THE PHARMACOKINETICS OF MOXALACTAM IN RENAL FAILURE PATIENTS

by

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for the degree of

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ACKNOWLEDGEMENTS

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I would like to offer my sincere thanks to the members of my research committee Dr. George Dukes, Dr. Sen-Maw Fang, Dr. Burt Janis, and especially my advisor, Dr. Mary Russo, for their time and support in evaluating this research paper.

UNIVERSITY OF UTAH COLLEGE OF PHARMACY

FINAL READING APPROVAL

TO THE DOCTOR OF PHARMACY COMMITTEE OF THE UNIVERSITY OF UTAH COLLEGE OF PHARMACY:

I have read the clinical research project report of Linda Stone Tyler in its final form and have found that 1) its format, citations, and bibliographic style are consistent and acceptable; 2) its illustrative materials including figures, tables, and charts are in place; and 3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Doctor of Pharmacy Committee.

30 March 1981
Date

Chairman, Supervisory Committee

Approved for the Department of Pharmacy Practice

Chairman

Approved for the Doctor of Pharmacy Committee

Chairman, Doctor of Pharmacy Committee

UNIVERSITY OF UTAH COLLEGE OF PHARMACY

SUPERVISORY COMMITTEE APPROVAL

of a clinical research project report submitted by

Linda Stone Tyler

We, the undersigned, have read this clinical research project report and have found it to be of satisfactory quality for a Doctor of Pharmacy Degree.

30 March 1981
Date

Chairman, Supervisory Committee

3-25-81
Date

Member, Supervisory Committee

3/27/81
Date

Member, Supervisory Committee

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Date

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INTRODUCTION

Moxalactam is a semi-synthetic beta-lactam antimicrobial agent currently undergoing Phase III clinical trials in human subjects (see Figure 1). In vitro studies demonstrate that moxalactam is effective against most gram-positive and gram-negative organisms, except Streptococcus, Group D.* The drug is excreted almost entirely by renal mechanisms.* Moxalactam is 38 to 50% plasma protein bound, based on in vitro studies.*

The elimination half-life of moxalactam is two to three hours in patients with normal renal function, and 19 hours in patients with end-stage renal disease.*,3,9 No investigations thus far have determined the hemodialyzability of moxalactam. Pharmacokinetic data of moxalactam in renal failure patients are important not only to provide adequate dosage guidelines for therapeutic efficacy, but also to prevent potential dose-related neurologic, hematologic, and renal toxicities that have been reported with other cephalosporins.[4,5,7,8,11,13]

PURPOSE

The purpose of this study was: to determine the pharmacokinetic parameters of moxalactam in patients with severe renal impairment, undergoing hemodialysis therapy; to determine the effect of hemodialysis on the pharmacokinetic parameters; to develop appropriate guidelines for dosing moxalactam in hemodialysis patients.

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*LY127935: Investigators manual. Eli Lilly Laboratories, Indianapolis, Indiana, 1979.

MATERIALS AND METHODS

Subject Selection

The pharmacokinetics of moxalactam were studied in five volunteer subjects and two infected patients (see Table I). All subjects were at least 15 years of age and receiving hemodialysis therapy. Subjects 1 through 6 had chronic renal failure and required maintenance hemodialysis. Subject 7 had acute renal failure secondary to trauma. Informed written consent was obtained from all subjects (see Appendix A). Subject 7 was comatose, thus informed consent was obtained from his next of kin.

Patients were excluded from the study for any one of the following criteria: concurrent administration of a second systemic antimicrobial agent during the study; systemic antimicrobial therapy within one week prior to the study; a known history of allergic reactions to penicillin or cephalosporin antibiotics; pregnancy.

A complete blood count with differential and platelet count, and a blood chemistry series were performed within 72 hours prior to the start of the study, and within 24 hours after the end of the study (see Tables IIA and IIB).

Study Design

Subjects 1 through 5 received a single 2 gram dose of moxalactam administered intravenously over 2 minutes. Subject 6 received 2 grams initially and 1 gram every 12 hours, and subject 7 received 2 grams every 12 hours for treatment of an infection. A heparinized needle was used as an access site for blood sampling in subjects 1 through 6 while an arterial catheter was used in subject 7. The first 1 to 2 mls

of blood were discarded to clear heparin from the needle prior to obtaining the sample for antibiotic analysis. Three ml of blood were collected for each sample. A solution of 100 units heparin sodium per ml of 0.9% normal saline solution was instilled into the heparinized needle to maintain patency between sampling intervals.

Samples were obtained from each subject prior to the administration of the drug and at 5, 10, 15, 30 minutes, 1, 2, 4, 6, and 8 hours after the initial dose. The subjects who received a single dose of the drug also had samples drawn at approximately 24 hours after the dose, just prior to the initiation of hemodialysis therapy. Three additional blood samples were collected on subjects 4 and 5 between 19 and 24 hours after the dose. They were drawn 90 minutes apart.

On all subjects blood samples were obtained pre-dialysis and immediately after the end of dialysis. Dialyzer input and output samples were obtained at 1, 2 and 3 hours after the start of hemodialysis. All of the dialysate was collected. The total volume was measured and two 3 ml aliquots were obtained for analysis. Each patient was dialyzed on the equipment that they routinely used.

All blood samples obtained were placed in an empty vacutainer and centrifuged for 5 min at 1000 g in a Model K International centrifuge. The serum was then transferred by pipette into empty, pre-labeled vacutainers, and frozen at -70°C. This procedure was completed within 60 minutes after collecting the specimen. The samples were assayed within 4 days after collection.

Assay Method

Moxalactam levels were determined by a microbiological assay procedure using the modified method described by Bennett et al[2] (see Appendix B). All samples were assayed five times with five control samples. Standard solutions were prepared by diluting moxalactam 1000 mcg/ml to 500 mcg/ml with 1% sodium phosphate buffer, pH 6.0. Further dilutions were made with human serum from a single known donor to obtain concentrations of 2.5, 10, 20 and 50 mcg/ml. These dilutions were made with normal saline when the dialysate samples were analyzed.

Serum samples with drug concentrations that fell above the range of the concentration of the control samples were diluted 1 part sample in 9 parts normal serum before analysis. Since dialysate samples fell below the control concentrations, 1 ml of each dialysate sample was lyophilized then reconstituted with 0.2 ml sterile water prior to analysis.

Pharmacokinetic Analysis

Serum concentration versus time curves were visually inspected to determine if the data best fit a one-compartment or two-compartment model. The data in the elimination phase were subject to linear regression analysis using the method of least squares, as determined by a curve fitting program (Hewlett-Packard, HP-67). The negative slope of this regression line represented the elimination rate constant (or beta for the two-compartment model). Since the data best fit a two-compartment model, the distribution rate constant (alpha) was determined by the method of residuals.[6,12] The rate constants,

half-lives, volumes of distribution and clearance were calculated according to accepted methods[6,12] (see Appendix C). Data collected during hemodialysis was analyzed by a one-compartment model.

Statistical Analysis

Correlation analyses were performed on some of the data collected during hemodialysis. A programmable calculator was used to calculate the coefficient of determination (r^2) values. Using this value, significance was determined using a two-tailed t-test for significance. The analyses were used to validate relationships that were expected to have a positive correlation.

RESULTS

The seven subjects admitted to the study ranged from 20 to 65 years of age with a mean of 40.3 years. Six of the subjects were male and one was female. They ranged in weight from 49.0 kg to 84.0 kg with a mean of 66.5 kg. Subjects 1 through 6 had chronic renal failure requiring hemodialysis therapy, but only subject 6 was surgically anephric. Subject 7 had acute renal failure for which he was receiving hemodialysis therapy.

By visual analysis the data appeared to exhibit two-compartment, first order kinetics. All data were analyzed by a two-compartment open model except for the data from subject 1. No distinct distribution phase could be identified from his data.

Individual serum concentrations are presented in Tables III, IV, and V. The calculated mean (± SD) serum concentration 24 hours after the dose would be a mean of 59.8 ± 13.0 mcg/ml. Data from subjects 6 and 7 were extrapolated. The mean observed peak serum concentration

at 5 minutes after the dose was 179.3 ± 49.5 mcg/ml. This was during the distribution phase and does not reflect the concentration of drug in the central compartment once pseudoequilibrium between the central and peripheral compartment is established. The extrapolated theoretical peak serum concentration in the central compartment at time zero is a mean of 127 ± 31.0 mcg/ml. ("Peak serum concentration" when used in this text shall be the extrapolated value, discounting the distribution.) Distribution appeared to be complete in most subjects by 4 hours after the dose. Graphical representations of the serum concentration versus time data on each subject are shown in Figures 2 through 8, with a graph of the mean data shown in Figure 9.

The pharmacokinetic parameters for each subject and the mean data are presented in Tables VIA and VIB. The mean beta elimination half-life was 27.5 ± 15.4 hours. The mean alpha distribution half-life was 25.8 ± 25.8 minutes. The mean volume of distribution at steady state (Vd_{ss}) was 0.279 ± 0.093 l/kg, while the mean plasma clearance was 7.26 ± 3.06 ml/kg/hr. These calculations were based on total body weight.

No subject reported any side effects of the drug except for subject 3 who said he could taste the drug. No change in laboratory parameters were noted pre- and post-study in any subject.

The serum concentrations that were collected during hemodialysis are presented in Table VII. The characteristics of each dialyzer are listed in Table VIII. The acrylnitrile membranes (as used on subject 6) are considered to be high-flux dialyzers and are expected to have

a higher rate of clearance per unit of surface area than those dialyzers with Cuprophan® membranes.*

The dialyzer extraction ratios calculated for each patient are presented in Table IX. The mean ratio was used for the calculation of clearance while on dialysis. Table X summarizes the pharmacokinetic parameters for each patient during hemodialysis. The half-life of moxalactam while on hemodialysis was 5.78 ± 2.56 hours. The mean plasma clearance was 27.4 ± 4.2 ml/min.

Table XI presents the dialysate data collected. With the dialysis equipment used on subject 6, it was possible to collect the ultrafiltrate separately. The concentration in the ultrafiltrate was 8.72 mcg/ml. This was similar to the 7.25 mcg/ml measured in the total dialysate collected.

Subject 7 was critically ill during the course of the study. He required numerous procedures that precluded obtaining blood samples at the desired times. The data used to calculate the elimination rate constant (beta) were collected after the third dose. Data collected after the first dose were used to calculate an alpha value. The B constant reported is calculated as if the elimination data were collected after the initial dose. Serum samples used to calculate hemodialysis pharmacokinetic parameters were collected at a different time than the dialysate samples. The same dialysis equipment was used both times.

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*Based on the performance characteristics data available from the manufacturer of each dialyzer.

Figures 17 through 19 show the results of the correlation analyses performed. Figure 17 represents the correlation between the pre-dialysis serum concentration of moxalactam and the amount of drug recovered in the dialysate. This was a significant correlation (r^2=0.9209, $p < 0.001$).

Figure 18 shows the correlation between the ratio of total drug recovered to pre-dialysis serum moxalactam concentrations versus the time on hemodialysis. The ratio was used to correct for the fact that each subject had a different amount of drug in their body at the start of dialysis. This correlation was also significant (r^2= 0.8378, $p < 0.01$).

The correlation between dialyzer surface area and clearance during hemodialysis is shown in Figure 19. This was a significant correlation (r^2=0.8053, $p < 0.025$). Only dialyzers with Cuprophan® membranes were used in this analysis since the acrylnitrile membrane has a greater clearance rate per unit of membrane surface area.

DISCUSSION

The half-life of moxalactam is considerably prolonged in patients with end-stage renal disease. The mean elimination half-life in this study was 27.5 hours with a range from 14.8 to 54.0 hours.
If the data from subjects 6 and 7 are excluded, the mean half-life is 18.1 hours. Subjects 6 and 7 who had the longest half-lives of the subjects in this study were critically ill and were receiving moxalactam for treatment of a severe infection. The other five subjects were volunteers who received a single dose. Subjects 6 and 7 also had a different etiology of their renal disease than the rest of

the subjects. The patient population is too small to draw any conclusions, but it is possible that being critically ill or having a specific type of underlying renal disease alters the pharmacokinetics of moxalactam.

Bolton et al[3] also examined the pharmacokinetics of moxalactam in renal failure patients. Their data were based upon single dose administration of the drug in healthy volunteers with varying degrees of renal failure. Those patients with a creatinine clearance $\leq$ 5 ml/min had a mean elimination half-life of 19.3 ± 8.73 hours with a range from 7.99 to 34.9 hours. This is comparable to the half-life observed in this study in subjects 1 through 5 who were also healthy volunteers receiving a single dose of moxalactam.

Hemodialysis increased the plasma clearance of moxalactam almost fourfold. The mean half-life during hemodialysis in these patients is 5.78 hours. This profile is similar to that of other cephalosporins except cefamandole (see Appendix D).

The correlation analyses validated the expected relationships within the data. Although these were significant, many other factors contribute to this. For instance in Figure 17, the point that fell furthest from the line is from subject 7. He was only on hemodialysis for 3 hours while the other subjects were dialyzed from 4 to 5 hours. If a wider range of length of time on dialysis were used this relationship might not be significant. It would be expected that the longer the subject is on hemodialysis the greater the percentage of drug recovered in relation to the amount in the body, as demonstrated by the correlation in Figure 18. It was also expected that the greater

the surface area of the Cuprophan® membranes the greater the clearance rate as demonstrated in Figure 19.

The current dosage recommendation for moxalactam is 250 to 500 mg every 12 hours for mild uncomplicated infections and 500 mg to 2 grams every 8 to 12 hours for moderate to severe infections.

Based on the data from this study, patients with renal failure should be given a loading dose of moxalactam. If a loading dose is not given, it would take these patients four days or longer to reach steady state levels. A loading dose of 1 to 2 grams would give "peak serum concentrations" of greater than 50 to 100 mcg/ml in most patients.

By extrapolating the single dose data collected in this study, guidelines for maintenance doses were determined. A maintenance dose of 500 mg to 1 gram should be given every 24 hours. At steady state, the subject in this study with the shortest half-life would be expected to have theoretical peak serum concentrations between 50 and 100 mcg/ml with trough levels between 16 and 32 mcg/ml. The subject with the longest half-life would be expected to have theoretical peak serum concentrations between 80 and 160 mcg/ml with trough levels between 60 and 120 mcg/ml. Based on the minimum inhibitory concentration (MIC) data for moxalactam (see Appendix E), these levels should be adequate to treat most infections except for many Pseudomonas strains. In this case, a predicted loading dose of 3 grams with a maintenance dose of 2 grams every 24 hours should maintain adequate levels.

In patients who are hemodialyzed, a maintenance dose of moxalactam is required post-dialysis. The maintenance dosage schedule should then be continued from that dose thereafter.

