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The disposition of tetracycline (T C) in sheep

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SUMMARY

The absorption, distribution and excretion of tetracycline were studied in sheep. The drug was administered via intravenous and oral routes, blood and urine samples were collected at specific times following drug administeration. The concentrations of tetracycline in plasma and urine were determined by high performance liquid chromatographic column(HPLC).

Following intravenous administration of tetracycline, plasma concentrations of the drug exceeded 4 ug/ml for 12 hours. The fraction of the intravenous dose excreted unchanged in urine was 54.86%. No metabolites of tetracycline were detected in plasma and urine samples. About 50% of the drug eliminated in urine was excreted during the first 60 hours. The remainder of the drug remaining to be eliminated in urine was excreted during the next 252 hours. The prolonged urinary excretion of a small fraction of the intravenous dose suggested that some of the drug was sequestered in deep tissues or was involved

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in enterohepatic recycling.

Tetracycline was slowly and incompletely absorbed by sheep following oral administration. The concentrations of tetracycline in the plasma of sheep receiving the drug orally were much lower than those obtained when a tenfold smaller dose was administered intravenously. A A two-compartment model was used to describe the pharmacokinetic behavior of tetracycline in sheep.

INTRODUCTION

Subtherapeutic concentrations of antibacterial drugs have been added to animal feeds to increase rate of gain, improve feed efficiency, and control disease.Quite often, drugs consumed by animals are retained in blood and tissues for variable periods of time. If the animals are slaughtered for food before drugs are cleared from the tissues the antibiotics enter the human food chain (5). To prevent the concentration of human food with harmful concentrations of antibacterial substances the United States Food and Drug Administration(FDA) establishes dosage regimens and drug withdrawal periods which, if followed, insure the absence of antimicrobial substances in meats (1&12).

Antibiotic residues in meats may constitute a human health hazard since continuous or intermittent exposure to these drugs may produce hypersensitization.In addition, there has been growing concern that the consumption of meats containing subtherapeutic concentrations of anti-

microbial drugs may select for microbial populations consisting primarily of drug resistant mutants(5,6,7,8,10&12)

The feasibility of using the concentration of antibiotics in animal plasma to predict coexistent concentrations of the drugs in tissues have been demonstrated elsewhere (2,3&13). These findings have practical utility since the Food and Drug Administration has attempted to develop accurate and economical methods to routinely monitor the concentrations of antibiotics in animals being slaughtered for human consumption.

The purpose of this study was to collect preliminary information concerning the disposition of tetracycline in sheep following intravenous and oral administration. The information provided by this study will form the basis for a second study designed to establish the feasibility of using plasma concentrations of tetracycline to predict coexistent concentrations of the drug in the tissues of sheep.

MATERIALS AND METHODS

A.Experimental animals

Six suffolk ewes weighing 42.2-53.0 Kg were used in this study.The animals were rested for two weeks prior to the initiation of the study.Two days prior to dosing,the animals were weighed, sheared around the jugular veins, fitted with Foley[1] urinary retention catheters and assig-

1- Bardex Foley Catheter,16 French,C.R.Bard,Inc.,Murray Hill, NJ.

ned to individual slot-floored metabolism cages.The urinary catheters were connected to 4-liter polyethylene bottles. Control blood and urine samples were collected prior to drug administration.

B. Drug administration and sample collection

1. Drugs

Aqueous solutions of tetracycline hydrochloride,U.S. P.(TC)[1] containing 50 mg TC/ml or 100 mg TC/ml were prepared.

2. Intravenous drug administration

A solution containing 50 mg TC/ml was administered to each animal(11 mg TC/Kg b.w.) by rapid intravenous injection via the right jugular vein. Following drug administration, blood and urine samples were collected from the left jugular vein in heparinized syringes at 0,.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48, and each twelve hours thereafter. Blood sample collection was terminated at the 120-th post-dosing hour. Urine samples were collected for 312 hours following drug administration. The volume of urine voided during the interval between samples was recorded. Following collection, blood samples were centrifuged at 650 xg for about 7 minutes, the plasma was transferred to screw cap tubes and stored at 4^{o}C until assayed. Urine samples were stored in plastic botties at -20^{o}C.

