

Doxycycline pharmacokinetics in the absence of renal function

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Doxycycline pharmacokinetics in the absence of renal function. Doxycycline is a new tetracycline that is now in widespread clinical use. It differs from the other tetracycline drugs in many important respects including small daily dosage schedules, essentially complete upper gastrointestinal absorption and excretory characteristics that are independent of renal function. Our studies demonstrate that in anephric patients and patients with varying degrees of renal function the plasma $t_{1/2}$ of biologically active doxycycline is not significantly extended and that in such a clinical situation the usual therapeutic regimen of the drug is necessary. Clearance rate of the compound from the systemic circulation by hemodialysis is only 10 ml/min or less. In addition, our investigations identify the importance of the nonhepatic gastrointestinal pathway of elimination of doxycycline from the systemic circulation. Doxycycline therefore appears to be unique among the tetracyclines in that it may be utilized as a drug of choice for the therapy of systemic infections when a tetracycline compound is indicated in the clinical setting of impaired renal function.

Pharmacocinétique de la doxycycline en l'absence de fonction rénale. La doxycycline est une nouvelle tétracycline dont l'usage clinique est maintenant largement répandu. Elle diffère des autres tétracyclines à plusieurs égards importants parmi lesquels la faible posologie quotidienne, l'absorption totale dans la partie haute du tractus digestif et des modalités d'excrétion indépendantes de la fonction rénale. Notre travail démontre que chez les sujets anéphriques et les malades atteints d'insuffisance rénale de sévérité variable la demie vie de la doxycycline biologiquement active n'est pas significativement allongée et que dans ces situations cliniques les modalités thérapeutiques habituelles sont nécessaires. La clearance du composé observée au cours de l'hémodialyse est égale ou inférieure à 10 ml/min. De surcroît nos travaux identifient l'importance de la voie d'élimination hépatique non intestinale de la doxycycline. La doxycycline apparaît donc être unique parmi les tétracyclines en ce sens qu'elle peut être utilisée comme une drogue de choix pour le traitement des infections systémiques quand une tétracycline est indiquée et qu'il existe une altération de la fonction rénale.

Doxycycline (α -6-deoxyoxytetracycline) is the most recent of the tetracycline class of drugs to become available for oral and intravenous therapy and is now in widespread clinical use. It demonstrates a broad spectrum of antibacterial activity [1-3] and from the practical therapeutic point of view differs from the other tetracyclines in a number of important respects. It is a long-acting drug that is essentially completely absorbed from the upper gastrointestinal tract [4-7]; smaller daily dosage schedules are required (100 to 300 mg orally) [5]; and studies reported from outside the United States, where the drug has been therapeutically available for a longer period of time, indicate that its biologic half-life ($t_{1/2}$) appears to be independent of renal function such that the usual dosage regimen of this antibiotic is well tolerated by patients with impaired renal function [8-10]. However, in humans the mechanism of elimination from the systemic circulation or the pathways of biodegradation of the drug within the body have not been characterized.

Our studies were undertaken 1) to define the duration of the drug's antibacterial activity in the anephric state and in the presence of renal impairment; 2) to evaluate its removal from the systemic circulation by hemodialysis; and 3) to identify the route of excretion or biodegradation of the drug in the absence of renal function. One would expect that as the urinary excretion of the drug decreases in renal failure the percentage of unchanged and/or metabolized doxycycline would increase in the feces. However, the rate of the latter elimination or biodegradation has not been identified for doxycycline and is of therapeutic importance. We therefore focused particular attention on the intestinal excretory characteristics of the drug since data obtained in

experimental animals indicate that secretion of unchanged drug into the bowel is a major route of excretion [5, 6]. The drug was administered as tritiated doxycycline to facilitate identification of metabolites and routes of excretion.

Methods

All patients were admitted to the Metabolic Investigative Unit of the Johns Hopkins Hospital. Five anephric patients maintained on chronic hemodialysis participated in the studies (Table 1). Following an overnight fast and omission of antacids for a 24-hour period each patient was given a fat-free breakfast and a solution containing 200 mg of doxycycline base and 250 μ Ci of radioactivity. These precautions prior to doxycycline administration ensured essentially complete absorption of the drug from the upper gastrointestinal tract [5, 6, 11]. No further doses of doxycycline or any other antibacterial or radioactive compound were administered during the remainder of the study period. Plasma antibacterial activity and radioactivity of the drug were then followed for the next 120 hours. All stools were saved for an 8- to 13-day period following administra-

tion of the compound. Repeat studies after a three-month interval were undertaken in patients 1 and 2, since stool collections were inadequate during their first hospitalization.