CONCLUSION

Moxalactam is a cephalosporin-like antibiotic with broad spectrum antimicrobial activity. The drug is known to be excreted primarily renally. This study examined the pharmacokinetics of moxalactam in seven subjects with severe renal disease requiring hemodialysis therapy. The mean half-life of moxalactamwas 27.5 hours while the half-life during hemodialysis was 5.78 hours. Based on the data collected, a loading dose of moxalactam would be necessary to initiate therapy in this patient population so that adequate drug concentrations are rapidly achieved. Maintenance doses should be given every 24 hours. In patients receiving hemodialysis therapy, a maintenance dose should be given at the end of each dialysis.

FIGURES

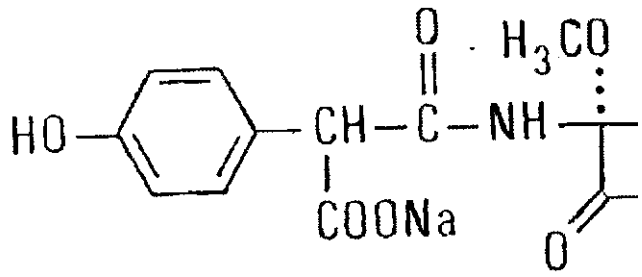
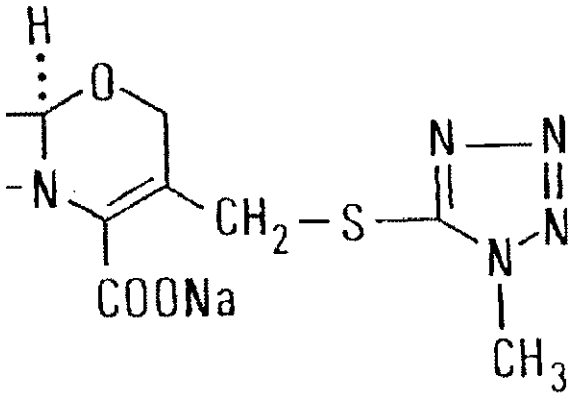


Figure 1. The structure of moxalactam.



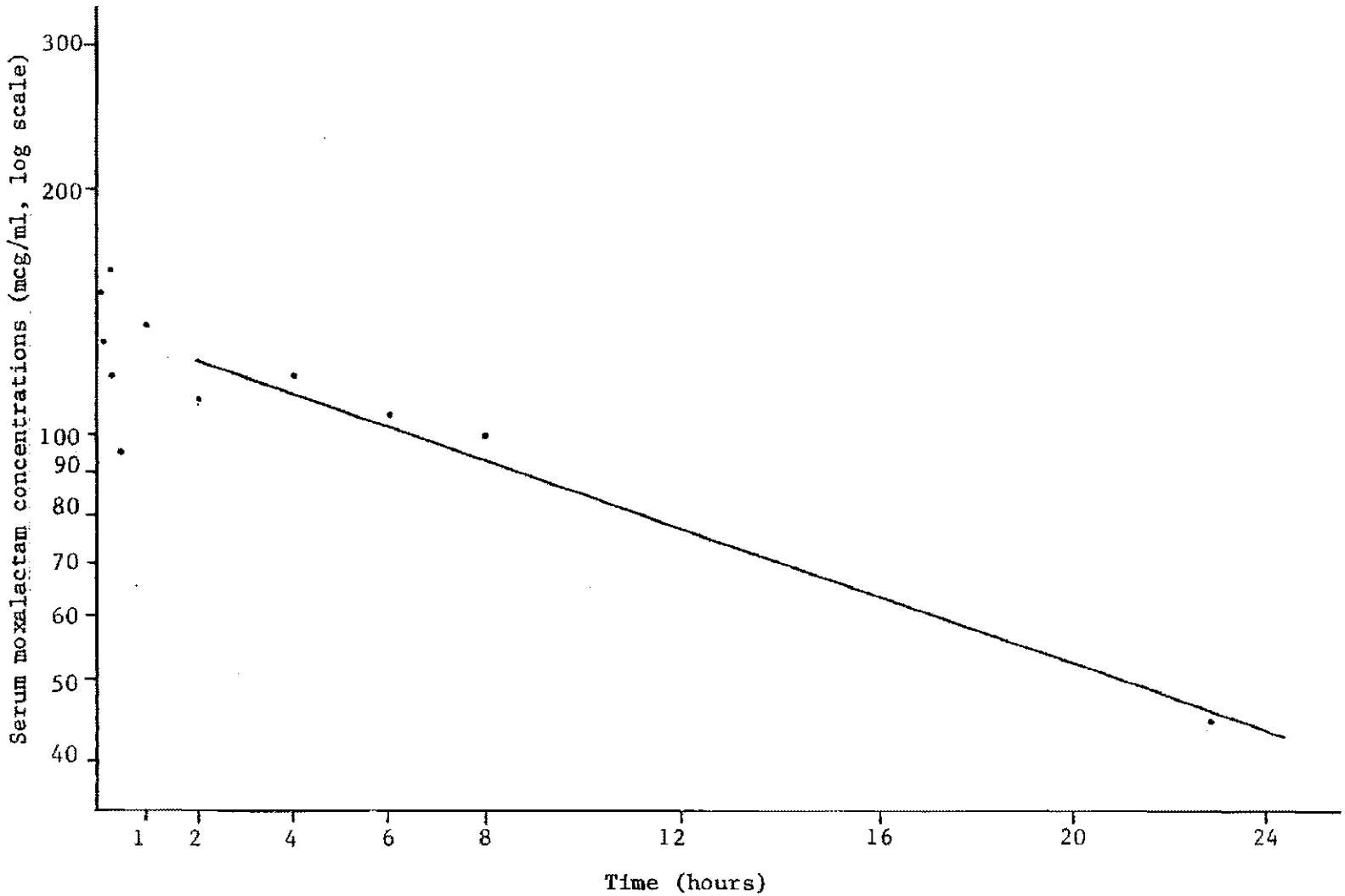


Figure 2. Graph of the data collected from Subject 1 after subject received 2 grams of moxalactam by intravenous bolus on a day when the subject was not dialyzed.

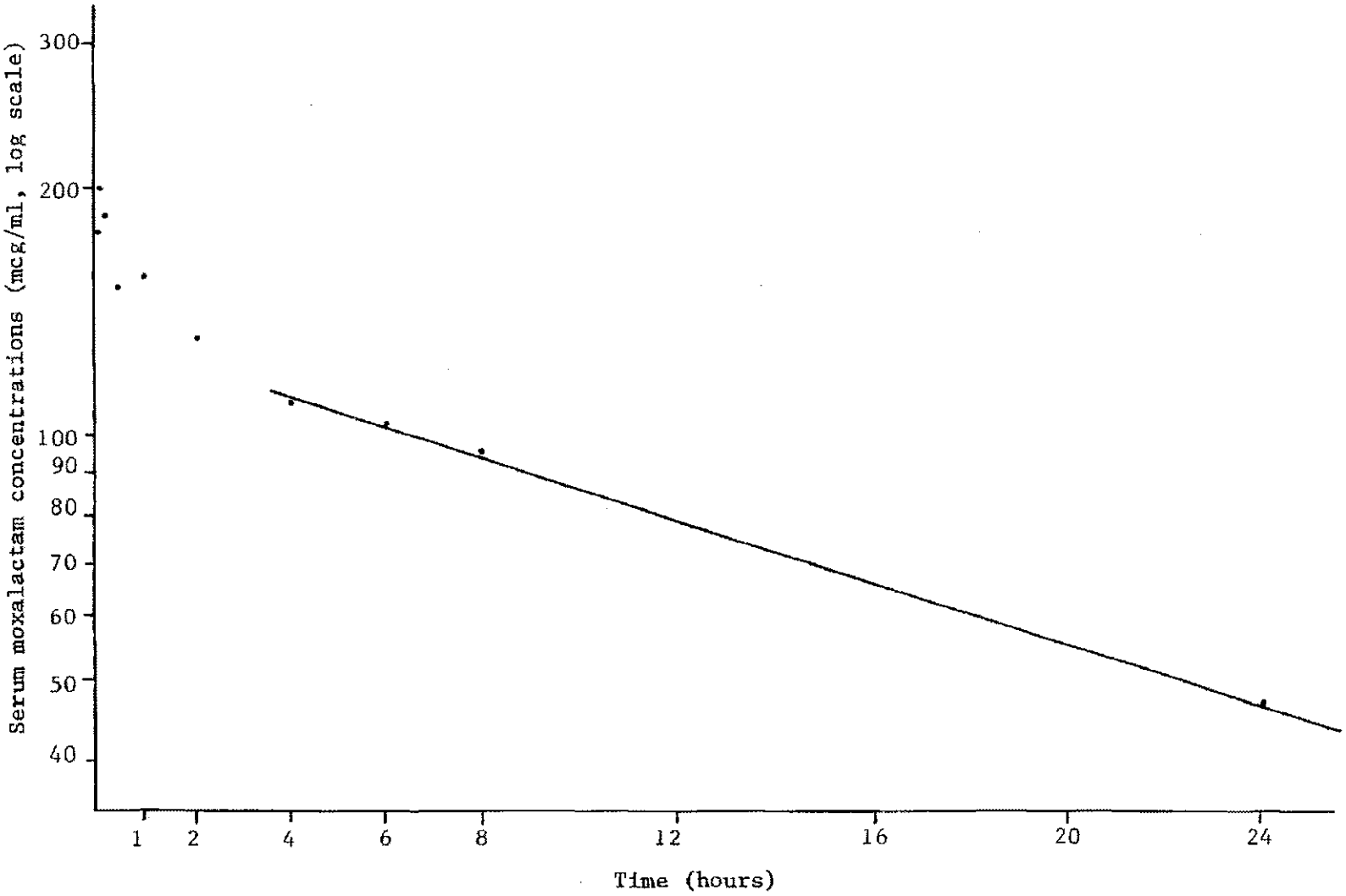


Figure 3. Graph of the data collected from Subject 2 after subject received 2 grams of moxalactam by intravenous bolus on a day when the subject was not dialyzed.

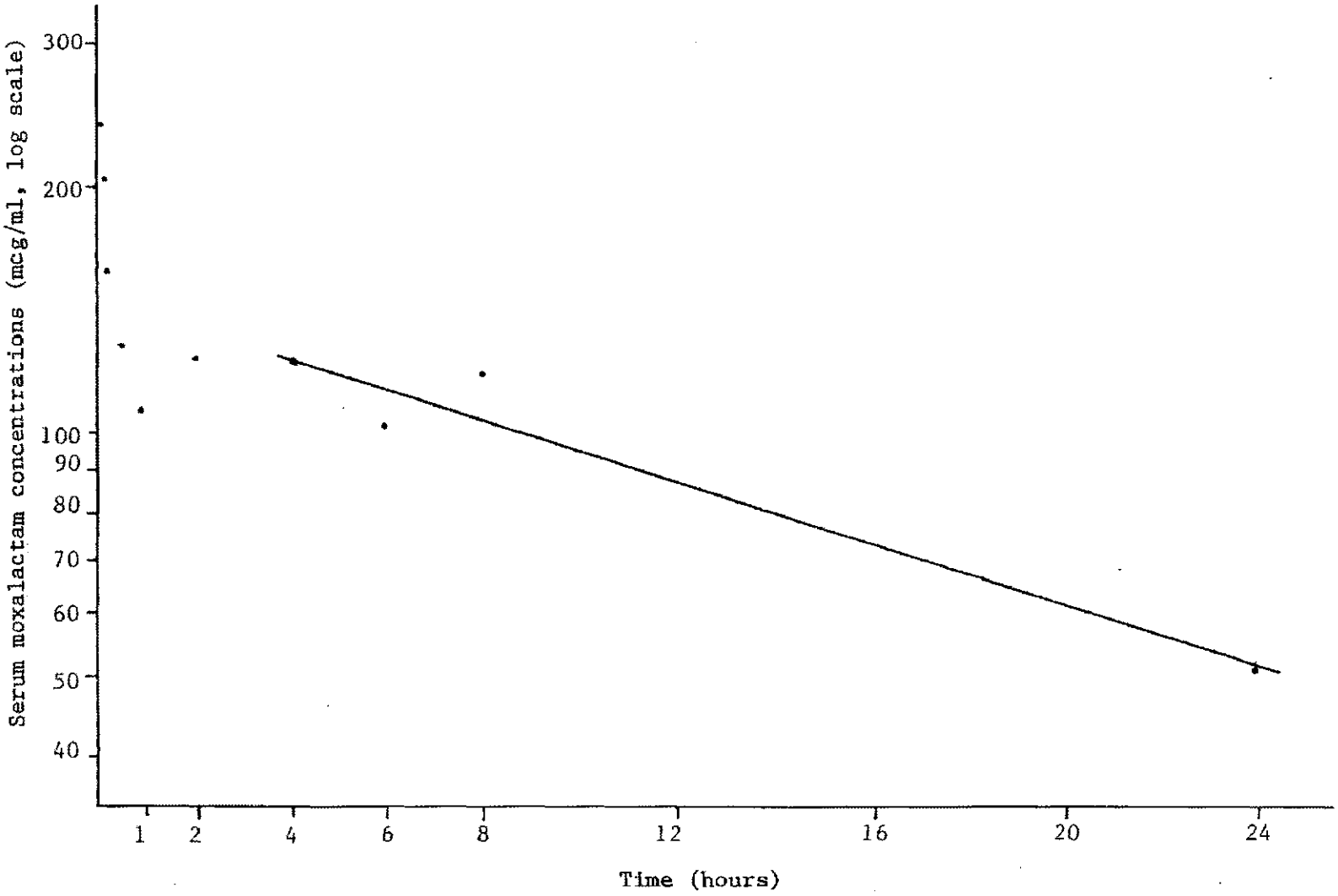


Figure 4. Graph of the data collected from Subject 3 after subject received 2 grams of moxalactam by intravenous bolus on a day when the subject was not dialyzed.