1- American Cyanamid Co., Lot.No. 48355-597.

3. Oral study

Following the completion of the intravenous study, the six ewes were rested for two weeks prior to the initiation of the oral dosing study. Two days prior to dosing, the animals were reweighed, fitted with Foley urinary catheters, and returned to the slot-floored metabolism cages. Feed was withdrawn and control blood and urine were collected 24 hours prior to dosing.

Each animal was dosed orally with 110 mg TC/Kg body weight. The drug was administered via a stomach tube as a solution (100 mg TC/ml). Blood and urine samples were collected for 168 and 444 hours following dosing,respectively. These samples were collected, handled, and stored in the same manner as described in the intravenous study.

C.Analytical method

The concentrations of tetracycline in plasma and urine were determined by the method of internal standards utilizing the extraction method (11).Prior to extraction, 1 ml of oxytetracycline solution (4 ug/ml internal standard) was added to each glass tube containing 2 ml of plasma or urine. Phenylbutazone (20%), sodium barbital (0.8 N), calcium chloride solution (4%) and ethylacetate (0.15, 1, 1, and 8 ml, respectively)were added to the tubes containing fortified plasma or urine. The tubes were agitated for 4 minutes and then centrifuged for 10 minutes at 1000g. The ethylacetate layers (6.5 ml) were

subsequently transferred to tubes containing 0.5 ml of phosphoric acid (1 N). The tubes were agitated for 2 minutes and then centrifuged for 5 minutes at 1000g. The ethylacetate layer was discarded and the acid layers were injected (2 or 5 or 10 ul) on the octadecylsilane column of the high-performance liquid chromatograph. Each analysis was performed in duplicate. The heights of the recorded peaks corresponding to tetracycline and oxytetracycline were measured.

RESULTS AND DISCUSSION

1. Intravenous drug administration

The average concentrations of tetracycline in plasma collected at various times following the intravenous administration of the drug to sheep are presented graphically in Figure 1. An average plasma tetracycline concentration of 13.10 ug/ml was present in samples collected 0.5 hours following intravenous drug administration. No tetracycline was detected in plasma samples collected after the 96-th post-dosing hour.

The average rates of tetracycline excretion and the average cumulative amounts excreted in urine are included in Figures 1 and 2, respectively.

As shown in Figure 2, about 50% of the tetracycline injected intravenously was excreted in urine during the 60 hours following dosing and an additional 4.42% was excreted via this route during the next 252 hours.

Trace amounts of tetracycline were detected in urine

collected 312 hours following drug administration. The prolonged urinary excretion of tetracycline following an intravenous dose suggested that some of the drug was initially sequestered in a deep tissue compartment and then slowly released into body fluid.

No metabolites of tetracycline were detected in plasma or urine, but 54.86% of the intravenous dose of tetracycline was recovered in urine. Since no metabolites were found, the remainder of the intravenous dose may have been excreted in the bile. Elimination of the drug in the bile and its subsequent reabsorption from the intestinal tract into blood provided an alternate explanation as to why trace concentrations of the drug were excreted in urine for a prolonged time period.

2. Oral drug administration

The average concentrations of tetracycline in plasma of sheep at specific times following the oral administration of the drug are presented graphically in Firure 3. These data indicated that tetracycline was slowly absorbed following oral administration since the average peak plasma concentration of the drug(2.98ug/ml)was not achieved until the 24-th post-dosing hour.No drug was detected in plasma after the 120-th post-dosing hour. The peak concentrations of tetracycline in the plasma of sheep receiving the drug per os were lower than those obtained when a smaller dose(10 x)was administered intravenously.

The average rates of tetracycline excretion and the average cumulative amounts of the drug excreted in urine are presented graphically in Figures 3 and 4,respectively. An examination of tables 3 and 6 indicated that tetracycline was detected in urine for a longer time period following oral drug administration(444 hours)as compared to intravenous administration(312 hours).However,the percentage of dose of tetracycline recovered in urine following oral administration was much less(7.30%)than that obtained following intravenous drug administration (54.86%). The difference in drug recovery in urine following oral and intravenous administration was significantly different as determined by student's t test(α=.05).Significant differences(α=.05)were also noted in the areas under plasma concentration-time curves(AUC'S)of the oral and intravenous studies as determined by gravimetric procedures.

