PERSISTENCE OF ANTIBIOTICS IN BLOOD OF PATIENTS WITH ACUTE RENAL FAILURE. I. TETRACYCLINE AND CHLORTETRACYCLINE * †

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The management of patients with severe renal disease is frequently complicated by infections; these commonly involve the urinary tract, but infections elsewhere are not unusual. Overwhelming infection, particularly with gram-negative bacteria, is often associated with shock and anuria (2) and antibiotic therapy is an integral part of the management in such cases. The persistence of a drug in the blood, once it is absorbed or after it is given systemically, depends on many factors which include: removal by the kidneys, binding to plasma proteins, sequestration in various organs and body compartments, excretion into the bile and feces, detoxification and degradation mechanisms and the inherent stability of the substance; most important for nearly all antibiotics, however, is their removal by the kidneys. Knowledge concerning the fate of antibiotics in patients with impaired renal function is, therefore, necessary for planning therapy so that it will insure adequate blood and tissue levels without undue retention that may be harmful.

A series of studies was, therefore, undertaken in patients with anuria or impaired renal function from various causes, who either were receiving antibiotics as part of their therapy, or were given test doses of some of the commonly used antibiotics. The half-life of the antibiotics in the blood of such patients was determined and correlated with the renal functional status. In addition, since hemodialysis by the artificial kidney may be employed in some patients with anuria who retain toxic drugs or excretory products, the effectiveness of this procedure in extracting antibiotics from the blood of suitable patients was included as part of these studies. Observations on chloramphenicol (3) and certain other antibiotics (4) (penicillin, streptomycin, erythromycin and kanamycin) are reported elsewhere.

The present paper deals with tetracycline and chlortetracycline. Antibiotics of the tetracycline group have shown very little direct toxicity when given in the usual therapeutic doses. However, under certain circumstances they may produce a negative nitrogen balance and increased riboflavin excretion in the urine (5–8) and prolonged therapy with large doses, particularly if administered intravenously, has given rise to changes in morphology and function of the liver (6–11). Impairment of renal function during prolonged, high-dosage therapy with oxytetracycline has also been reported (12). The results to be presented here should prove useful as a basis for selecting a dosage schedule of these antibiotics which would achieve adequate levels of the active drugs in uremic patients similar to those attained with the usual therapeutic doses in patients with normal renal excretory function and thus reduce the hazard of additional toxic effects from these drugs.

MATERIAL AND METHODS

Patients. Thirty-five patients whose renal functional status ranged from normal to protracted anuria due to various causes were studied on the wards of the Boston City and Peter Bent Brigham Hospitals. Anuria is arbitrarily defined, in this study, as the condition in which the patient excreted less than 400 ml. of urine per day

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TABLE I

Half-life of tetracycline in serum of five patients with acute renal failure

Patient	Age	Sex	Precipitating factor	Urine output	Tetracycline received*		Period of study†	Rate of decay of tetracycline in serum	Half-life of tetracycline in serum
	yrs.			*ml./day*	*Gm.*	*route*	*days*	%/hr.‡	
H	54	M	Hypotension following resection of aortic aneurysm	200–300	4.3	IV	3(*a*) 5(*b*)	0.64 ± 0.25	>3 da. 108 hrs.
C	49	F	Right nephrectomy, pyelonephritis	< 100	1.2	IM	2½		>2½ da.
S	43	F	Mismatched transfusion	100–300	2.0	IV	5	1.22 ± 0.29	57 hrs.
I	58	M	Postoperative hypotension	100–200	1.0	IV	5	0.69 ± 0.15	101 hrs.
A	72	M	Hepatic abscess and shock	< 100	2.0	IV	3	0.64 ± 0.06	108 hrs.

* Total amount given to patient before start of observations; IV = intravenous; IM = intramuscular.
† Two periods in patient H; (a) before dialysis; (b) after dialysis.
‡ Mean ± 1 standard error.

for three or more days; the eight anuric patients in this study excreted considerably less than this amount. The nonanuric patients had chronic glomerulonephritis, pyelonephritis or arteriolar nephrosclerosis. Two of the patients were twins, one of whom developed uremia from chronic glomerulonephritis, and was the recipient of a healthy kidney from the other, the donor, who was studied following removal of one of his kidneys. Among the control patients were a few otherwise normal individuals who had diminished creatinine clearance of undetermined etiology; some of them were elderly patients.