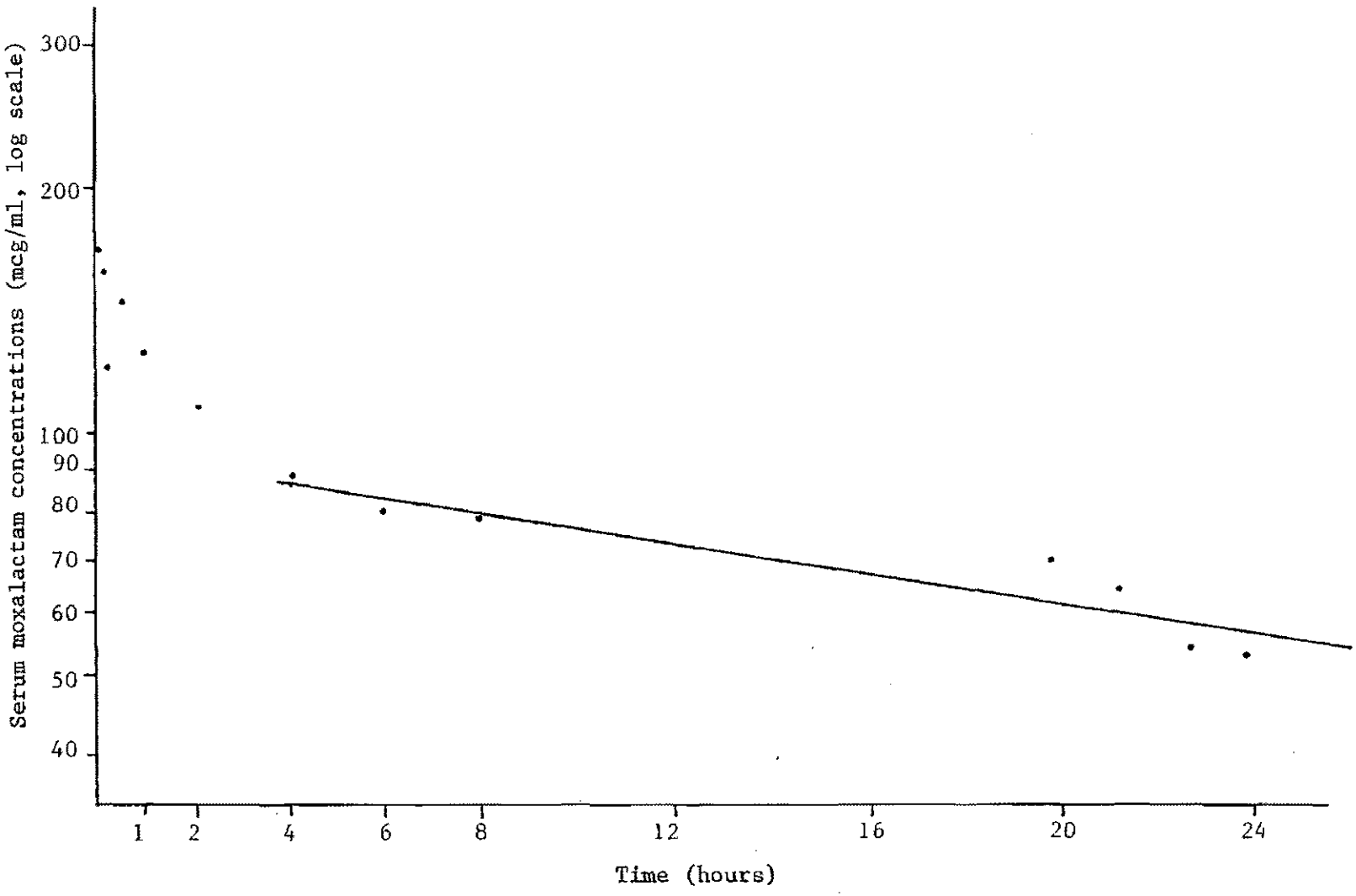


Figure 5. Graph of the data collected from Subject 4 after subject received 2 grams of moxalactam by intravenous bolus on a day when the subject was not dialyzed.

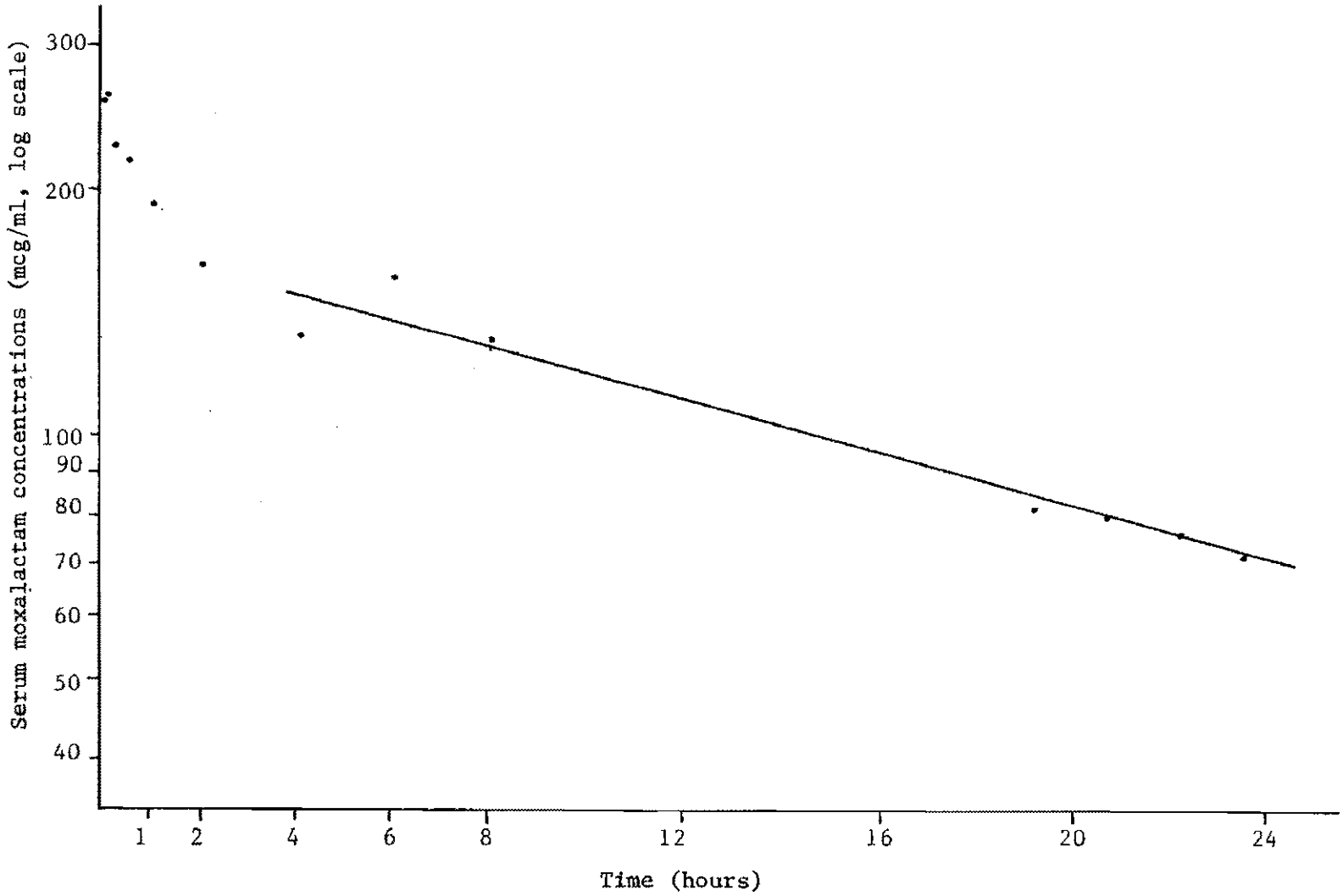


Figure 6. Graph of the data collected from Subject 5 after subject received 2 grams of moxalactam by intravenous bolus on a day when the subject was not dialyzed.

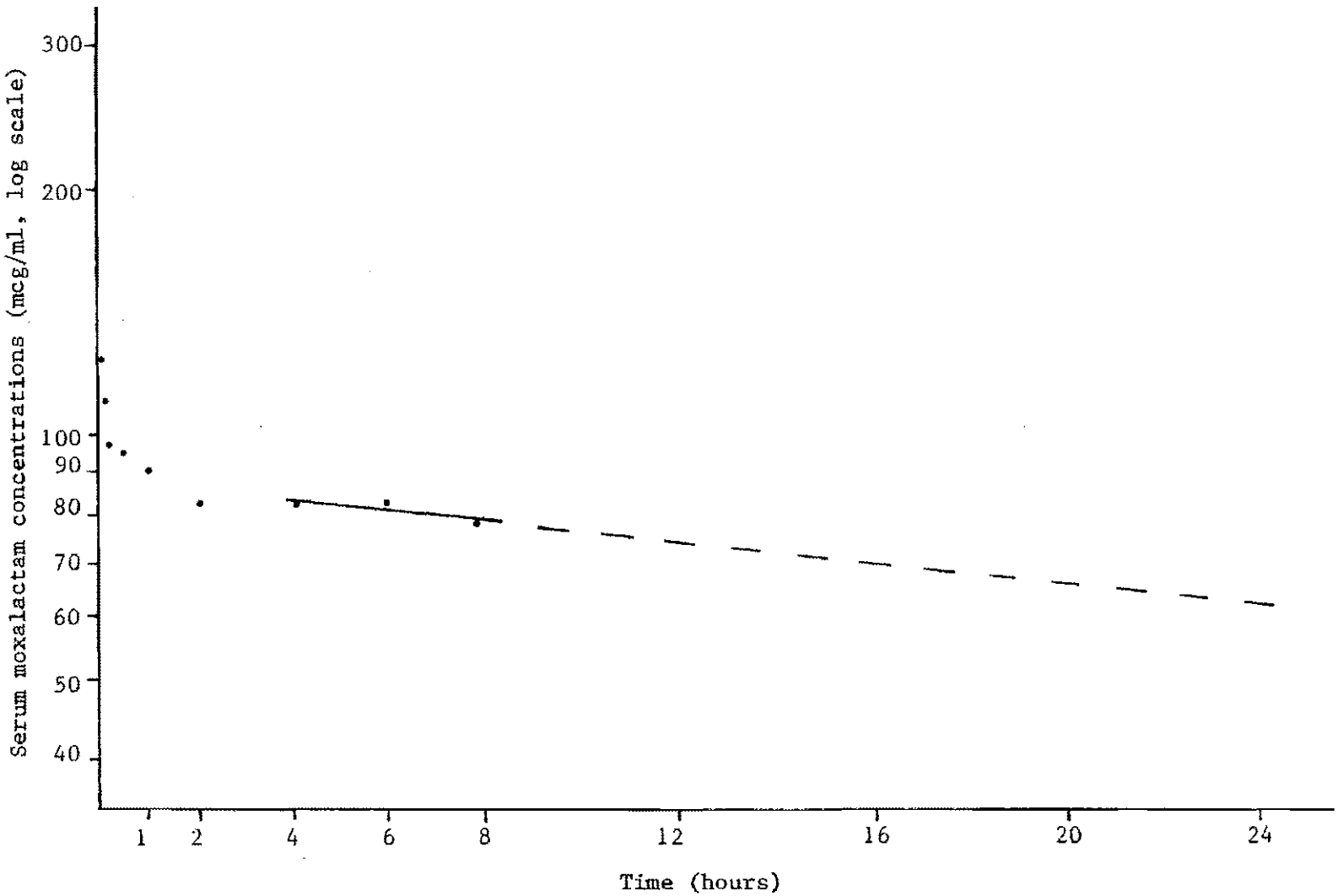


Figure 7. Graph of the data collected from Subject 6 after subject received 2 grams of moxalactam by intravenous bolus on a day when the subject was not dialyzed. Dotted line indicates the extrapolated portion of the line.

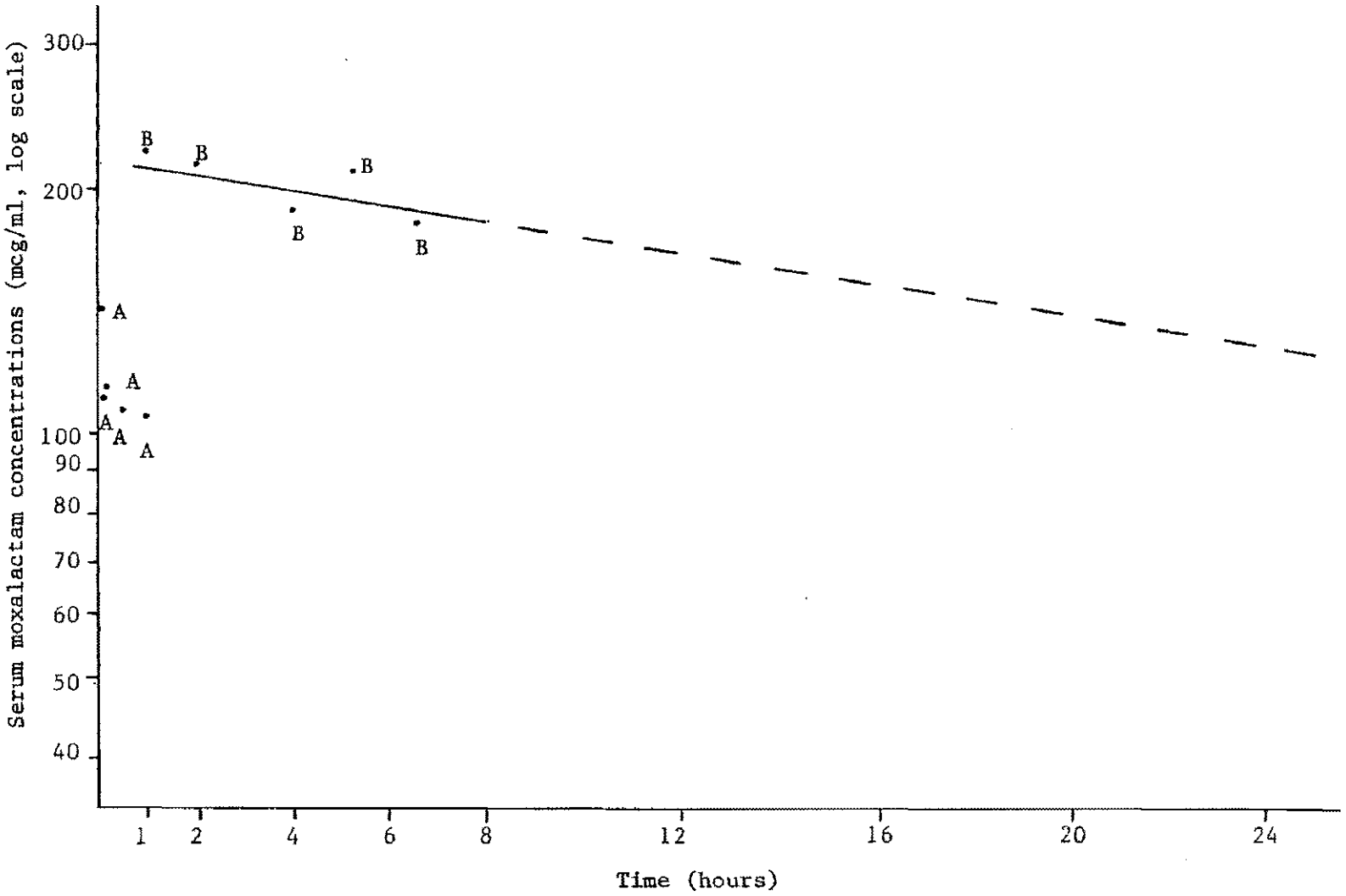


Figure 8. Graph of the data collected from Subject 7. Dotted line indicates the extrapolated portion of the line. Data labeled A were collected after the initial dose of 2 grams of moxalactam administered by intravenous bolus, while the data labeled B were collected after the third dose administered. These data were collected when the subject was not being dialyzed.