Prior to these investigations, informed consent was obtained from all the patients and the investigations were approved by the appropriate hospital committee.

Each patient was hemodialyzed 72 hours after doxycycline administration utilizing standard dialyzers (Kiil) and drug clearance periods were measured in four of the patients during hemodialysis.

Three patients with varying degrees of renal insufficiency also participated in the investigations (Table 2). In these patients the dosage of doxycycline and the precautions prior to drug administration were similar to those already described. No stool collections were undertaken but daily urine collections were made for five days following administration of labeled doxycycline. Plasma antibacterial activity and radioactivity were investigated for 120 hours after drug administration.

Preparation and analysis of 3 H-doxycycline. Radioactive doxycycline labeled with tritium in the C-6 and C-13 positions by hydrogenation of methacycline

Table 1. Hematocrit and blood chemistry determinations in five anephric patients who received 200 mg of 3 H-doxycycline orally

Patient No.	Age years	Weight kg	Hematocrit %	Predialysis creatinine mg/100 ml	Total protein g/100 ml	Total bilirubin mg/100 ml
1	22	60	10	22	6.7	0.6
2	31	54	11	19	6.6	0.3
3	33	51	16	17	6.8	0.3
4	28	68	16	16	6.2	0.5
5	51	56	18	17	6.3	0.3

Table 2. Diagnosis, hematocrit and blood chemistry determinations in three patients with impaired renal function who received 200 mg of 3 H-doxycycline orally

Patient No.	Diagnosis	Age years	Weight kg	Hematocrit %	Creatinine clearance ml/min	Total protein g/100 ml	Total bilirubin mg/100 ml
6	Gouty nephropathy	62	72	46	19	7.4	0.3
7	Chronic pyelonephritis	19	51	24	4	7.4	0.4
8	Chronic pyelonephritis	19	60	23	2.8	7.0	0.3

Table 3. Drug plasma concentrations ($\mu\text{g/ml}$)^a and $t_{1/2}$ values (hours)^b in five anephric patients following administration of 200 mg of doxycycline orally

Time hours	Patient No.							Mean values \pm SEM
	1	2	3	4	5	1	2	
$\frac{1}{2}$	2.2	3.6	1.8	1.5	2.7	1.5	3.9	2.4 ± 0.4
1	2.5	3.5	2.0	2.2	4.8	3.0	3.9	3.1 ± 0.4
2	4.1	6.5	4.9	3.9	6.7	3.3	4.1	4.8 ± 0.5
4	4.2	6.6	3.5	2.8	4.3	3.7	4.5	4.2 ± 0.5
6	3.6	4.0	3.2	2.6	4.4	3.0	3.8	3.5 ± 0.2
12	3.1	4.0	2.9	1.9	3.3	2.5	3.3	3.0 ± 0.3
24	2.3	3.2	2.1	1.5	2.6	1.9	3.1	2.4 ± 0.3
36	1.5	2.7	1.8	1.1	1.6	1.0	2.1	1.7 ± 0.2
48	1.1	1.7	0.7	0.7	1.2	0.7	1.3	1.0 ± 0.1
72	0.5	1.0	0.5	0.2	0.2	0.3	0.4	0.4 ± 0.1
$t_{1/2}$	31	29	21	24	23	19	28	25

^a As determined by microbiological assay.

^b Calculated by regression analysis of plasma decay curve in first 48 hours.

^c Repeat studies following three-month interval.

[5] was diluted with unlabeled analytical grade doxycycline hyclate to yield a specific activity of 4,107 $\mu\text{Ci-mg}$ of doxycycline base. The product was twice recrystallized. Radiochemical purity was found to be $>97\%$ as established by reverse isotope dilution techniques and radiochromatographic procedures using a paper chromatography system. Chemical purity was established as previously described [5]. The radio-labeled product had the expected antibacterial potency.

Measurements. All measurements were performed in duplicate. Standard bioassays appropriately modified were used for determination of unchanged doxycycline in plasma and urine [12]. A combustion procedure using an automatic oxidizer (Oxymat, Inter-technique Co., Dover, New Jersey) was used to measure radioactivity content of all plasma samples. Dialysate aliquots, urine and feces samples were appropriately prepared [5] and counted in a liquid scintillator.