The severity of renal impairment in each subject was determined by the 24 hour endogenous creatinine clearance test. A modification of the method of Bonsnes and Taussky (13) was used for determining creatinine in blood and urine. The anuric patients were arbitrarily assigned a creatinine clearance value of less than 1 ml. per minute.

Hemodialysis. The blood of six subjects was subjected to dialysis through the artificial kidney during the course of this study; a rotating drum apparatus (Kolff-Brigham type (14) was used in two patients and a Kolff-coil type (15) was used in the others. Determinations of tetracycline, chlortetracycline and creatinine were carried out on arterial and venous samples entering and leaving the artificial kidney, respectively. Levels of tetracycline in the venous blood of the patients prior to and on completion of dialysis were also determined. The extraction ratio (ER) of the substances was obtained by the formula:

$$ER = \frac{A - V}{A} \times 100,$$

where A and V represent the concentrations of the substance entering and leaving the device, respectively.

Serum levels and half-life of tetracyclines. A dose of 500 mg. of tetracycline hydrochloride [1] or chlortetracycline hydrochloride [1] in 150 ml. of 5 per cent dextrose in water was administered intravenously over a period of 15 to 30 minutes to most of the subjects. Five subjects received a similar dose orally and are considered separately since continued absorption could not be excluded. A few of the patients who were anuric or severely uremic were given tetracycline in larger doses by the intravenous route for therapeutic purposes. Blood was obtained two hours after the intravenous dose or six hours after the oral dose and then at intervals of two to 24 hours depending on the severity of renal impairment; a minimum of four specimens was obtained in each subject, and six to eight specimens were procured in most of them. The sera were separated as soon as possible and stored at − 20° C. Concentrations of tetracycline and chlortetracycline were determined by the serial twofold dilution method in brain heart infusion broth (Difco pH 7.4 per cent) using *B. cereus* No. 5 as the test organism, 0.5 ml. of a 10^4 dilution of the fully grown culture being added to an equal volume of the serum dilutions. In a few instances, the cup-plate assay method was also employed; [2] all serum levels in the hemodialysis experiments were determined by this method.

The method of least squares was used to calculate the slope of the tetracycline decay curve from which the half-life was determined (16). The standard error of each slope was also calculated. Care was taken, when feasible, to obtain sera at intervals greater than the estimated half-life of the antibiotic in order to minimize the error of the assay method. In a previous study (16) it was shown that although the results of the twofold dilution method had a greater standard deviation and were generally lower than those of the cup-plate method, the serum half-lives determined by either method were in close agreement.

RESULTS

Tetracycline

The half-life of tetracycline in four individuals with normal creatinine clearances given 0.5 Gm. intravenously ranged five to seven and six-tenths and averaged five and eight-tenths hours. The

[1] Supplied as Achromycin® and Aureomycin® by the Lederle Laboratories.

[2] We are indebted to A. C. Dornbush of Lederle Laboratories for the cup-plate assays of the tetracycline antibiotics.

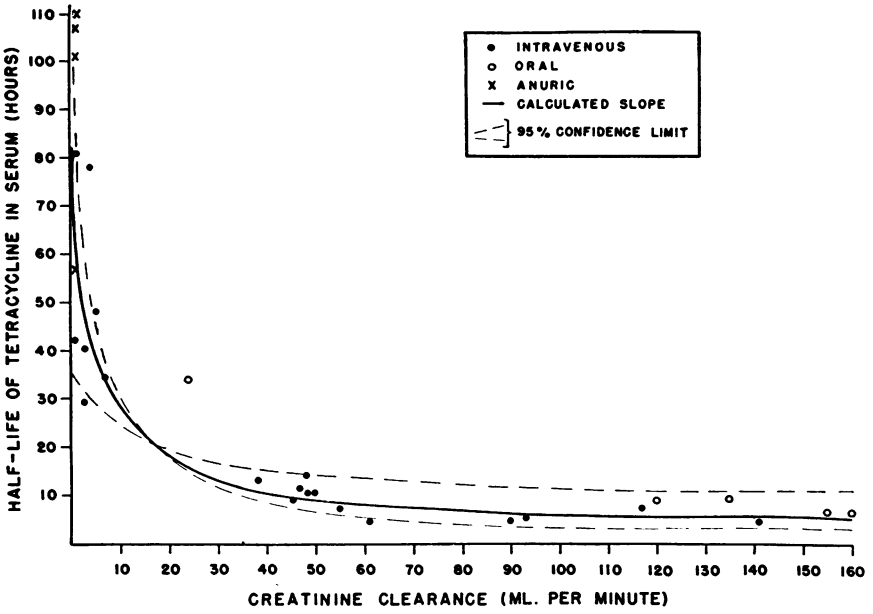

FIG. 1. RELATION OF HALF-LIFE OF TETRACYCLINE IN SERUM FOLLOWING AN INTRAVENOUS DOSE TO THE RENAL FUNCTION AS REFLECTED IN THE CREATININE CLEARANCE