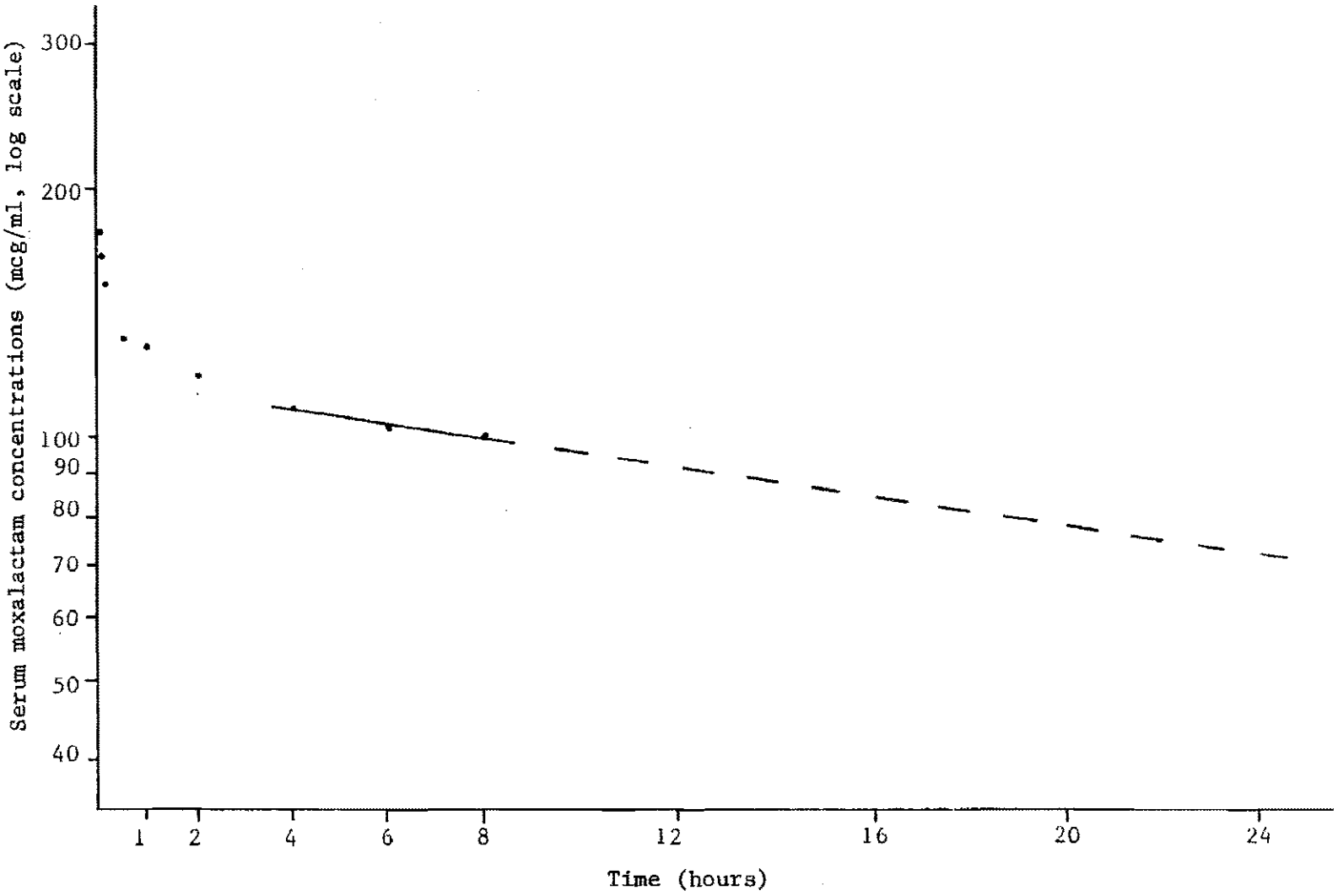


Figure 9. Graph of the mean of the data collected. Dotted line indicates the extrapolated portion of the line.

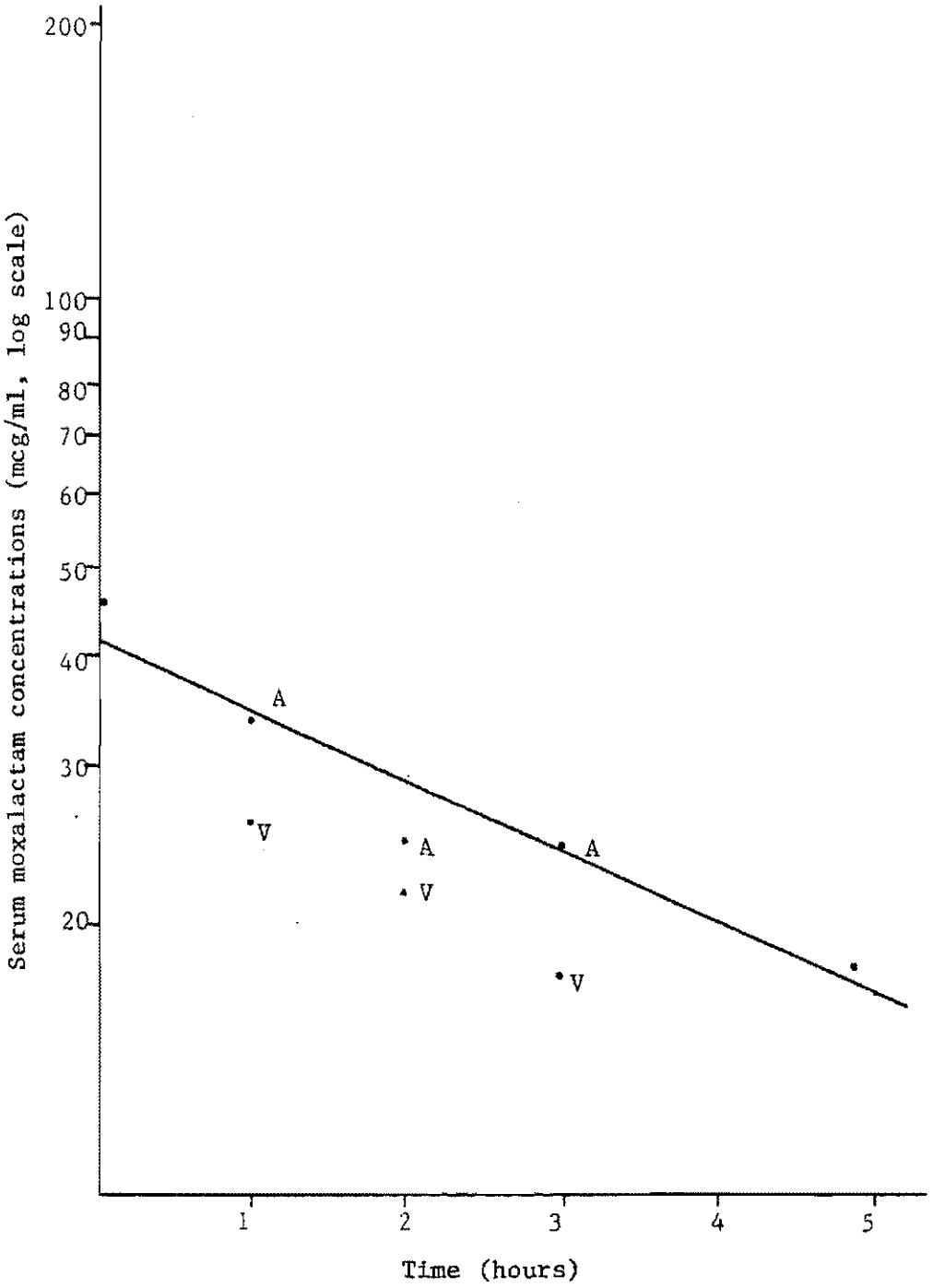


Figure 10. Graph of the data collected during hemodialysis on Subject 1. Data labeled A represent the concentration in serum entering the dialyzer, while data labeled V represent the concentration in serum leaving the dialyzer.

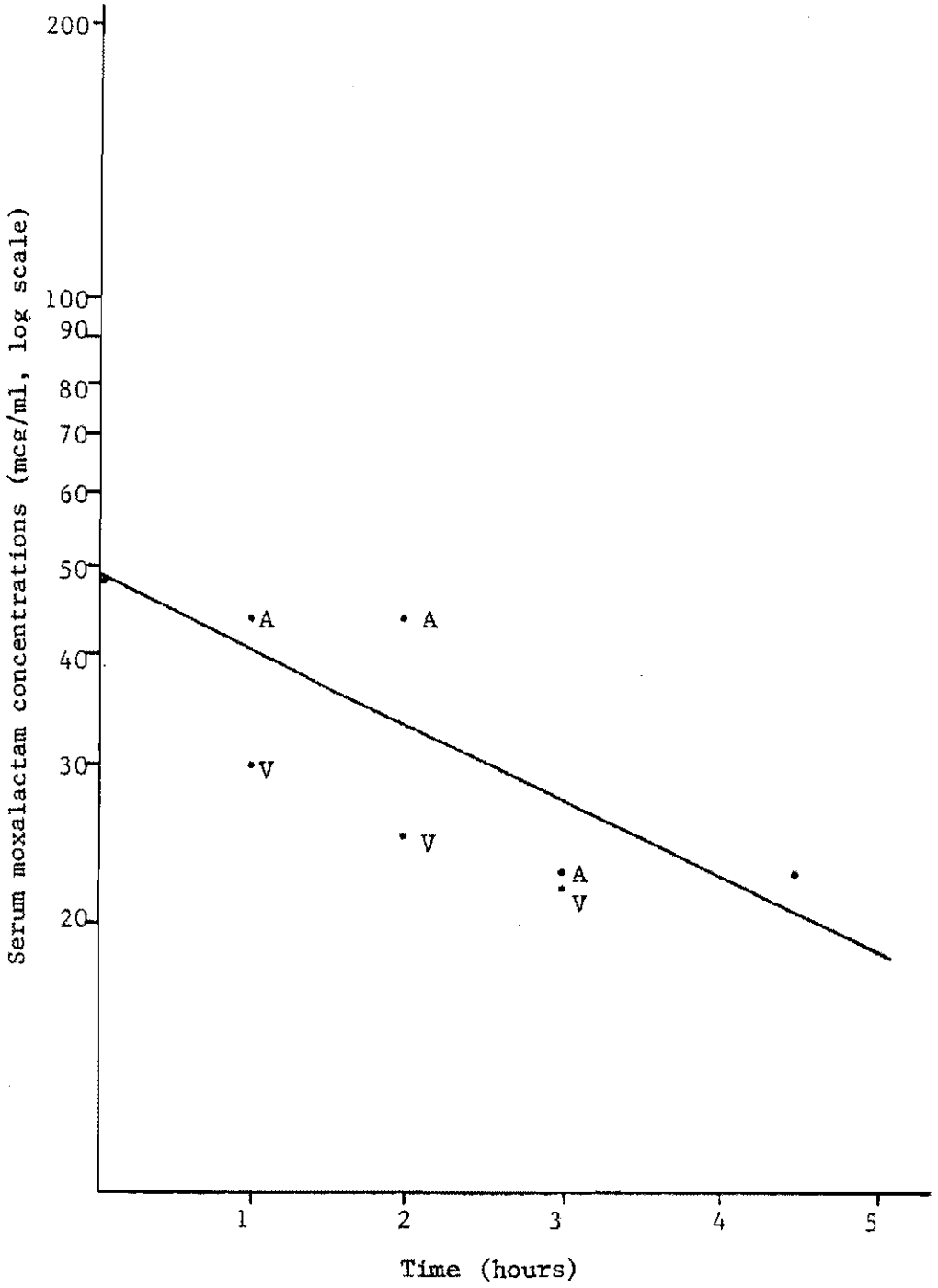


Figure 11. Graph of the data collected during hemodialysis on Subject 2. Data labeled A represent the concentration in serum entering the dialyzer, while data labeled V represent the concentration in serum leaving the dialyzer.

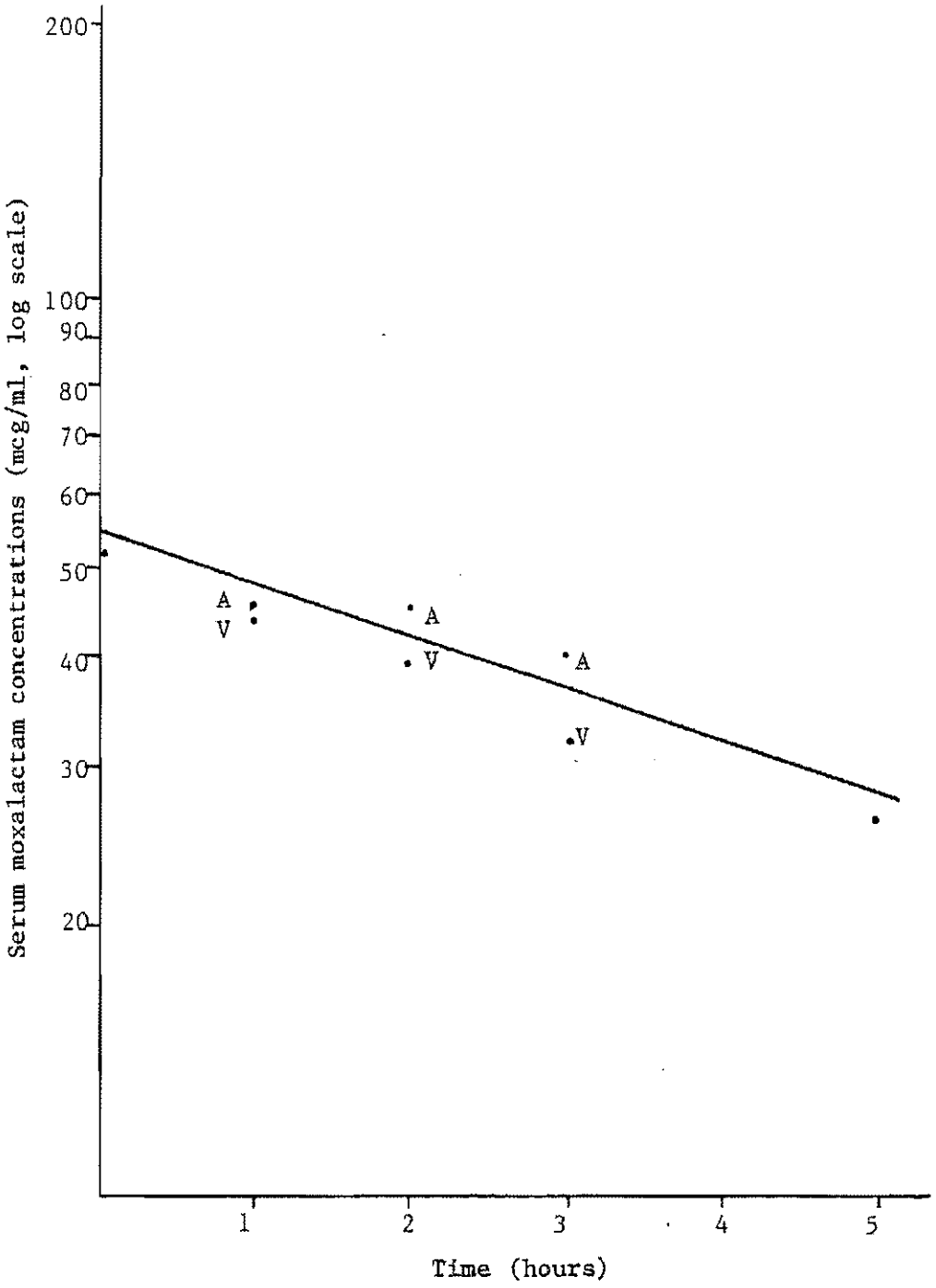


Figure 12. Graph of the data collected during hemodialysis on Subject 3. Data labeled A represent the concentration in serum entering the dialyzer, while data labeled V represent the concentration in serum leaving the dialyzer.