The rates of the percentage of tetracycline excreted in urine following oral and intravenous administration was 0.133 which indicated that 13.3% of the oral dose was absorbed by sheep. The reduced drug bioavailability associated with oral dosing may have been the result of dilution or degradation of the drug in the rumen.

The biphasic shape of the tetracycline plasma disappearance curve (Figure 1) suggested that a model containing two compartments would be required for a proper mathematical description of the data (4 and 9). Subsequently, the two-compartment open model presented in Figure 5 was proposed to describe the pharmacokinetic behavior

Figure 1

Average plasma concentrations and rates of urinary excretion of tetracycline following the intravenous administration of 11.0 mg of the drug/Kilogram of body weight to sheep.

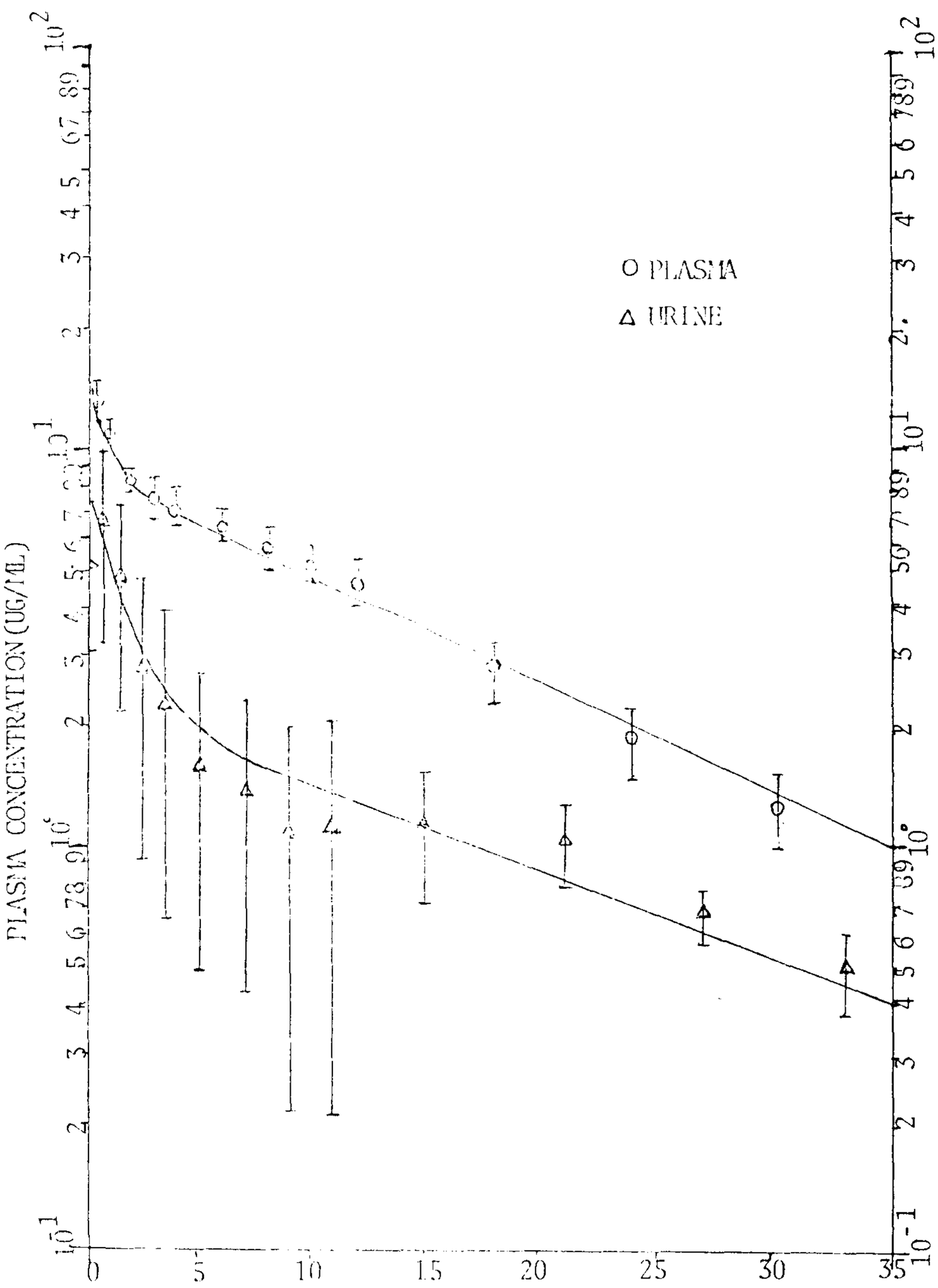


Figure 2

Average cumulative excretion of tetracycline in the urine of sheep following the intravenous administration of 11.0 mg of the drug/kilogram of body weight.