mean half-life of tetracycline in four normal subjects given the same dose orally was seven and two-tenths hours. Table I presents pertinent data in five anuric patients, three of whom subsequently died of their underlying illness. The serum levels of tetracycline in these patients declined slowly. In Patients H and C no decline was detectable during two and one-half and three days of observation, respectively. During longer observation periods in Patient H and also in Patients I

TABLE II

Half-life of tetracycline in serum after an intravenous dose of 500 mg. in nonanuric patients with different clearances of endogenous creatinine

Patient	Age	Sex	Etiology of renal disease	Creatinine clearance	Rate of decay of tetracycline in serum	Half-life of tetracycline in serum
	yrs.			*ml./min.*	*%/hr.**	*hrs.*
Mi	36	M	None	140.8	14.5 ± 1.7	4.8
Kn	39	M	None	117.4	9.1 ± 1.7	7.6
Gl	47	M	None	92.5	10.8 ± 2.0	6.4
Jo	34	M	None	89.8	13.9 ± 0.6	5.0
Tu	16	F	?	60.7	12.2 ± 0.7	5.7
McD	26	M	Unilateral nephrectomy	55.0	8.9 ± 0.4	7.8
Pe	66	M	? Arteriolar nephrosclerosis	49.6	6.5 ± 1.6	10.7
Yo	58	M	?	48.0	6.5 ± 0.8	10.7
Ka	75	M	? Arteriolar nephrosclerosis	47.8	4.8 ± 0.3	14.6
McD	26	M	Recipient kidney transplant	44.8	7.2 ± 0.4	9.6
Do	79	M	?	46.6	5.9 ± 0.7	11.8
Yu	67	M	?	37.8	5.1 ± 0.8	13.6
Li	56	F	?	7.0	2.1 ± 0.5	32.6
Wa	50	M	Polycystic kidneys	5.0	1.5 ± 1.3	47.9
Bu	50	F	Recovery phase, acute renal failure	4.0	0.9 ± 0.5	78.7
Mi	38	M	Polycystic kidneys	3.1	1.7 ± 0.4	41.2
Ne	50	M	Chronic pyelonephritis	2.3	2.4 ± 0.3	29.5
Me	44	F	Chronic pyelo- or glomerulonephritis	1.0	1.7 ± 0.3	42.4

* Mean ± 1 standard error.