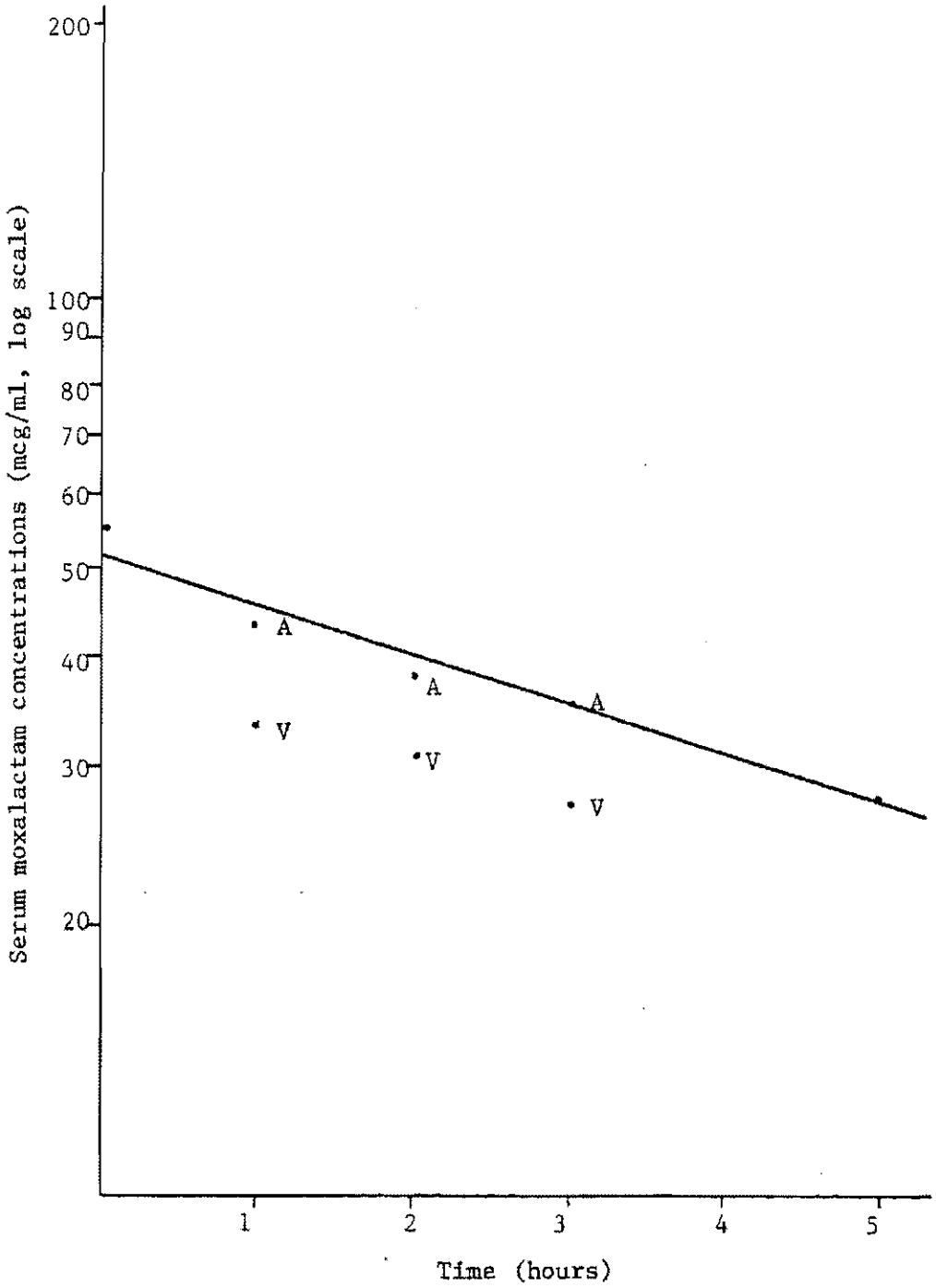


Figure 13. Graph of the data collected during hemodialysis on Subject 4. Data labeled A represent the concentration in serum entering the dialyzer, while data labeled V represent the concentration in serum leaving the dialyzer.

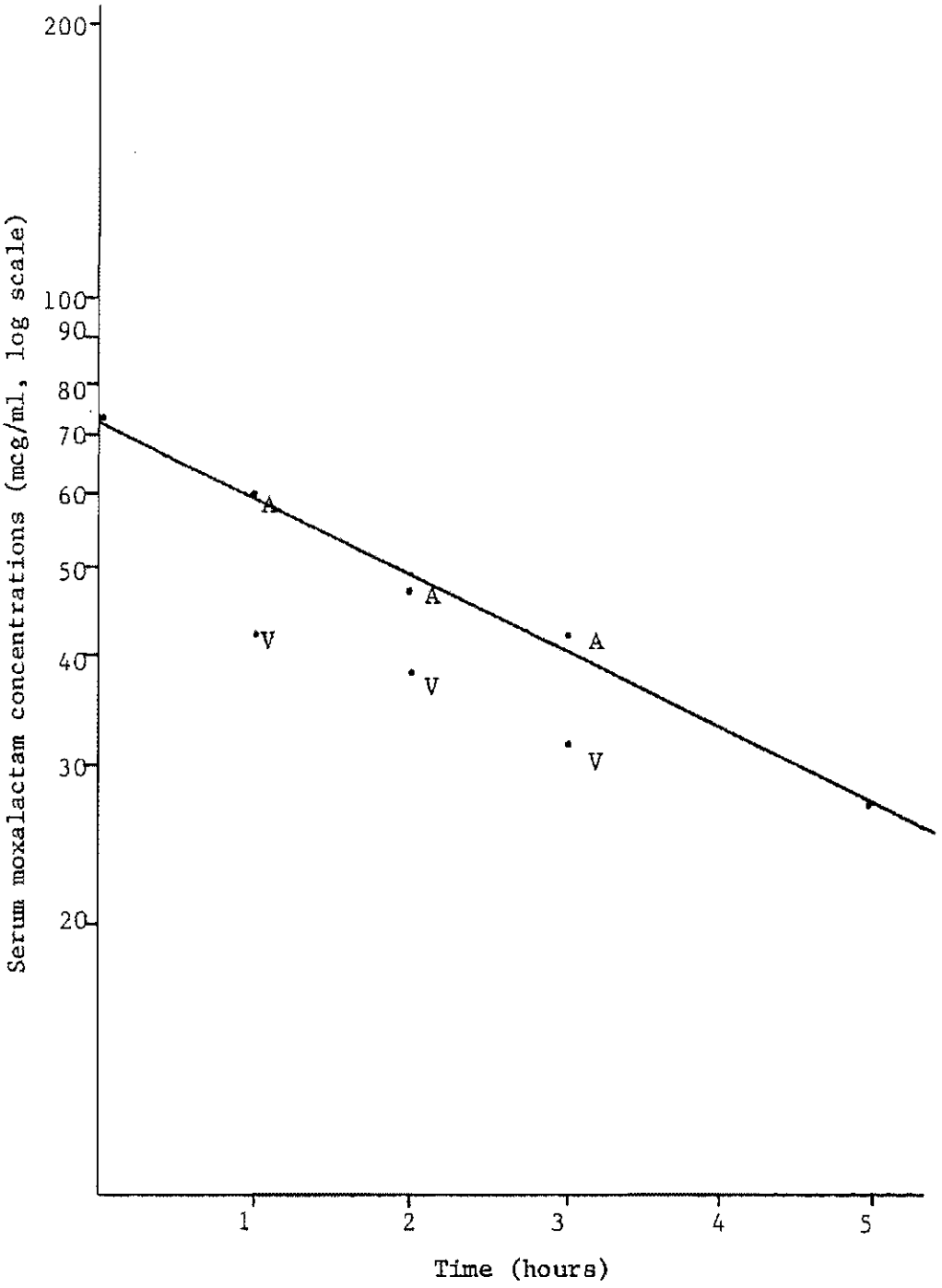


Figure 14. Graph of the data collected during hemodialysis on Subject 5. Data labeled A represent the concentration in serum entering the dialyzer, while data labeled V represent the concentration in serum leaving the dialyzer.

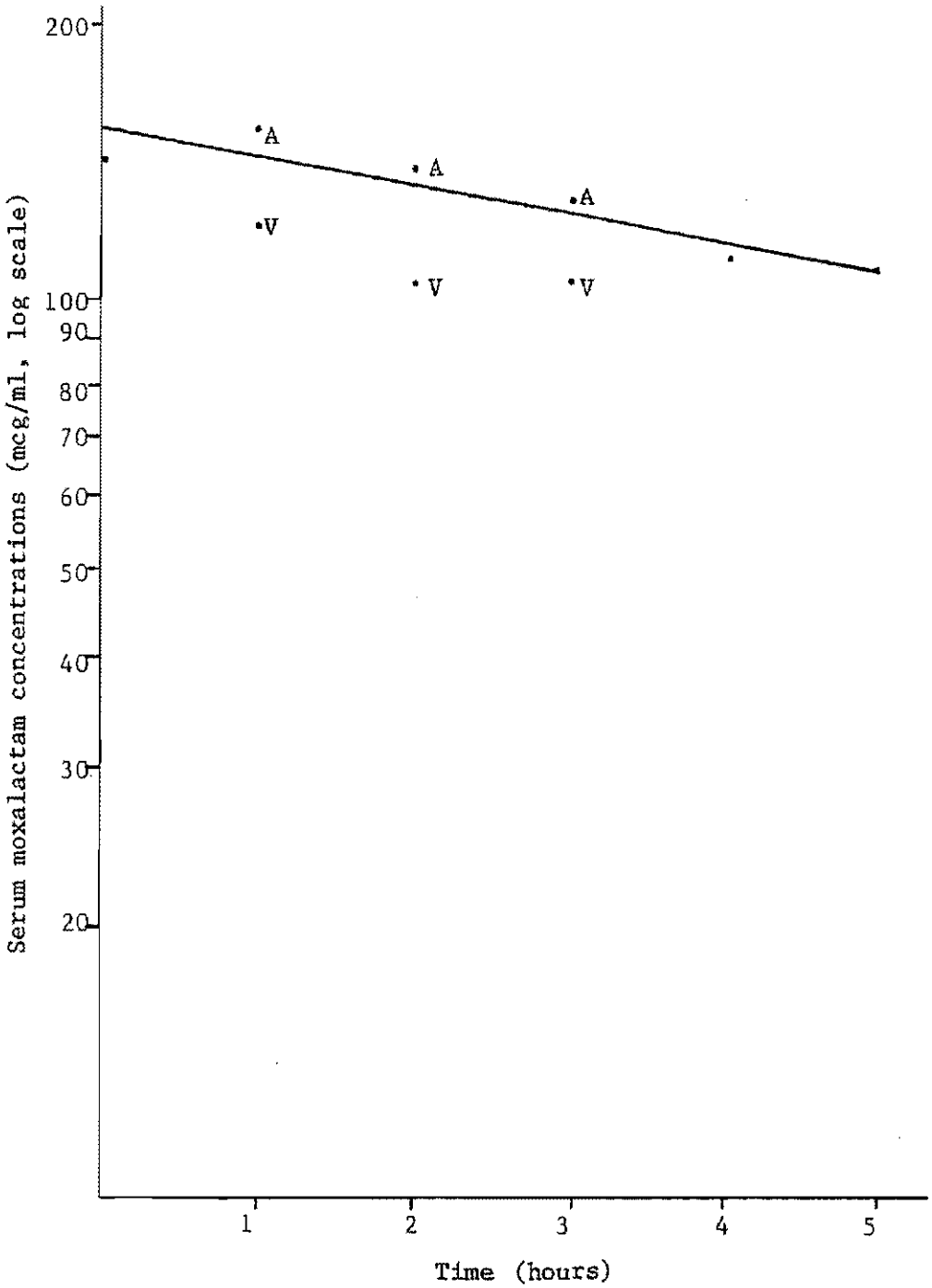


Figure 15. Graph of the data collected during hemodialysis on Subject 6. Data labeled A represent the concentration in serum entering the dialyzer, while data labeled V represent the concentration in serum leaving the dialyzer.

