (h)	1.64 (0.41)	1.75 (0.33)	2.04 (0.27)	2.06 (0.23)	2.15 (0.31)

[a] Values expressed as mean (SD).

Table III. Percent of SK&F 107647 Dose Recovered in the Urine in Healthy Volunteers

Time Interval	Percent[a] of SK&F 107647 dose recovered by dose group		
	10 μg/kg (n = 2)	100 μg/kg (n = 4)	1000 μg/kg (n = 4)
0–24 h	122[b]	81.9 (6.48)	97.5 (21.7)
0–72 h	122[b]	82.3 (6.29)	97.9 (21.7)

[a] Values expressed as mean (SD).
[b] Mean values were determined from two individual values, no standard deviations were calculated.

clearance for each patient averaged 7% based on 3 measurements. There was a good correlation between CL (ml/h) and weight (r^2 = 0.50) and between Vss (ml) and weight (r^2 = 0.70) when data from healthy volunteers and cancer patients were examined together. However, when the data from each group were examined separately, the correlations were weaker ($r^2 \leq 0.28$ for CL and r^2 = 0.52 for V_{ss}). Mean (SD) V_{ss} calculated on study day 1 was 150 (42) and 128 (33) ml/kg for the 0.1- and 1-μg/kg doses, respectively, suggesting limited tissue distribution. The CL, V_{ss}, and $t_{1/2}$ were similar in the 0.1- and 1-μg/kg dose groups. C_{max} and AUC increased in a dose-proportional fashion (Table IV).

At the 24-hour sampling time for study day 1, drug levels were measurable in only 1 patient, thus $AUC_{0-14\ hours}$ values were utilized in the calculation of the accumulation ratio. In 10/11 cancer patients, the percentage of extrapolated AUC was less than 15%, indicating that the majority of exposure to drug occurred within 14 hours of initiation of infusion. The mean observed accumulation ratio was 1.05 and 1.25 for the 0.1- and 1-μg/kg dose groups, respectively, indicating that there was little SK&F 107647 accumulation.

Safety

Healthy Volunteers

Overall, SK&F 107647 was well tolerated in the healthy volunteers and no healthy volunteers withdrew from the study. None of the reported adverse events were considered related to study medication.

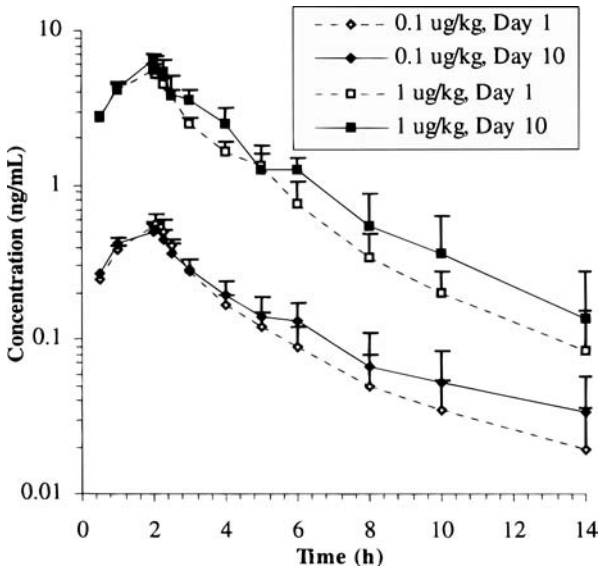

Fig. 3. Mean (+ S.E.) concentration-time profiles for SK&F 107647 following administration of a once-daily regimen of 0.1 μg/kg or 1 μg/kg of SK&F 107647 to patients with adenocarcinoma.

Cancer Patients

Overall, SK&F 107647 was well tolerated in this group of cancer patients. 23/24 cancer patients participating in this clinical study reported adverse events. The numbers of reported adverse events were similar across dose groups. The most commonly reported adverse experiences thought to be possibly or probably related to study medication included abdominal pain, nausea, headache, influenza-like symptoms, and rhinitis. There was 1 patient death due to progressive disease reported during this study.