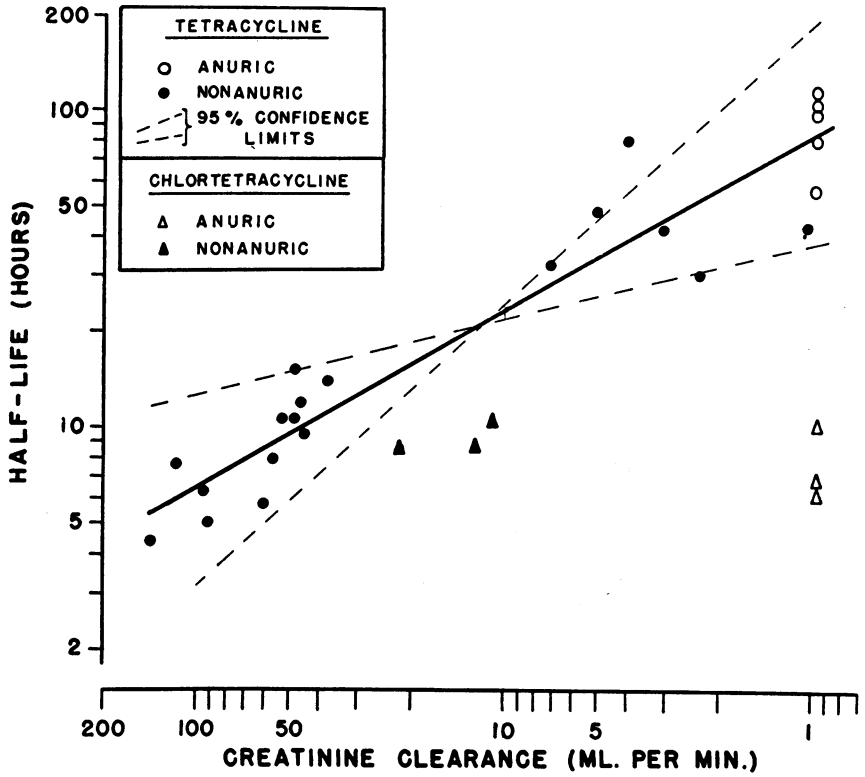

FIG. 2. DATA IN FIGURE 1 PRESENTED ON LOGARITHMIC SCALE
Some observations on half-life of chlortetracycline in serum of three anuric patients and three patients with normal renal function are also included.

and A, the mean half-life was found to be about four to five days. The relatively low value of 57 hours in Subject S will be discussed below.

Figure 1 presents the data for 28 patients in whom simultaneous measurement was made of creatinine clearance and tetracycline half-life. The five anuric patients were arbitrarily assigned a creatinine clearance value of 1 ml. per minute. The serum half-life was similar in all subjects whose creatinine clearance exceeded 60 ml. per minute. As the creatinine clearance fell below this value, the serum half-life of tetracycline rose steeply. The maximum value observed in an anuric patient was 110 hours.

Table II presents data in 17 of the patients depicted in Figure 1. All of them received tetracycline intravenosuly and the half-life of the antibiotic in the serum is shown together with the decay rate of the drug in the serum expressed as per cent fall per hour.

The data in Figure 1 and in Tables I and II may be used to formulate an equation which best expresses the relationship between the two variables, tetracycline half-life and creatinine clearance. The serum half-life may be considered as a geometric function and creatinine clearance as a linear function. A straight line relationship will then be expressed thus: $\log y = mx + b$, where y = tetracycline serum half-life, m = the slope, x = the creatinine clearance and b = the y intercept. When the slope of this line is calculated by the method of least squares, and a correlation coefficient between the two variables is determined, the latter is found to be 0.86. A better fit to the experimental data, however, is provided by the same formula with the creatinine clearance (x) also treated logarithmically; the correlation coefficient then becomes 0.95 and the relationship becomes more linear as shown in Figure 2. The slope of this relationship is 0.55 ± 0.16 and the y intercept is 82 hours. Athough creatinine clearance cannot be considered to be a logarithmic function, neither can it be considered purely linear when used to ascertain glomerular filtration in

uremic subjects. It has been pointed out that the creatinine clearance is less well correlated with the inulin clearance in patients with renal disease than in normal subjects (17), the former usually being somewhat higher (18, 19). It is recognized therefore that a log-log treatment of the data is somewhat arbitrary, but may be justified for purposes of prediction.

The solid line in Figure 1 is a theoretical slope determined by the formula $\log y = \log x + \log 82$ hours. The area enclosed by the broken lines encompasses two standard errors of this slope. The greatest variability is noted at very high and very low levels of creatinine clearance. This in part may explain the relatively short half-life of 57 hours obtained in Subject S. In calculating maintenance therapy, allowance must be made for this variability.

Figure 3 depicts data in a case that illustrates the dynamic relationship between the status of renal function and the tetracycline serum decay curve. The patient was a 23 year old woman who developed severe hypotension following a brisk hemorrhage from a placenta previa. She had been anuric before she received her first intravenous dose of tetracycline. At this time, she began to excrete slightly more than 500 ml. of urine per day and was considered to be in the early diuretic phase of acute tubular necrosis. The levels of tetracycline in the serum fell quite slowly following an intravenous dose of 1 Gm. and tetracycline was still detectable in her serum 10 days