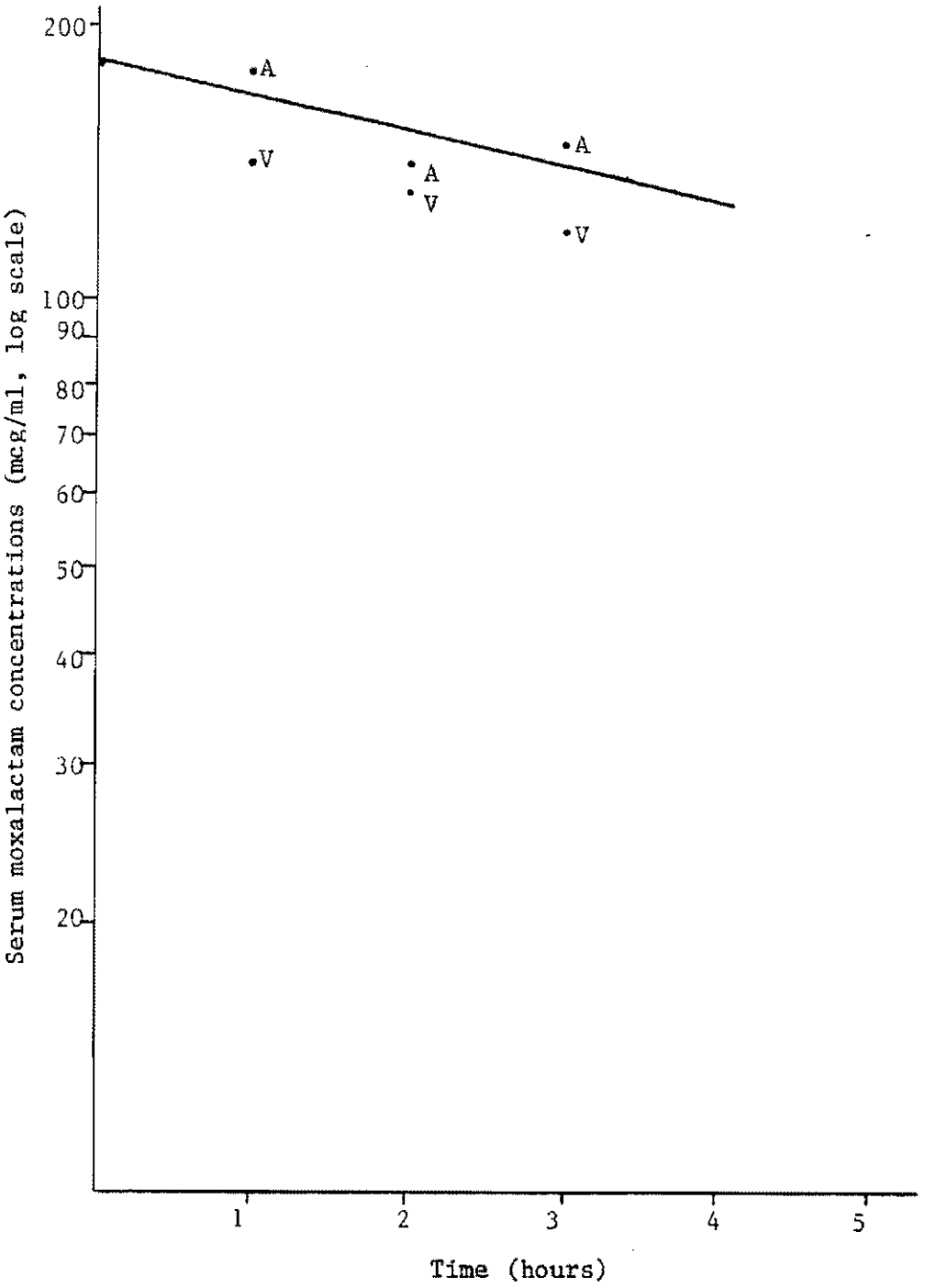


Figure 16. Graph of the data collected during hemodialysis on Subject 7. Data labeled A represent the concentration in serum entering the dialyzer, while data labeled V represent the concentration in serum leaving the dialyzer.

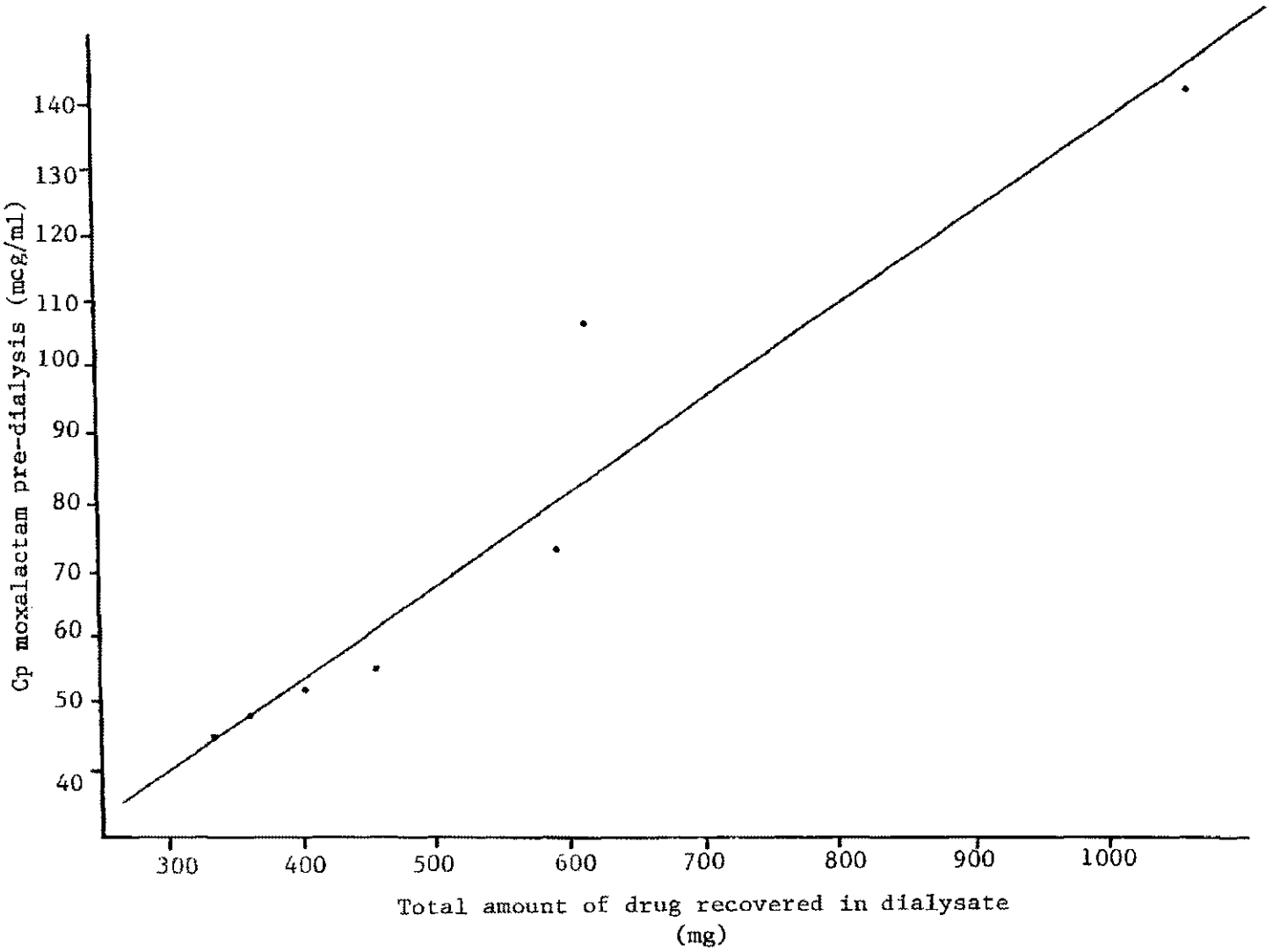


Figure 17. The correlation between the total amount of drug recovered in the dialysate and the serum concentration of moxalactam at the start of dialysis was significant (r^2=0.9209, p <0.001).

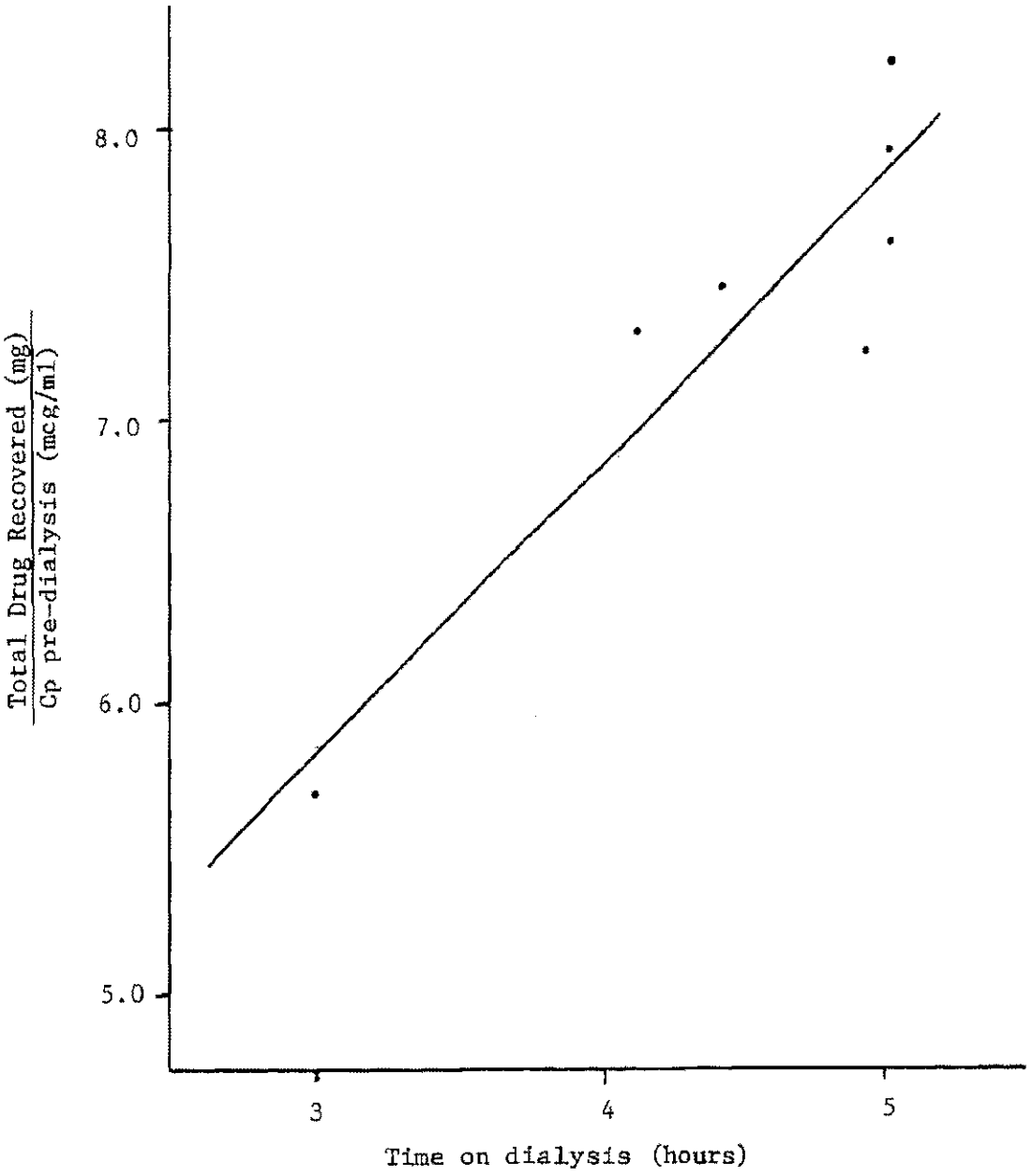


Figure 18. The correlation between time on dialysis and the ratio of total drug recovered in the dialysate to serum concentration of moxalactam taken just prior to dialysis was significant (r^2=0.8378, $p < 0.01$).

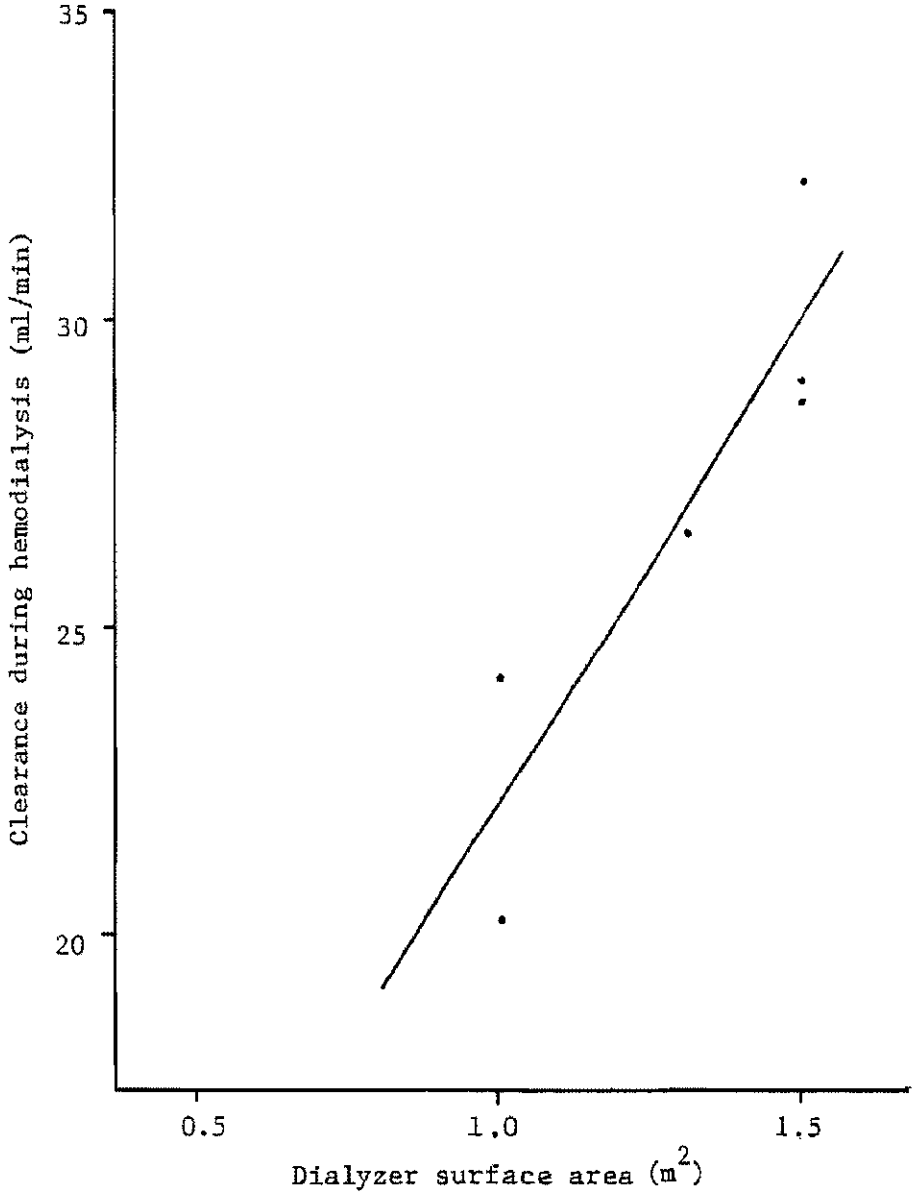


Figure 19. The correlation between dialyzer surface area and clearance during hemodialysis was significant (r^2=0.8053, $p < 0.025$). Only the dialyzers with Cuprophan® membranes were used in this analysis.