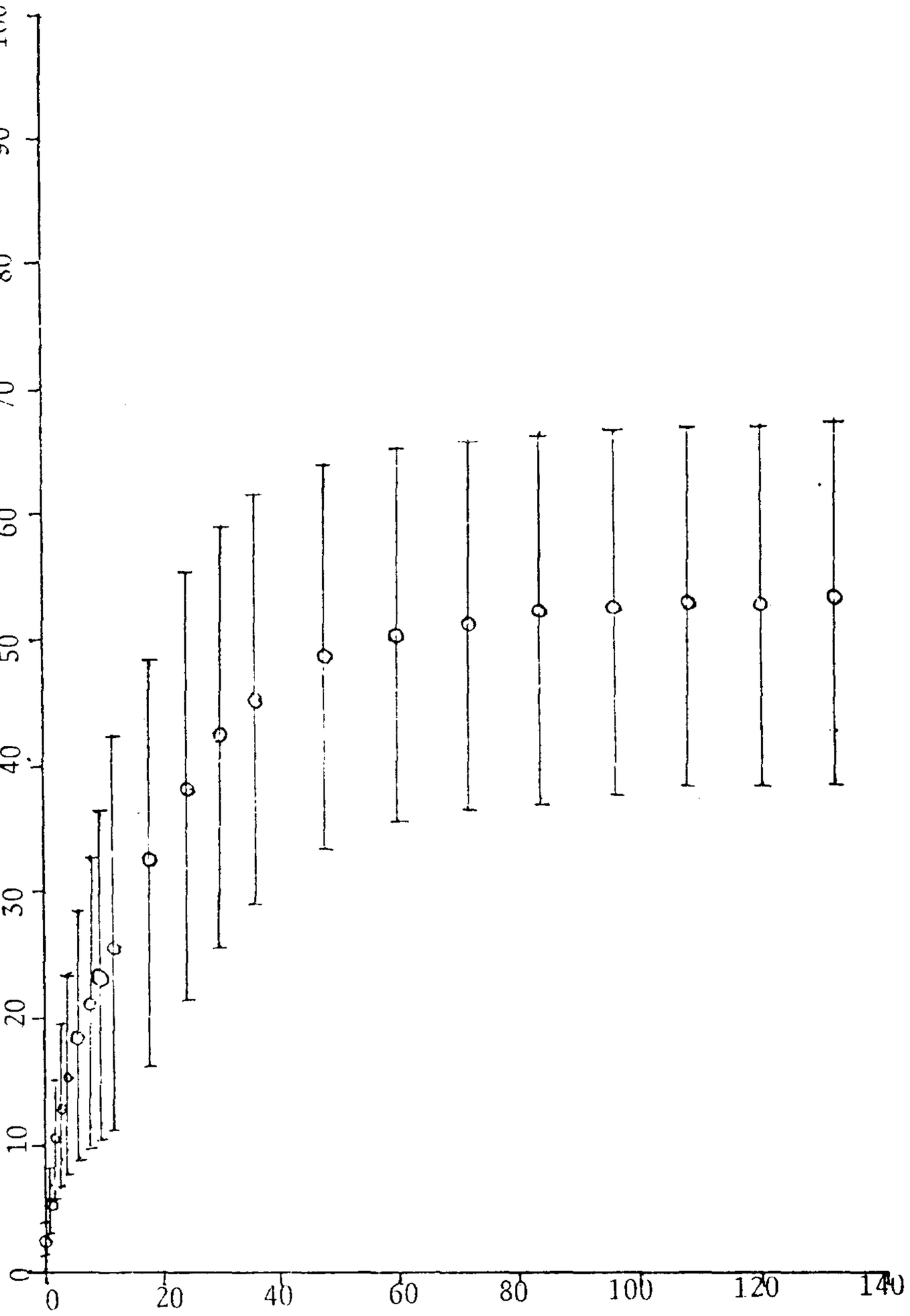


Figure 3

Average plasma concentrations and rates of urinary excretion of tetracycline following the oral administration of 110.0 mg of the drug/kilogram of body weight to sheep.