Results

Biologic and radioactive plasma $t_{1/2}$ in anephric patients. The results of the studies in the five anephric patients demonstrate a mean peak plasma doxycycline value of $4.8 \pm \text{SEM } 0.5 \mu\text{g/ml}$ at two hours following drug administration (Table 3). This value and the volume of distribution of the compound are similar to those noted when an equal quantity of doxycycline is administered parenterally [7] and thereby indicate

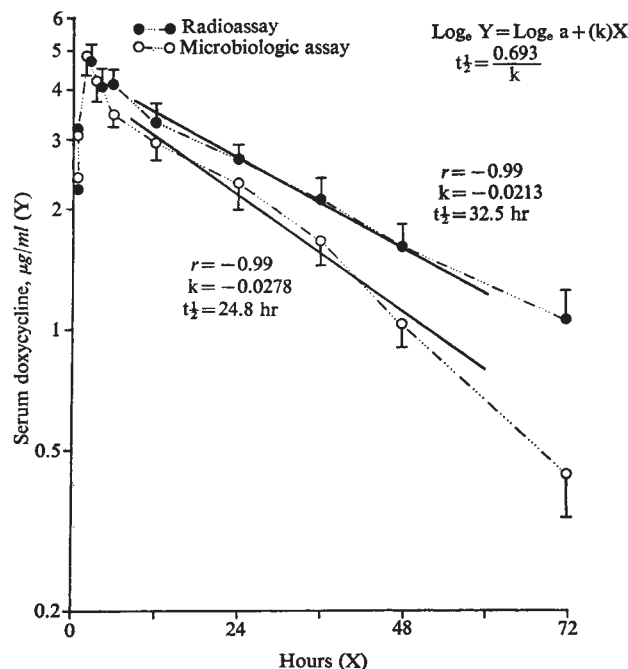


Fig. 1. Serum doxycycline concentrations as determined by radioassay and microbiologic assay following the oral administration of a single dose of 200 mg of ³H-doxycycline to five anephric patients maintained on intermittent hemodialysis. Biologic and radioactive plasma $t_{1/2}$ values are calculated on the basis of regression analysis of the plasma decay curves in the first 48 hours. Standard errors are included in the graph, and when the biologic and radioactive time-concentration curves are compared the difference is not significant up to 72 hours.

rapid and essentially complete absorption of the drug in these studies. The studies of Fabre et al [7] indicate a greater than 90% absorption of doxycycline from the gastrointestinal tract.

The mean plasma concentration data as determined by bioassay and radioassay in our anephric patients are detailed in Fig. 1. The mean biologic plasma $t_{1/2}$ was 25 hours when calculated by regression analysis of the plasma decay curve in the first 48 hours. In healthy normal individuals it ranges from 15 to 25 hours [7, 9-11]. The mean radioactive plasma $t_{1/2}$ was 32 1/2 hours; however, the difference between the biologic and radioactive plasma decay curves was not significant up to 72 hours [13].

Fecal recovery. Fecal recovery of radioactivity from the anephric patients demonstrated a mean recovery of 77% of the administered dose (Fig. 2). Although the stools were collected for several days, it can be seen that most of the drug was eliminated in the first two or three bowel movements.

Dialysance. The quantitative aspects of dialysance of radioactivity 72 hours after doxycycline administration are summarized in Table 4. By that time most of the drug had been eliminated from the circulation and only small concentrations could be detected by radioassay. Using radioassay, which could detect smaller drug concentrations than micro-