TABLES

Table I. Subject characteristics

Subject	Sex	Age (years)	IBW* (kg)	TBW+ (kg)	Height (cm)	Reason for renal failure
1	M	21	79.5	84.0	185	Chronic glomerulonephritis
2	F	33	50.0	49.0	158	Chronic glomerulonephritis
3	M	59	77.3	95.3	183	Polycystic kidney disease
4	M	65	75.0	55.3	180	Chronic glomerulonephritis
5	M	23	54.5	52.3	158	Chronic glomerulonephritis
6	M	61	77.3	63.6	183	Surgically anephric
7	M	20	77.3	66.3	183	Acute renal failure secondary to trauma

*IBW = ideal body weight calculated according to the following equation:
Female: 45.5 kg/5 ft of height + 2.3 kg/inch over 5 feet
Male: 50 kg/5 ft of height + 2.3 kg/inch over 5 feet

+TBW = total body weight

Table IIA. Laboratory Parameters*

Subject	Hgb gm/dl	HCT %	WBC k/cmm	PLT k/cmm	Na mEq/ml	K mEq/ml	Cl mEq/ml	BUN mg%	CR mg%
1	10.4	31.3	7.2	361	141	4.2	101	38	11.1
2	9.7	30.6	6.4	190	133	3.2	97	25	5.5
3	16.2	50.7	5.4	230	137	4.3	94	43	9.0
4	11.6	32.5	6.3	289	137	4.5	99	25	5.5
5	13.4	40.8	5.5	270	138	3.6	92	22	6.7
6	10.5	31.0	10.7	Adeq.	140	4.6	102	121	14.4
7	11.2	31.0	25.5	137	141	3.2	105	22	6.0

*Data are post-dialysis parameters, post-study.

Abbreviations with normal ranges

Hgb - hemoglobin 12.9-17.1 gm/dl

HCT - hematocrit 39-51.1%

WBC - white blood count 3.6-9.9 k/cmm

PLT - platelet count 140-440 k/cmm

Na - sodium 138-148 mEq/ml

K - potassium 3.3 - 5.3 mEq/ml

Cl - chloride 95-116 mEq/ml

BUN - blood urea nitrogen 6-23 mg%

CR - serum creatinine 0.4-1.6 mg%

Table IIB. Laboratory Parameters*

Subject	Ca mg%	Phos mg%	T.Bil. mg%	T.Pr. gm%	Alb. gm%	Alk.P. IU/L	SGOT IU/L	SGPT IU/L
1	9.8	7.8	0.4	5.9	3.7	140	9	21
2	9.3	4.8	0.2	6.3	4.0	87	14	19
3	11.8	2.7	0.4	7.4	4.2	160	17	20
4	10.7	2.7	0.4	6.7	4.1	169	20	26
5	9.2	4.8	0.5	8.6	5.1	86	88	176
6	7.3	6.0	0.4	7.3	3.8	92	14	18
7	8.1	0.9	18.7	5.4	3.0	161	6	-

*Data are post-dialysis parameters, post-study.

Abbreviations with normal ranges

Ca - calcium 9.3-11.1 mg%

Phos - phosphorus 2.1-4.9 mg%

T.Bil. - total bilirubin 0-1.0 mg%

T.Pr. - total protein 5.6-8.0 gm%

Alb. - albumin 3.8-5.0 gm%

Alk.P. - alkaline phosphatase 26-138 IU/L

SGOT - serum glutamate oxalacetate transaminase 1-51 IU/L

SGPT - serum glutamate pyruvate transaminase 4-46 IU/L

Table III. Serum moxalactam concentrations (mcg/ml) after initial 2 gram dose given by intravenous bolus

Subject	5 min	10 min	15 min	30 min	1 hr	2 hr	4 hr	6 hr	8 hr	pre-dialysis	time after dose
1	148	131	165	95	137	112	120	107	101	45.7	23.0 hrs
2	178	200	180	151	156	133	111	104	97	47.6	24.0 hrs
3	240	207	162	129	109	125	125	102	120	52.3	23.95 hrs
4	168	157	132	146	128	109	89.2	80.1	79.6	55.0	23.88 hrs
5	254	255	227	209	192	163	134	158	133	73.3	23.52 hrs
6	125	112	96.5	94.8	90.4	81.8	83.3	83.8	79.4	*	–
7	142	112	116	107	106	+	–	–	–	*	–
Mean ± SD	179.3 ± 49.5	167.7 ± 54.6	154.1 ± 43.6	133.1 ± 40.5	131.2 ± 34.5	120.6 ± 27.1	110.4 ± 20.2	105.8 ± 27.9	101.7 ± 21.6	54.78 ± 11.0	–

* Dialysis data were not collected after the first dose.

+Patient placed on dialysis one hour after dose. No further first dose data could be collected.

Table IV. Additional serum concentrations obtained during the elimination phase on subjects 4 and 5

t (hours)	Serum Concentration (mcg/ml)
Subject 4	
19.6	70.1
21.1	65.5
22.6	55.7
Subject 5	
19.1	84.7
20.6	83.6
22.1	78.5

Table V. Serum moxalactam concentrations after 2 gram dose given by intravenous bolus: subject 7*

t+ (hours)	Serum Concentration (mcg/ml)
1	211
2	208
4	191
5.6	206
6.8	186

*Third dose patient received

+Multiple procedures precluded drawing levels at desired times

Table VIA. Pharmacokinetic parameters*

Subject	Constants (mcg/ml) A	B	Rate Constants (hr^{-1}) α	r^{2+}	β	r^{2+}	k_{10}	k_{12}	k_{21}	$t_{1/2}$ α (min)	$t_{1/2}$ β (hour)
1	-	137.7	-	-	0.0467	0.96	-	-	-	-	14.8
2	50.3	134.7	0.8345	0.76	0.0431	0.99	0.0580	0.2003	0.6193	49.8	16.1
3	263.9	148.4	10.78	0.91	0.0429	0.94	0.1183	6.797	3.908	3.60	16.1
4	64.4	94.6	0.6385	0.85	0.0203	0.88	0.0334	0.2873	0.3881	65.4	34.1
5	128.2	174.7	2.486	0.95	0.0364	0.95	0.0625	1.011	1.448	16.7	19.0
6	29.8	88.7	2.646	0.76	0.0128	0.67	0.0171	0.6583	1.984	15.7	54.0
7	78.0	107.9	11.75	0.92	0.0168	0.52	0.0289	4.910	6.825	3.54	41.2
Mean ± SD	106.1 ± 78.9	126.7 ± 31.1	4.856 ± 5.041		0.0313 ± 0.0142		0.0530 ± 0.0364	2.311 ± 2.823	2.529 ± 2.452	25.75 ± 25.76	27.5 ± 15.4

*See Appendix C for definition and calculation of parameters

+r^2 = coefficient of determination

Table VIB. Pharmacokinetic parameters*

Subject	Volumes of Distribution (l/kg) V_c	V_p	V_{ss}	V_{area}	V_{ext}	AUC mg·hr/l	Mean Plasma Clearance (ml/kg/hr)
1	-	-	-	-	0.173+	2954+	8.06+
2	0.220	0.069	0.290	0.293	0.303	3186	12.8
3	0.051	0.088	0.138	0.140	0.141	3484	6.02
4	0.227	0.169	0.396	0.380	0.382	4761	7.59
5	0.126	0.088	0.215	0.216	0.219	4850	7.89
6	0.266	0.088	0.353	0.354	0.354	6943	4.53
7	0.163	0.117	0.279	0.279	0.280	6429	4.69
Mean ± SD	0.175 ± 0.079	0.103 ± 0.036	0.279 ± 0.093	0.277 ± 0.089	0.280 ± 0.089	4942 ± 1514	7.26 ± 3.06

*See Appendix C for definition and calculation of parameters

+Data were analyzed by one-compartment model; not included in calculation of mean values

Table VII. Moxalactam serum levels (mcg/ml) during dialysis

Subject	Pre-dialysis	1 hr		2 hr		3 hr		Post-dialysis	Time After Start of Dialysis
		A*	V*	A	V	A	V		
1	45.7	34.5	26.0	24.9	22.0	24.9	19.8	18.5	4.91 hrs
2	47.9	43.9	30.1	34.0	25.2	23.0	22.0	22.8	4.42 hrs
3	52.3	45.9	44.1	45.9	31.9	40.5	32.4	26.7	5.00 hrs
4	55.0	42.8	33.8	38.5	30.8	35.9	27.6	28.4	5.00 hrs
5	73.3	60.3	41.7	47.5	38.8	42.0	32.4	27.4	5.00 hrs
6	143	156	121	138	104	130	104	112	4.08 hrs
7	186	180	143	143	133	150	121	+	3.00 hrs

*A = sample taken from blood entering dialyzer
V = sample taken from blood leaving dialyzer

+Same as 3 hr A sample

Table VIII. Dialyzer characteristics

Subject	Dialyzer model used	Type of dialyzer	Surface Area (m^2)	Membrane Type	Membrane Thickness
1	Terumo Clirans TH-15	Hollow fiber	1.5	Cuprophan	16 microns
2	Terumo Clirans TH-15	Hollow fiber	1.5	Cuprophan	16 microns
3	Gambro, 11.5 micron	Parallel plate	1.0	Cuprophan	11.5 microns
4	Terumo Clirans TH-15	Hollow fiber	1.5	Cuprophan	16 microns
5	Extracorporeal Tri-Ex 1	Hollow fiber	1.0	Cuprophan	11 microns
6	Hospal-607	Parallel plate	0.67	Acrylonitrile AN-69	30 microns
7	Cobe, PPD 1.3	Parallel plate	1.3	Cuprophan	13.5 microns

Table IX. Dialyzer extraction ratios*

Subject	1 hr	2 hr	3 hr	Mean ± SD
1	0.2463	0.1165	0.2040	0.1890 ± 0.0662
2	0.3144	0.2588	0.0435	0.2060 ± 0.1431
3	0.0392	0.3050	0.2000	0.1814 ± 0.1339
4	0.2103	0.2000	0.2312	0.2138 ± 0.0159
5	0.30845	0.1832	0.2285	0.2400 ± 0.0634
6	0.2244	0.2464	0.2000	0.2236 ± 0.0232
7	0.2101	0.0610	0.1918	0.1543 ± 0.0813

*Ratio calculated by $\frac{A - V}{A}$. Data were collected at 1, 2, and 3 hours after the start of dialysis

Table X. Pharmacokinetic parameters during hemodialysis

Subject	k_{el} (hr^{-1})	$t_{1/2}$ (hr)	Mean dialyzer extraction ratio	Blood flow rate (ml/min)	Plasma clearance during dialysis* (ml/min)	r^2 for k_{el}+
1	0.1763	3.93	0.189	250	32.5	0.92
2	0.1931	3.59	0.206	200	28.6	0.90
3	0.1287	5.38	0.181	225	20.1	0.91
4	0.1228	5.64	0.214	200	28.9	0.96
5	0.1946	3.56	0.240	170	24.2	0.99
6	0.0664	10.4	0.224	200	30.9	0.75
7	0.0873	7.94	0.154	250	26.6	0.73
Mean	0.1380	5.78			27.4	
±SD	±0.0512	±2.56			± 4.2	

*Clearance calculated by: extraction ratio x blood flow rate x (1 - hematocrit)

+r^2 = coefficent of determination

Table XI. Dialysate data

Subject	Total Volume of dialysate (liters)	Time on Dialysis (hours)	Conc. of Moxalactam in dialysate (mcg/ml)	Total Drug Recovered (mg)	Cp pre-dialysis (mcg/ml)
1	140.0	4.91	2,38	333	45.7
2	134.6	4,42	2,66	358	47.9
3	141.3	5.00	2,84	400	52,3
4	138.8	5.00	3.30	455	55.0
5	142.7	5.00	4.10	585	73.3
6	144.6	4,08	7,25	1048	143
7	115.9	3.00	5.20	603	106

APPENDIX A

CONSENT FOR PARTICIPATION IN INVESTIGATIONAL STUDY

I. INFORMATION

You are invited to participate in this drug study because of your kidney disease. The drug that we are investigating is a cephalosporin-like antibiotic, named moxalactam. This drug has already been given to over 1,000 patients with good results and a high level of safety. To date, moxalactam appears as safe as other cephalosporin-like antibiotics given by injection. This drug is still investigational, but this study has been approved by the Federal Food and Drug Administration.

The purpose of this study is to see how the drug, moxalactam, behaves in patients, as yourself, who have kidney disease requiring hemodialysis. You will receive one dose of moxalactam by intravenous injection within one day before hemodialysis. Blood samples will be taken from your arm before the antibiotic is given, and 5, 10, 15, 30 minutes, and 1, 2, 4, 6, and 8 hours after the dose. One sample will be taken from your arm just prior to hemodialysis and one after hemodialysis. Six samples will be taken from your blood during hemodialysis as it is entering and leaving the dialyzer. Each blood sample will contain approximately 2-3 ml (about one-half teaspoonful). The total amount of blood drawn for the study will be about two ounces (60 ml). Blood for 4 routine lab tests will be necessary also if your doctor has not already ordered the tests.

Some patients may experience mild discomfort when blood samples are taken. Other than this, you may experience only minimum discomfort during the study. You will be watched closely for any side effects you may experience.

Although you may not receive any direct benefits from participation in this study, the information collected will help clinicians develop better dosing schedules for this drug when you or other patients may need this drug for treating an infection.

You are under no obligation to participate in this study. Participation in this study may be ended at any time by withdrawing your consent without prejudice to your future care.

Any questions that you have will be answered.

In the event you sustain physical injury resulting from the research project in which you are participating, the University of Utah will provide you, without charge, emergency and temporary medical treatment not otherwise covered by insurance. Furthermore, if your injuries are caused by negligent acts or omissions of University employees acting in the course and scope of their employment, the University may be liable, subject to limitations prescribed by law, for additional medical costs

and other damages you sustain. If you believe that you have suffered a physical injury as a result of participation in this research program, please contact the Office of Research Administration, Phone No. 581-6903.

II. CONSENT

I have read the foregoing and my questions have been answered. I desire to participate in this study. I give my permission for information gathered in this study to be released to the prinicipal investigator, Mary E. Russo, Pharm.D., Department of Pharmacy Practice, and co-investigators Burton Janis, M.D., Division of Infectious Diseases, and Linda S. Tyler, Pharm.D. Candidate, Department of Pharmacy Practice, University of Utah Medical Center.

_____ _____

Signature of Patient Date

_____

Witness

APPENDIX B

ANTIBIOTIC ASSAY USING LARGE SQUARE PLATES FOR MOXALACTAM

Seed Organism

Escherichia coli ATCC 10536 (Lilly Research Laboratories)

Medium Used

Antibiotic Medium #1 (manufactured by Difco)

Assay Plates

Large 14 x 14 inch square glass plates with lids

Antibiotic Standards

All standards for serum samples were diluted in single donor serum (known donor).

All standards for dialysate samples were diluted in normal saline

Seed Organism Preparation

E. coli broth suspension is prepared ahead and kept in the refrigerator until needed.

To 250 ml of the media is added 0.75 ml of seed organism broth suspension. Swirl and pour into one large square glass plate allowing the plate to rest on a flat surface until the agar solidifies.

ANTIBIOTIC ASSAY USING THE LARGE PLATES

(Square 14 x 14" Glass Plates)

1. Grow seed organisms up overnight if not ready.

2. Prepare 250 ml of the appropriate antibiotic media early in the morning or make it the night before and melt it.

3. While the media is melting or autoclaving read yesterdays run if one had been done.

4. Once the media is melted or autoclaved place in water bath 56°C.

5. Pre-warm the large 14 x 14" glass plate in an incubator (35°C).

6. Get the moxalactam standards out and dilute them.

7. Seed the cooled 250 ml agar (cooled to about 50°C) with the appropriate amount and organism to be used. Swirl and pour into the large plate that has been transferred to a flat surface at room temperature.