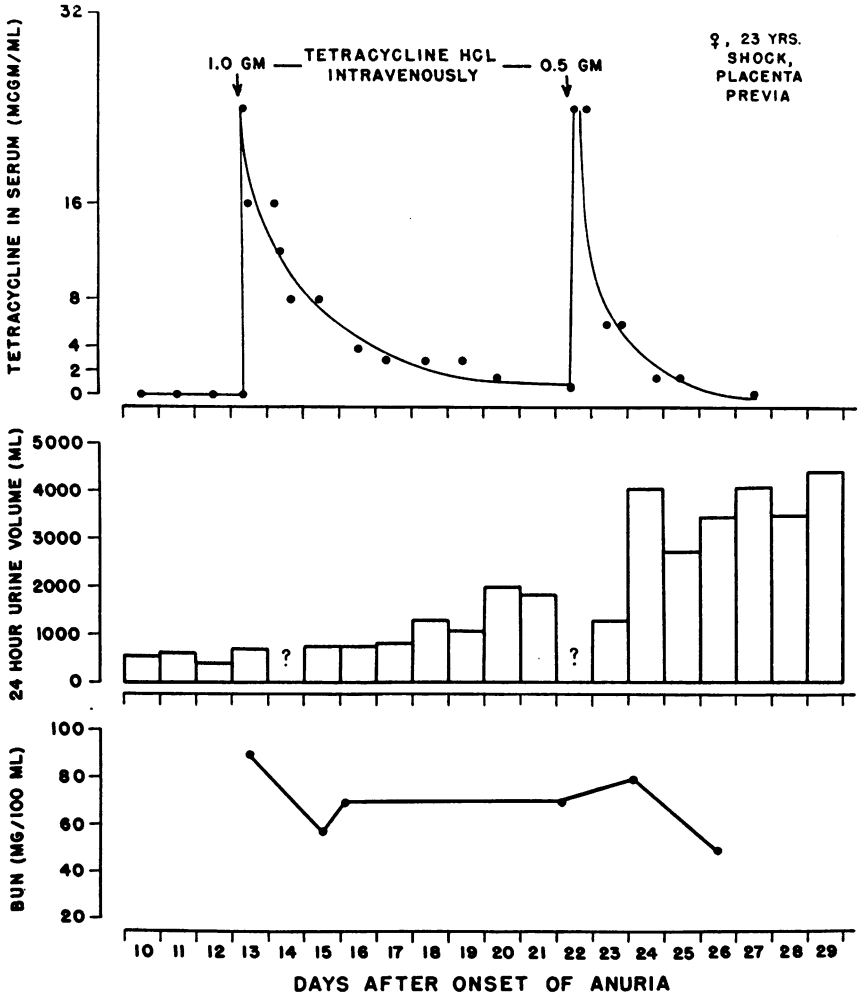

FIG. 3. LEVELS OF TETRACYCLINE IN SERUM FOLLOWING INTRAVENOUS DOSES GIVEN TO A PATIENT DURING THE EARLY DIURETIC AND THE DIURETIC PHASES OF RECOVERY FROM ACUTE RENAL INSUFFICIENCY

TABLE III

Reduction in concentration of tetracycline in blood following dialysis in the artificial kidney

Patient	Type of artificial kidney	Duration of dialysis	Tetracycline in serum		Tetracycline extracted*
			Before dialysis	After dialysis	
		hrs.	*μg./ml.*	*μg./ml.*	%
H†	Drum	4	31.0	22.5	27
C	Coil	3½	6.3	5.4	14
S	Coil	4	14.5	12.0	17

* Expressed as per cent of predialysis level.
† In this patient the blood urea nitrogen concentration dropped from 271 to 189 mg. per 100 ml. (30 per cent) during the same period.

later. During the full diuretic phase of her disease, she was given 0.5 Gm. of tetracycline intravenously; after this dose the levels of drug in the serum fell more rapidly, but tetracycline was still detectable at the end of four days, which is still abnormally prolonged. Thus, as her renal status slowly improved, so did her ability to clear tetracycline from her serum.

Effect of hemodialysis by the artificial kidney on tetracycline serum levels

Table III presents data on three patients subjected to hemodialysis by the artificial kidney because of severe renal disease. Each of these dialyses was accompanied by a fall in tetracycline levels ranging from 14 to 27 per cent of the predialysis level. This fall was much greater than would be expected to occur spontaneously, but was not as great as that usually observed for readily dialyzable substances such as urea or creatinine; however, in Patient H, the tetracycline level fell 27 per cent while the blood urea nitrogen fell 30 per cent. Creatinine and blood urea nitrogen values were not obtained immediately prior to and on completion of dialysis on the other two subjects.