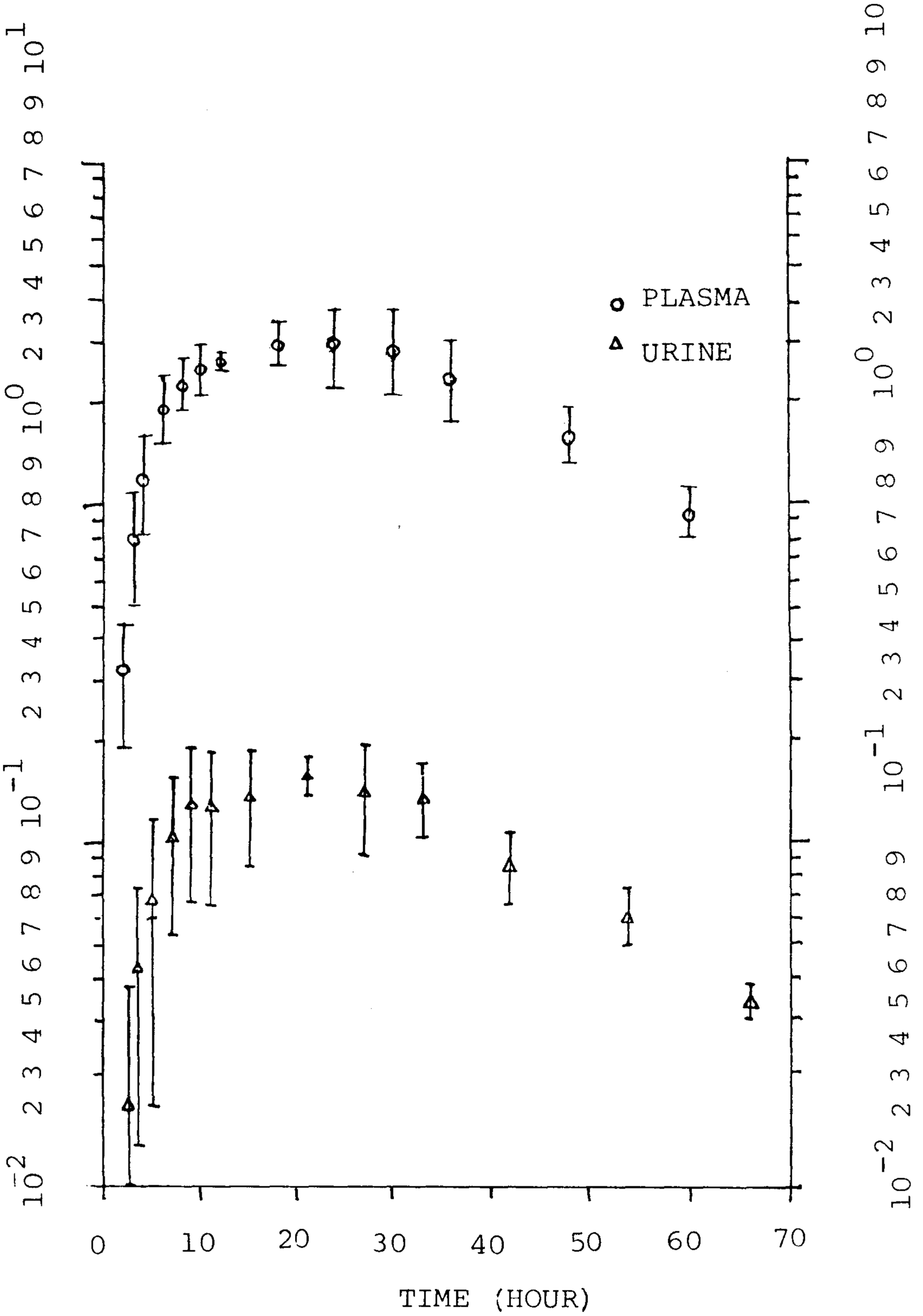