DISCUSSION

The pharmacokinetics of SK&F 107647 were examined in healthy volunteers at 1, 10, 100, 500 and 1000 μg/kg dose levels and in cancer patients at 0.1 and 1 μg/kg dose levels. Consistent with the observations previously described for small peptides (MW < 5000 Da) (9, 10), the majority of the SK&F 107647 dose was recovered in the urine as intact peptide in healthy volunteers. Similarly, following intravenous administration of [^{3}H]SK&F 107647 at a dose level of 10 μg/kg to

Table IV. Mean Pharmacokinetic Parameters of SK&F 107647 in Cancer Patients

Parameter[a]	SK&F 107647 dose group			
	0.1 μg/kg		1 μg/kg	
	Day 1 (n = 6)	Day 10 (n = 6)	Day 1 (n = 5)	Day 10 (n = 5)
$AUC_{(0-t)}$ (ng·h/ml)	1.8 (0.7)	2.0 (1.1)	17.7 (3.8)	22.5 (8.4)
C_{max} (ng/ml)	0.59 (0.18)	0.53 (0.17)	5.59 (1.20)	6.33 (2.64)
CL (ml/h/kg)	57.6 (21.2)	—	57.6 (12.6)	—
V_{ss} (ml/kg)	149.6 (42.4)	—	128.0 (33.4)	—
$t_{1/2}$ (h)	2.73 (1.59)	3.41 (2.43)	2.15 (0.57)	2.50 (0.62)

[a] Values expressed as mean (SD).

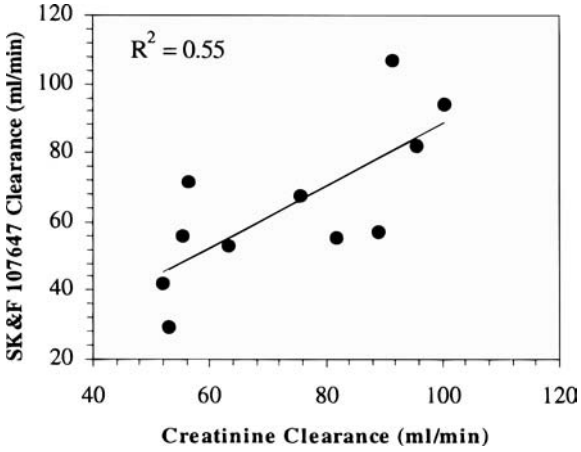

Fig. 4. Creatinine clearance versus clearance of SK&F 107647 for patients with adenocarcinoma.

dogs and rats in previously conducted studies, radioactivity was excreted almost exclusively by the renal route. Tentative evidence was obtained that almost the entire excreted radioactivity was in the form of the parent compound. As expected for compounds whose clearance is mainly due to physical processes, such as biliary or renal excretion of unchanged drug (11), good interspecies scaling has been demonstrated for SK&F 107647 (3). The observation of greater than 100% recovery in the urine in the current report may have been due to urine collection or assay variability. The clearance of SK&F 107647 in cancer patients was moderately lower than that observed in the healthy volunteers and similar to that previously observed in another group of patients (3). The modest difference in clearance between the patients and healthy volunteers is likely due to age and weight differences between the two groups (Table I). In general, cancer patients with lower CL_{Cr} values tended to have lower SK&F 107647 clearance values suggesting that renal impairment may affect elimination of the drug. CL_{Cr}, as calculated by the Cockcroft-Gault equation (8) accounted for approximately 55% of the variability in SK&F 107647 clearance. This correlation may have been limited by the relatively small range of CL_{Cr} values measured in the patients in this study. The observed correlation between CL and weight is expected considering the fact that renal filtration is proportional to weight (as illustrated by Cockroft & Gault equation).

The approximately dose-proportional increases observed in C_{max} and AUC parameters were consistent in healthy volunteers (dose range of 1 to 1000 μg/kg) and in cancer patients (doses of 0.1 and 1 μg/kg). The low degree of SK&F 107647 accumulation during the 10-day dosing period is consistent with the short half-life of this drug. Greater accumulation may be expected in patients with a significant degree of renal impairment. The limited volume of distribution observed in healthy volunteers and in cancer patients suggests that SK&F 107647 does not extensively distribute into tissues. This observation is consistent with the polar nature of this compound. SK&F 107647 was well tolerated in healthy volunteers and in cancer patients and adverse events were generally mild.

In conclusion, SK&F 107647, at doses ranging from 1 to 1000 μg/kg in healthy volunteers and from 0.1 to 1 μg/kg in cancer patients, displayed approximately linear pharmacokinetics with a relatively short terminal half-life, a low volume of distribution, and a mean clearance that approached GFR. The majority of the dose was excreted in the urine and clearance of SK&F 107647 correlated with CL_{Cr} in cancer patients. There was little SK&F 107647 accumulation during the 10-day dosing period in cancer patients.

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