Table IV presents data on the extraction ratios observed during six runs performed on three subjects. The extraction ratio of the antibiotic was quite variable, ranging from 5.3 to 24.5 per cent with a mean value of 14.3 per cent; it also varied during different runs in the same patient. The extraction ratio of tetracycline in Patient A also varied with each run and was 21 to 38 per cent of that of creatinine.

Chlortetracycline

Observations on the serum half-life of chlortetracycline in six patients with severe renal disease, three of whom were anuric, are presented in Table V. The mean values of the half-life in each patient ranged from six and eight-tenths to 11.0 hours, but are not significantly different in the anuric patients from those in patients with chronic renal diseases who had better filtration capacity. Also, the chlortetracycline serum half-life in these severely uremic patients was not very much longer than the corresponding values obtained in patients with normal renal function following a similar dose of tetracycline. This is presented graphically in Figure 2. Whereas there is a progressive prolongation in serum half-life of tetracycline as the creatinine clearance falls, such a relationship is not evident for chlortetracycline.

One of the anuric patients (Ken) who received chlortetracycline was subjected to hemodialysis by the artificial kidney (Table VI). Although there was good extraction of creatinine

TABLE IV

Extraction of tetracycline and creatinine by the artificial kidney

Patient*	Sampling period	Tetracycline			Creatinine			$\frac{A}{B}$
		Arterial†	Venous†	ER (A)	Arterial†	Venous†	ER (B)	
		μg./ml.	*μg./ml.*	%	*mg. %*	*mg. %*	%	%
A	I	13.4	12.0	10.4	18.3	9.8	46.5	22.3
	II	12.7	10.7	15.7	13.9	8.2	41.1	38.1
	III	11.2	10.6	5.3	10.9	8.1	25.1	21.1
W	I	6.0	5.2	13.4				
C	I	11.2	8.5	24.5				
	II	10.0	8.4	16.5				

* Subjects A and W were dialyzed on a coil type kidney; Subject C was dialyzed on a rotating drum type apparatus.
† "Arterial" blood represen ts blood entering the artificial kidney and "venous" blood represents the effluent return.

TABLE V

Half-life of chlortetracycline (CTC) in serum of patients with severe renal disease after an intravenous dose of 500 mg.

Patient	Age	Sex	Type of renal disease*	Precipitating factor for anuria	Urine output	Creatinine clearance	BUN	Decay of CTC in serum	Half-life of CTC in serum
					ml./da.	*ml./min.*	*mg. %*	*%/hr.†*	*hrs.*
Kel	17	M	Anuria	Ethylene glycol intoxication	50–100		67	10.0 ± 0.8	6.9
Ken	35	F	Anuria	Posteclampsia	100–200		117	6.3 ± 0.4	11.0
Wr	21	M	Anuria	Chronic glomerulonephritis	50–100		NPN‡ 146	10.2 ± 0.5	6.8
Ta	70	M	Chronic			22.7	NPN 166	8.3 ± 0.5	8.4
Hu	55	F	Chronic			11.6	NPN 136	6.9 ± 0.3	10.1
Mi	64	M	Chronic			18.2	NPN 70	7.8 ± 0.6	8.9

* The etiology of the renal disease in the nonanuric patients was not known.
† Mean = 1 standard error.
‡ Nonprotein nitrogen.

during the two sampling periods, no detectable decrease in chlortetracycline serum levels was noted. This is in contrast to the findings with tetracycline and suggests that chlortetracycline may be more tightly bound to serum proteins; however, the levels of chlortetracycline in the serum were also much lower when the dialysis was begun in this patient.

DISCUSSION

Although tetracycline and chlortetracycline differ in their structure by only a single chlorine atom and they have very similar therapeutic activity, the data presented in the present report indicates that there is a marked difference in the persistence of these drugs in the serum of patients with renal failure. On the one hand, the serum half-life of active chlortetracycline is very little affected by the presence of uremia, whereas that of tetracycline may increase from six to eight hours, as observed in patients without renal disease, to up to 110 hours in anuric patients. This is not entirely surprising in view of the instability of chlortetracycline in serum or in alkaline aqueous solutions which interfere with certain biologic assays (20, 21). However, when the broth dilution method is employed, as in the present study, and the specimens are assayed together with a suitable standard preparation, the serum decay curve is probably valid.