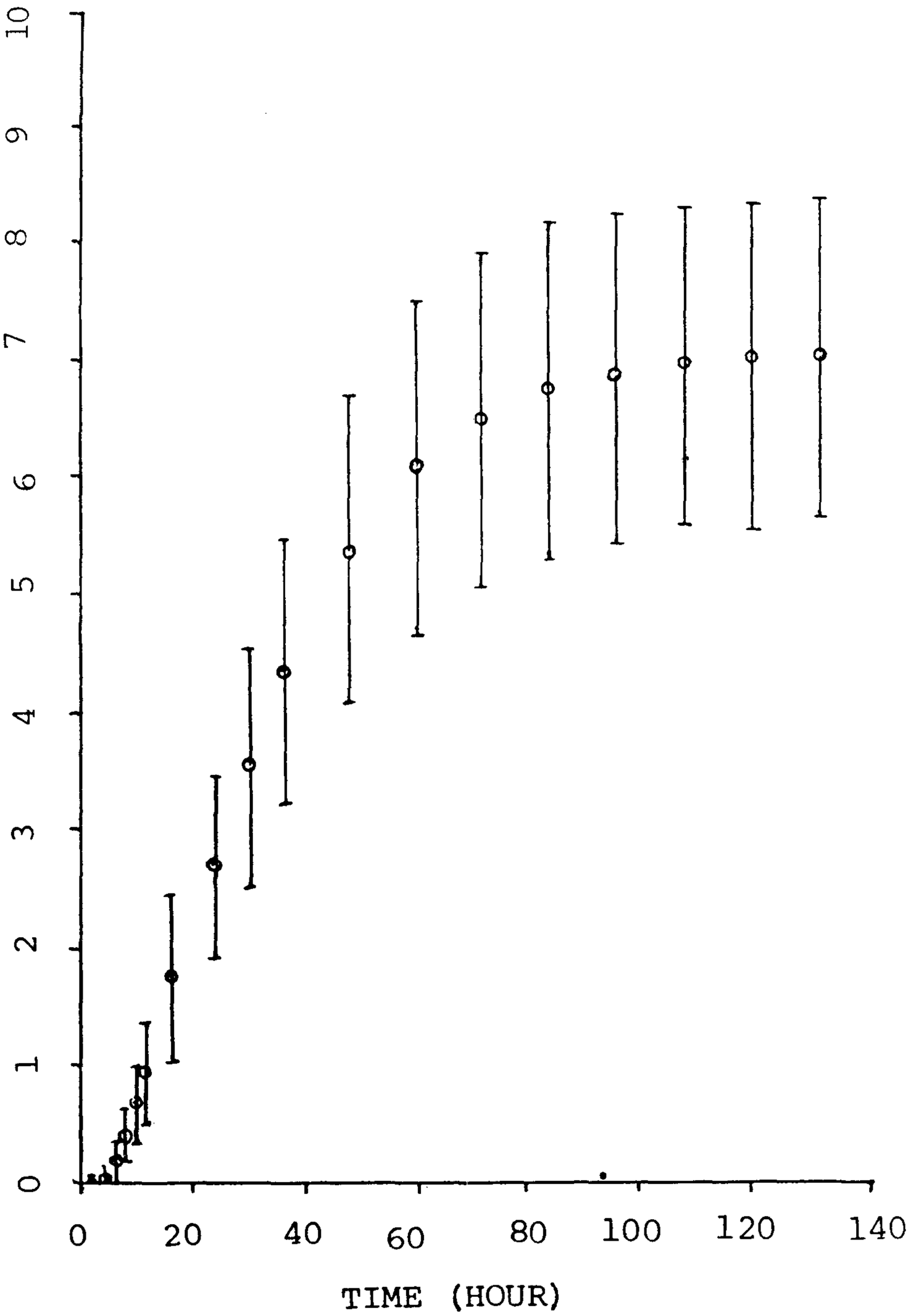