8. While the agar plate is solidifying, which takes about one-half to one hour, start placing serum samples and controls on the discs that have been placed out on a large screen. Use tape on the screen to identify each sample. Make a template out of a large piece of mylar (this can be rubbed clean and used the next day). Use an Eppendorf pipetter (0.02 ml) or a variable Eppendorf pipetter or a similar pipetter to deliver 0.02 ml to each disc. Make five discs for each patient serum sample and five discs for each antibiotic standard. Discs to be used are blank Penicillin Assay discs one-fourth inch in diameter. To equalize results the discs need to dry and the time it takes for the agar to solidify is about right with Salt Lake City humidity.

9. Make a paper template to indicate spots where the discs are to be located. It is best to have the mylar template line up with the paper template.

10. Place discs on agar surface pressing down on each disc.

11. Incubate level at 35°C overnight.

12. Read zones of inhibition the next day and average the five zones for each patient's serum and average the five zones for each standard. Plot the standards on two cycle semi-log paper using a curve fitting program (Hewlett Packard HP-67) to determine the best fitting line.

APPENDIX C

DEFINITION AND CALCULATION OF PHARMACOKINETIC PARAMETERS

The following is a brief discussion of the definition and formulae used to calculate all of the parameters discussed. Wagner and Gibaldi give a more detailed explanation.

I. ONE COMPARTMENT OPEN MODEL

This model assumes instantaneous distribution into the body tissues. Because no definite distribution phase could be identified, this model was chosen to analyse the data from subject 1 and the elimination rate constant and half-life during dialysis. The following is a list of definitions and derivations of parameters calculated:

1. kel = elimination rate constant of first order kinetics. This is calculated from the negative slope of the line during elimination. This is the same as β of the two compartment model.

2. $t_{\frac{1}{2}}$ = half-life of the drug is calculated as follows:

$$t_{\frac{1}{2}} = \frac{0.693}{kel}$$

3. V_d = apparent volume of distribution = $\frac{dose}{C_{po}}$ where C_{po} = plasma concentration at time zero. C_{po} is the y- intercept of the line used to calculate kel.

4. Total body clearance is equal to kel x V_d and is also equal to dose/$AUC_{cp\ vs\ t}$.

5. AUC = area under the curve is mathematically equivalent to:

$$AUC_{cp\ vs\ t} = \frac{dose}{kel\ V_d}$$

II. TWO COMPARTMENT OPEN MODEL

This model is used when a distribution phase can be identified based on a graph of the data. This was an appropriate model for the data from subjects 2 through 7.

1. β = beta = is the apparent first order elimination rate constant. It was derived graphically by determining the slope of the line of the terminal portion of the graph of the ln C_p vs t. β is the negative slope of the line.

2. B is the y intercept of the line that derived above with the slope β.

3. α - alpha is the negative slope of the line derived by method of residuals (or feathering) representing the rate constant of the distribution phase.

4. A is the y intercept of the line described above with the slope α.

5. k_{21} = rate constant of the drug distributing from compartment 2 to compartment 1. It is equal to:

$$k_{21} = \frac{A\beta + B\alpha}{A + B}$$

6. k_{10} is the rate constant representing drug going from compartment 1 to outside the body. It is equal to:

$$k_{10} = \frac{\alpha\beta}{k_{21}} = \frac{A + B}{A/\alpha + B/\beta}$$

7. k_{12} is the rate constant describing the rate of the drug moving from compartment 1 to compartment 2. It is equal to:

$$k_{12} = \alpha + \beta - k_{10} - k_{21}$$

As a rule the relationships below hold:

$$k_{10} > \beta$$

$$\alpha > k_{21} > \beta$$

8. Volume of distribution: In a two compartment model there are several volumes of distributuion, each representing a different part of the distribution characteristics of the drug described by a multicompartment model.

V_c is the apparent volume of the central compartment, also denoted V_1. It is equal to:

$$V_c = \frac{Xo}{A+B}$$ where X_o is equal to the dose.

V_{ss} is the apparent volume relating to the amount of drug in the serum at steady state. It is equal to:

$$V_{ss} = \frac{k_{12} + k_{21}}{k_{21}} V_c$$

V_p is the apparent volume of the peripheral compartment. It is equal to:

$$V_p = V_{ss} - V_c$$

V_{area} is the apparent volume of distribution of a drug that confers upon the body characteristic of a multicompartmental model.

It is actually a proportionally constant that relates the amount of drug in the body to the drug concentration in the plasma at any time during the post distributive phase. It is equal to:

$$V_{area} = \frac{V_c \, k_{10}}{\beta}$$

V_{ext} is the extrapolated volume of distribution. It is equal to:

$$V_{ext} = \frac{dose}{B} = \frac{\alpha - \beta}{k_{21} - \beta} \, V_1$$

The following relationships generally hold true:

$$V_{ext} > V_{area} > V_{ss} > V_c$$

9. Clearance (Cl) represents the rate the drug is cleared from the body. Mean body clearance and total body clearance are mathematically equivalent.

$$Cl = \frac{dose}{AUC} = V_c k_{10} = V_{area} \, \beta$$

10. AUC is equal to area under the curve. In the 2 compartment model AUC is equal to:

$$AUC_{C_p \text{ vs } t} = \frac{A}{\alpha} + \frac{B}{\beta}$$

11. The half-life of the β and α phases can be calculated as for the 1 compartment model.

$$t_{\frac{1}{2}} \alpha = \frac{0.693}{\alpha}$$

$$t_{\frac{1}{2}} \beta = \frac{0.693}{\beta}$$

APPENDIX D

Half-life of cephalosporin antibiotics in patients with severe renal failure

Cephalosporin	Half-life (hr) In renal failure	On dialysis
Cephalothin	2.82 12.00 19.00	3.3
Cephaloridine	22.45	4.3 2,4
Cephalexin	19.28 18.20	2.64 3.60
Cefazolin	39.81	14.25 6.38
Cephapirin	---	1.75
Cephacetrile	22.10	4.7
Cefoxitin	17.5	---
Cefamandole	7.95	6.22

Adapted from J Infect Dis 137:S90, 1978.

APPENDIX E

Moxalactam Minimum Inhibitory Concentration (MIC)
Data for Selected Organisms*

Organism	Mean MIC (mcg/ml)	Range (mcg/ml)
Staph. aureus	4.5	2-16
Staph. epidermidis	14.5	4->32
Strep. spp.	2.3	0.3->64
Escherichia coli	0.1	0.1-8.0
Enterobacter spp.	0.3	0.1-16
Klebsiella spp.	0.1	0.1-0.5
Proteus mirabilis	0.1	0.1-0.3
Proteus spp. (Indole +)	0.1	0.1
Serratia marcescens	1.0	0.3-8.0
Pseudomonas aeruginosa	16.0	8-32
Neisseria gonorrhoeae	0.1	0.1
Haemophilus influenzae	0.2	0.1-32
Gram + anaerobic rods	1.9	0.3->64
Gram + anaerobic cocci	0.2	0.1->64
Gram - anaerobes	0.7	0.1-8.0
Bacteroides fragilis	1.6	0.3-8.0

*Data compiled from Antimicrob Agents Chemother 17:412-16, 1980

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CURRICULUM VITAE

Linda Stone Tyler

PERSONAL

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Children:	None
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EDUCATIONAL BACKGROUND

Bachelor of Science in Pharmacy, University of Utah, Salt Lake City, Utah, June 10, 1978.

Certificate of Residency in Hospital Pharmacy, University of Nebraska Medical Center, Omaha, Nebraska, June 30, 1979.

Doctor of Pharmacy, University of Utah, Salt Lake City, Utah, anticipated June 1981.

EDUCATIONAL EXPERIENCES

Residency

Experience included Clinical Services (22 weeks), Drug Information (10 weeks), Inpatient drug distribution, manufacturing, and parenteral admixtures (9 weeks), Outpatient Services (4 weeks), and Administration (4 weeks)

Doctor of Pharmacy

Clinical Rotations:

Adult Internal Medicine (24 weeks), University Hospital
Infectious Disease (6 weeks), University and Veteran's Administration Hospital
Cardiology, Adult (6 weeks), LDS Hospital
Surgery (6 weeks), University Hospital
Critical Care (6 weeks), LDS Hospital
Drug Information (6 weeks), University Hospital
Nutrition (3 weeks), Primary Children's Medical Center
Pediatrics (6 weeks), Primary Children's Medical Center
Pediatric Neurology (3 weeks), Primary Children's Medical Center
Psychiatry (6 weeks), Veteran's Administration Hospital
Ambulatory Care (6 weeks), University Hospital Clinics, and Veteran's Administration Geriatric Unit
Obstetrics and Gynecology (6 weeks), University Hospital, and Utah State Division of Health

Special Problems in Pharmacokinetics:

Co-authored a problem syllabus to supplement coursework in Advanced Pharmacokinetics class for Doctor of Pharmacy Candidates

PROFESSIONAL EXPERIENCES

Pharmacy intern for Grand Central, a chain drug store, Bountiful, Utah, December 1976 to June 1977 and September 1977 to June 1978

Pharmacy intern for SavOn Drugs, a chain drug store, Huntington Beach, California, June 1977 to September 1977.

Pharmacist, part-time, Intermountain Regional Poison Control Center, Salt Lake City, Utah, November 1979 to present

RESEARCH PROJECTS

The Effect of Gentamicin on Heparin Activity, Linda Stone Tyler, Terry L. Rehder, Pharm.D., Richard B. Davis, M.D., completed June 28, 1979, in fulfillment of the requirements of Residency Certificate

The Pharmacokinetics of Moxalactam in Hemodialysis Patients, Linda Stone Tyler, Mary E. Russo, Pharm.D., Burton Janis, M.D., funded by Eli Lilly Company for $1,425. Fulfills research requirements of the Doctor of Pharmacy Program.

PUBLICATIONS

The Effect of Gentamicin on Heparin Activity, Linda S. Tyler, Terry L. Rehder, Richard B. Davis. Submitted to Am J Hosp Pharm.

Chloramphenicol Interaction with Phenytoin and Phenobarbital, Kelly D. Mutchie, Pharm.D., Linda Stone Tyler, B.S., Joel A. Thompson, M.D. Submitted to J Pediatr.

INVITED LECTURES AND PRESENTATIONS

"Treatment of Hypercalcemia: A Case Presentation", Midwestern Clinical Conference for Preceptors and Residents of Pharmacy, Omaha, Nebraska, May 4, 1979.

"Treatment of Complications of Diabetes in the Elderly", presented to nurses and other health professionals, Rocky Mountain Geriatric Center, Health Screening Clinic, Salt Lake City, Utah, October 1979.

"Comparing Antipsychotic Agents", presented to the staff at Veteran's Administration Hospital, Psychiatric Unit, Salt Lake City, Utah, November 1979.

"The Effect of Gentamicin on Heparin Activity", a contributed paper at the Midyear Clinical Meeting, December 1979,

"Alzheimer's Disease, OBS, Confusion, and Their Treatment", presented to undergraduate pharmacy students taking the class, Drug Use in the Elderly, April 1980.

"Diabetes in the Elderly", presented to undergraduate pharmacy students taking the class, Drug Use In the Elderly, April 1980.

"Alzheimer's Disease", a presentation to the medical and nursing staff at the Veteran's Administration Hospital, Geriatic Therapeutic Unit, May 1980.

"Pharmacokinetics of Disopyramide", presented to first-year Doctor of Pharmacy Candidates taking Advanced Pharmacokinetics, August 1980.

Conducted weekly problem sessions for Doctor of Pharmacy Candiates taking Advanced Pharmacokinetics, August-September 1980.

"Pharmacokinetics of Phenytoin", presented to the Neurology staff and residents, Primary Children's Medical Center, September 1980.

"Pharmacokinetics of Disopyramide", presented to undergraduate pharmacy students taking Pharmacokinetics, November 1980 and February 1981.

"Management of Streptomycin-Induced Pseudomembranous Colitis in a Patient with Tuberculosis", a poster presentation, Midyear Clinical Meeting, December 1980.

"Drug Fever", presented at Infectious Disease Grand Rounds, November 1980.

"Cephalosporin Review", presented at Infectious Disease Grand Rounds, December 1980.

"Careers in Pharmacy", a presentation to freshmen college students taking a Health Careers Class, February 1981.

"Signs and Symptoms of Pulmonary Disease", presented to undergraduate pharmacy students taking Pathophysiology, February 1981.

"Treatment of Deep Vein Thrombosis and Pulmonary Embolus", presented to undergraduate pharmacy students taking Pathophysiology, February 1981.

"Treatment of Deep Vein Thrombosis and Pulmonary Embolus", presented to first-year Doctor of Pharmacy Candidates taking Advanced Pharmacotherapeutics, March 1981.

"Drugs Known to Affect Hearing", to Audiology Graduate students, April 1981.

"Systemic Lupus Erythematosus", to be presented to undergraduate pharmacy students taking Pathophysiology, May 1981.

TEACHING FELLOWSHIPS

In Internal Medicine for instruction of undergraduate students on clinical clerkships, Winter Quarter 1980 and 1981.

In Clinical Toxicology for instruction of Doctor of Pharmacy Candidates and undergraduate students, in didactic and clerkship activities, Spring quarter 1981.

PROFESSIONAL AWARDS AND ACTIVITIES

Volunteer, Cystic Fibrosis Camp, Salt Lake City, Utah, Summer 1976.

Coordinator in establishing a Hypertension Screening Clinic, University of Utah, Salt Lake City, Utah, 1976-1977.

Elected Member of Student Advisory Committee, College of Pharmacy, University of Utah, 1977-1978.

Chairman, Preceptor of the Year Selection Committee, University of Utah, 1978.

Recipient of the Upjohn Achievement Award, for outstanding public service, May 1978.

Recipient of the Squibb Industry Seminar Award, for Hospital Pharmacy Residents based on a submitted proposal for Quality Assurance for Clinical Pharmacists, May 1979.

Reviewer, Hospital Formulary, 1980.

Recipient of the Grace P. Swinyard Scholarship Award, from the University of Utah College of Pharmacy, May 1980.

Volunteer at Camp UTADA, a camp for diabetic children, Salt Lake City, Utah, August 1980.

Coordinator, Journal Club, for Doctor of Pharmacy Candidates, Post-doctoral Fellows, and Department of Pharmacy Practice faculty, University of Utah, 1980-81.

Elected Member of Curriculum Committee, College of Pharmacy, University of Utah, 1980-81.

PROFESSIONAL ORGANIZATIONS

American Society of Hospital Pharmacists
Utah Society of Hospital Pharmacists
American Pharmaceutical Association (past)
Nebraska Pharmacists Association (past)
Nebraska Society of Hospital Pharmacists (past)