There is some evidence that chloretetracycline may be more stable *in vivo* than *in vitro*. The studies of Womack and co-workers (22, 23) demonstrated that a fraction of chicken egg yolk exerted a protective effect on chlortetracycline *in ovo* and *in vitro* and studies on the urinary excretion of the drug in man indicated that small amounts of the drug could be recovered in the urine as late as 48 to 72 hours after administration (24–26). The data presented in the present report suggest that there is no great protective effect on chlortetracycline in the uremic patients *in vivo*. The delayed excretion of the drug, noted in other reports, may be explained on the basis of the slow renal clearance and its sequestration and release from certain organs, primarily the liver. This sequestration by the liver has been recently found with oxytetracycline by Leevy, Zinke and Chey (27) and has been observed by Böttiger (28) in mice given chlortetracycline.

TABLE VI

*Extraction of chlortetracycline and creatinine by the artificial kidney * in patient Ken*

Sampling period	Chlortetracycline			Creatinine		
	Arterial†	Venous†	ER	Arterial	Venous	ER
	μg./ml.	*μg./ml.*	*%*	*mg. %*	*mg. %*	*%*
I	3.6	3.6	0	20.8	10.8	48.1
II	2.4	2.4	0	13.7	9.4	31.4

* A coil type apparatus was used for this dialysis.
† "Arterial" and "venous" indicate blood entering and leaving the device, respectively.

Sirota and Saltzman (29) using the fluorometric assay method, observed that intravenously injected chlortetracycline was cleared by the kidney at about 37 per cent the rate of a simultaneously performed creatinine clearance. These authors concluded from this and from studies of the binding of chlortetracycline by human albumin that the renal clearance of the antibiotic could be explained on the basis of glomerular filtration alone. In a study on the total body and renal clearance of four tetracycline analogues in normal subjects using the cup-plate microbiological assay method, Kunin, Dornbush and Finland (26) found that chlortetracycline was cleared by the kidneys at a rate equivalent to about 30 per cent of a simultaneous creatinine clearance, whereas tetracycline was cleared twice as rapidly, at 62 per cent of the creatinine clearance. The somewhat slower clearance of chlortetracycline noted in the latter study may have been, in part, due to the degradation of the drug during the collection and preservation of the urine (30).

Thus, chlortetracycline appears to be cleared by the kidneys more slowly than tetracycline. That this was not due to retention of active drug in the body is evidenced from the fact that recovery of the former drug in the urine over a period of four days was found to be only about 25 per cent of the amount injected, whereas about 70 per cent of the tetracycline could be recovered in the urine during a similar period (26); much of the difference is probably ascribable to deterioration of the drug *in vivo* (30).

It has been reported that chlortetracycline given by the intravenous route may be recovered from various parts of the intestinal tract(31) and may be found in the bile at levels eight to 16 times that of the serum concentration (32, 33). This, however, will not adequately explain the discrepancy between the half-lives of the two tetracycline analogues in the uremic patients since tetracycline may also be recovered from the bile in appreciable quantities (34, 35). It can therefore be concluded that chlortetracycline is inactivated much more rapidly than tetracycline *in vivo* as well as *in vitro*.

The data presented in the current study were obtained by the twofold dilution method and were thus hampered by the greater inherent error of this method when compared with that of the cup-plate method (16). Thus, the normal values of six to seven hours for the half-life of tetracycline in serum as reported here is somewhat less than the mean of eight and one-half hours observed in another study in which the cup-plate method was used (26). In the latter, the serum half-life of intravenously administered chlortetracycline was five and six-tenths hours although its renal clearance was slower than that of tetracycline. This further supports the inference that chlortetracycline is fairly rapidly inactivated *in vivo*.

The extraction ratios of the two antibiotics across the artificial kidney indicate that both diffuse much more slowly than creatinine, presumably due to their binding to plasma protein. Chlortetracycline, which was not perceptibly altered in the serum by hemodialysis in the one patient studied, presumably is more tightly bound than tetracycline. This was also found in *in vitro* dialysis experiments (26). Thus, the use of hemodialysis in attempts to lower the serum levels of either drug, but particularly chlortetracycline, in patients who are presumed to have inordinately high and possibly toxic levels could not be expected to prove very effective.