Figure 4

Average cumulative excretion of tetracycline in the urine of sheep following the oral administration of 110.0 mg of the drug/kilogram of body weight.



of tetracycline in sheep. In this model the elimination of tetracycline was assumed to be a first-order process. The biologic half-life following intravenous administration was 11.2 hours. The apparent volume of distribution of tetracycline following intravenous administration approximated 62% of the body weight of sheep.(Table 1)

On the basis of results obtained in this study,tetracycline appeared to behave as follow:upon entering the circulation, tetracycline distributed into two major compartments, a central compartment containing the plasma and rapidly perfused tissues, and a peripheral compartment of more slowly perfused tissues.Immediately following intravenous drug injection,there was a rapid initial decrease in plasma concentrations of the drug, the so-called distributive phase. The rapid decrease continued until an approximate equilibrium between the two compartments was achieved. The distributive phase lasted about 3 hours (Figure 1). Disappearance of the drug from the central compartment was the result of distribution into the less perfused peripheral compartment and excretion of tetracycline in urine.

Figure 5

The two-compartment open model describing the disposition of tetracycline (TC) in sheep.

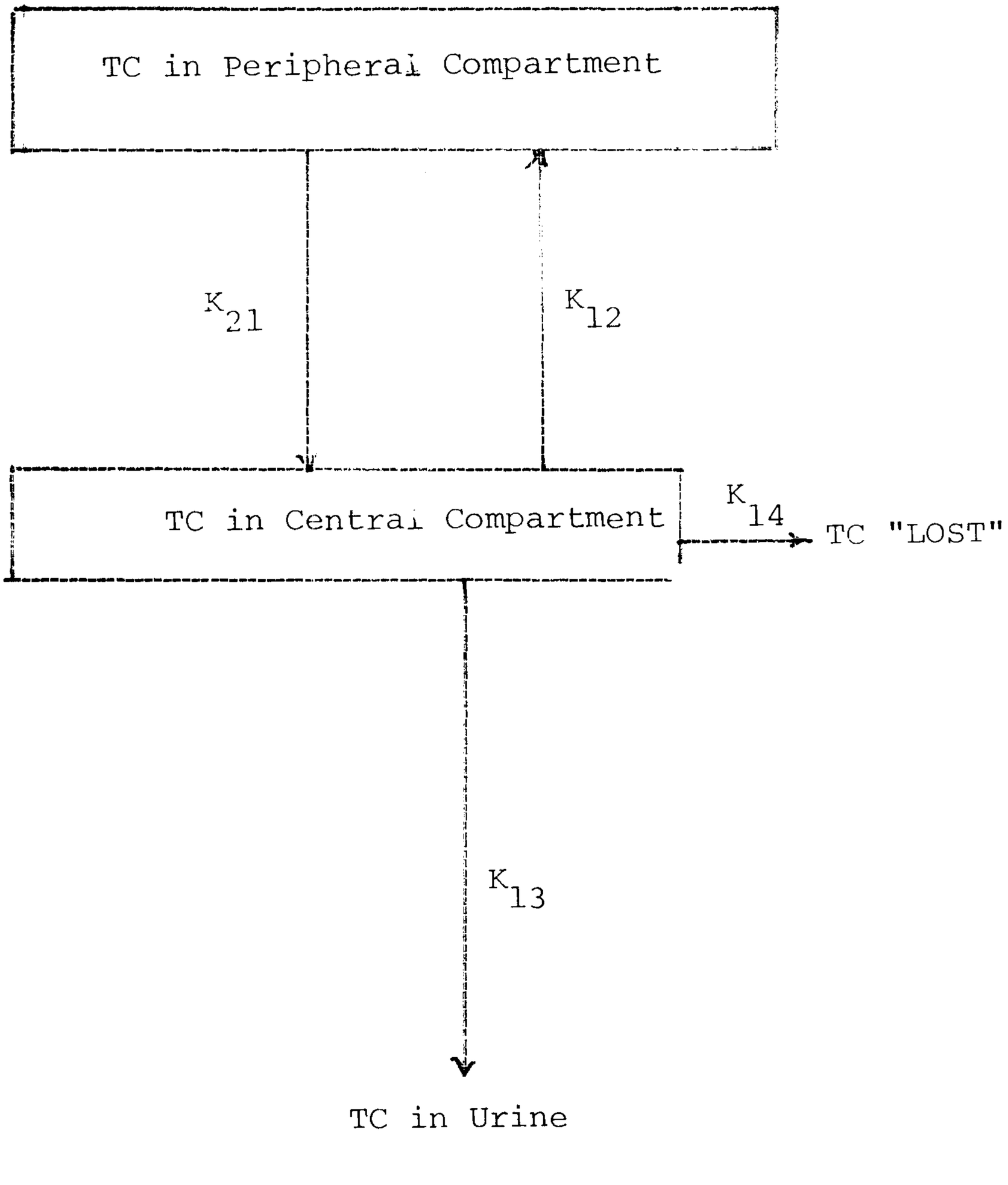


Table 1

Average Parameters of the Two-Compartment Open Model Describing the Disposition of Tetracycline in Sheep

Parameters	α*	β*	K_{12}*	K_{21}*	K_{13}*	K_{14}*	K_{el}*	K_a*	$t_{1/2}$+	V_d**
Intravenous Study	1.544	0.062	0.70	0.79	0.07	0.05	0.12		11.2	0.62
Oral Study		0.05						0.10	14.0	

*α,β and all K values are first order rate constant ($hour^{-1}$)

+half-life (hour)

**Apparent volume of distribution in liters/kg body weight

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مجلهٔ دانشکدهٔ دامپزشکی ،دانشگاه‌تهران ،دوره (۴۳)شمارهٔ (۱و۲و۳و۴)تهران (۱۳۶۷)

فارماکوکی نتیک تتراسیکلین درگوسفند

دکتر سید محمدفقیهی *

مطالعه فارماکوکی‌نتیک‌تتراسیکلین (جذب و پخش، ودفع) درگوسفند متعاقب تجویز وریدی وخوراکی‌آن صورت گرفت . بدینمنظور غلظتهای تتراسیکلین در نمونه های خون وادرار که درزمانهای معین پس از تجویز دارو از راههای وریدی وخوراکی جمع‌آوری شده بودند بوسیله دستگاه کروماتوگرافی مایع با فشار زیاد (H P L C) تعیین شدند .

دارو ازطریق تجویزوریدی ،غلظت پلاسمائی‌مناسبی برای‌مدت ۱۲ ساعت ایجاد نمود و بطور تقریب ۵۰% مقدار داروی‌تجویز شده ، در خلال ۶۰ ساعت اول ، بدون تغییر از راه ادرار دفع گردید .قسمتی از مقدار وریدی دارو برای مدت طولانی تری از راه ادرار دفع شد که احتمالا" مبین این موضوع می‌تواند باشد که این بخش از دارو در بافتهای عمقی حیوان ذخیره‌شده و بآهستگی دفع گردیده‌ویا درسیکل‌مجددرودهای ـ‌کبدی‌گرفتار بوده است .

جذب دارو پس‌ازتجویز خوراکی بمیزان کم صورت گرفته بطوریکه با وجود تجویز مقدار ۱۰ برابرمیزان وریدی آن ازاین‌راه ،غلظتهای پلاسمائی بدست آمده بمراتب‌کمتراز غلظتهای پلاسمائی وریدی آن بود .هیچگونه‌متابولیتی‌ازتتراسیکلین در نمونه های‌پلاسما وادرارازهیچیک از راههای‌تجویز شده‌بدست‌نیامد .فراهم‌زیستی(Bioavailability) دارو متعاقب تجویز خوراکی آن ۱۳/۳% بود که‌این‌کاهش، احتمال دارد مربوط به رقیق‌یا تجزیه شدن‌دارو در مایعات شکمبه حیوان باشد . برای تفسیر فارماکوکی نتیک تتراسیکلین درگوسفندازمدل بازدوقسمتی (Two- Compartment Open Model) استفاده گردید .

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