On the basis of the observations presented here, the following empirical approach to dosage of tetracycline would appear to be reasonable. Following the administration of a loading dose of 0.5 to 1.0 Gm. orally or intravenously, 0.5 Gm. should be given every six or eight hours for subjects having a normal serum creatinine, urea nitrogen or nonprotein nitrogen level. Individuals with renal function ranging from normal to a 75 per cent reduction shoud be treated in the same manner. For patients in frank uremia, but with glomerular filtration rates estimated to be between 10 to 30 ml. per minute as determined by creatinine clearance, a maintenance dose given once every one or two days should suffice. For the very severely uremic patient who is anuric or has a creatinine clearance of less than 10 ml. per minute, a maintenance dose every two to four days would seem reasonable.[3] A periodic check on the serum

[3] A more precise basis for the dosage schedule in patients with different degrees of renal functional impairment can be obtained from the data presented in Figure 1 and in the following formula: Log half-life tetracycline = 0.55 ± 0.16 (log Ccr) + log 82 hrs.

level would still be advisable. For the patient with acute tubular necrosis undergoing recovery, a sequence of improving degrees of renal function must be anticipated and dosage schedules changed accordingly. The limited observations with chlortetracycline suggest that similar dosage regimens would be required to sustain levels of this drug in patients with either normal or impaired renal function.

Although the therapeutic index of the tetracyclines during ordinary dosage schedules may be considered rather high, evidence has slowly accumulated that large quantities of the tetracycline drugs in the body are undesirable. Gabuzda and co-workers (5) studied the effect of chlortetracycline at a dose of 3 Gm. per day in seven undernourished subjects and observed the development of a negative nitrogen balance, a presumably related rise in blood nonprotein nitrogen, increased urinary excretion of riboflavin in all subjects and of tryptophan, histidine and threonine in some of them. These changes could not be corrected by the administration of riboflavin and were not observed with oral administration of bacitracin or polymyxin B. Similar observations were made with oxytetracycline by the same authors and with tetracycline by Faloon, Noll and Prior (6). Womack and co-workers (36) noted an elevation in the blood urea nitrogen in patients during oxytetracycline therapy, and Bateman and associates, (12) using oxytetracycline in patients in the terminal stages of carcinoma who already had elevated blood urea nitrogen values, observed a further marked rise during treatment and this was associated with severe nausea and vomiting. It is difficult, however, to dissociate the effect of drug from the complications of the underlying disease in these cases.

Farhat, Schelhart and Musselman (37) gave rabbits large doses of tetracycline and observed rising nonprotein nitrogen levels, anorexia, weight loss, lethargy, convulsions and respiratory failure starting at serum levels of 20 μg. per ml.; oxytetracycline concentrations of 80 to 320 μg. per ml. of serum were found to be lethal. We have observed serum levels up to 32 μg. per ml. in uremic patients after relatively short courses of tetracycline, and Wood and co-workers (38) reported a serum concentration of 80 μg. per ml. in an oliguric patient on the fourth day of therapy. Since in the rabbit experiments referred to above (37), the signs of presumed drug toxicity and uremia were very similar, the potential toxic effect of the drug could easily be overlooked in the patient who is already severely ill. For this reason, it would seem wise to attempt to achieve and maintain in these patients serum levels that are not much in excess of those which are therapeutically effective. Since the metabolic effect of *in vivo* inactivated chlortetracycline is unknown, it cannot be assumed that this drug would be less toxic than tetracycline in uremic patients.

SUMMARY

The persistence of tetracycline and chlortetracycline in serum has been studied in patients with varying degrees of renal impairment up to almost total anuria. The half-life of intravenously administered tetracycline in individuals with normal renal function was about six to seven hours when measured by the twofold dilution method. With decreasing renal functional capacity as measured by the endogenous creatinine clearance, the half-life was prolonged and markedly so when the creatinine clearance fell below 30 ml. per minute; in the anuric patients it was as long as four to five days.

Tetracycline is cleared to a lesser extent than is creatinine or urea by hemodialysis across the artificial kidney; this is presumed to be due to the binding of the antibiotic to the plasma proteins.

In contrast to the findings with tetracycline, the half-life of chlortetracycline in serum in patients with severe renal disease is only slightly elevated over normal values, and hemodialysis by the artificial kidney did not result in lowering of the serum levels of this drug. The reasons for concluding that this difference is due to the rapid *in vivo* inactivation of this antibiotic are discussed. The poor extraction of tetracycline and particularly of chlortetracycline, by the artificial kidney is interpreted as being the result of binding of these drugs to serum protein.

The implications of these data for the potential toxicity of these drugs in uremic patients are discussed and an empiric dosage schedule is offered for use in such patients.

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