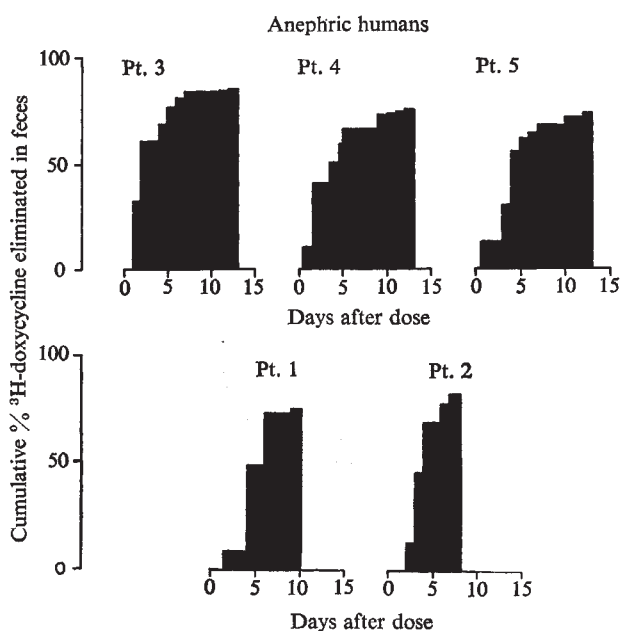


Fig. 2. Cumulative percent of label recovered from the feces of five anephric patients who were each administered orally a single dose of 200 mg of ^3H -doxycycline. A mean 77% of the compound was excreted with the feces.

Table 4. Radioactivity removed by 7 hours of hemodialysis, 72 hours after administration of a single dose of 200 mg of ^3H -doxycycline

	Patient No.			
	1	2	3	4
Mean serum ^a concentration, $\mu\text{g/ml}$	1.3	1.9	0.8	0.9
Amount ^b dialyzed, mg	12.8	17.5	11.8	6.4

^a Values obtained by radioassay scintillation counting.

^b Expressed as drug equivalent. Approximately 50% of radioactivity removed during hemodialysis was titrated water.

biologic assay, it was noted that when the mean doxycycline concentration was $1.2 \pm \text{SEM } 0.2 \mu\text{g/ml}$, a total of 12 mg of drug equivalent (i.e., radioactive drug and radioactive metabolites) was removed from the systemic circulation by seven hours of hemodialysis. Since approximately 50% of the radioactivity removed during dialysis could be dissociated from ^3H -doxycycline and identified as $^3\text{H}_2\text{O}$ by standard analytic procedures [5], at most some 6 mg of doxycycline could have been removed during the course of a routine hemodialysis. Plasma clearance rate of doxycycline was therefore 10 ml/min or less (Table 4).

Doxycycline plasma $t_{1/2}$ and urinary excretion in renal impairment. Plasma concentrations of doxycycline as determined by bioassay and radioassay in

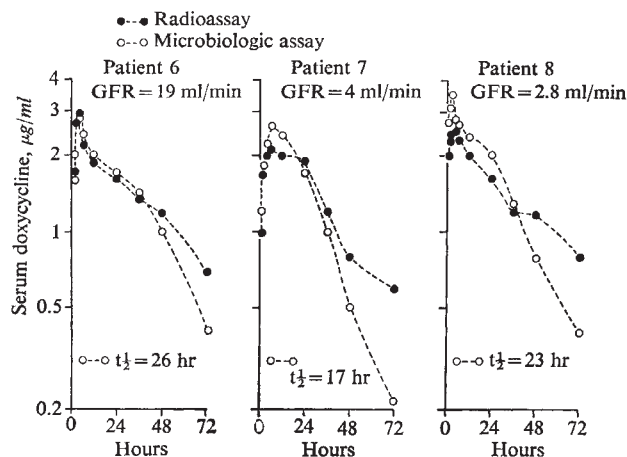


Fig. 3. Doxycycline serum concentrations following a single dose of 200 mg of ^3H -doxycycline administered orally to three patients with varying degrees of renal impairment. Glomerular filtration rates (GFR) as determined by creatinine clearances are included for each patient.

the three patients with varying degrees of impaired renal function are presented in Fig. 3. The plasma data indicate that within the first 48 hours a relatively parallel decrease in serum biologic and radioactive potency took place.

The percentage of administered ^3H -doxycycline recovered in the urine in these patients in order of decreasing renal function was 20.3% (patient 6), 5.6% (patient 7) and 2.9% (patient 8). The mean urine concentration of biologically active doxycycline in these patients was 7.1, 2.1 and 1.9 $\mu\text{g}/\text{ml}$ within the first 24 hours after drug administration, and 3.6, 0.5 and 0.7 $\mu\text{g}/\text{ml}$, respectively, in the 48- to 72-hour urine collection.

Discussion

The principal objective of our studies in the anephric individuals was achieved by the demonstration of essentially complete gastrointestinal absorption of the compound followed by recovery of an average of 77% of radioactivity eliminated with the feces. Previous studies with normal individuals suggest that this radioactivity represents almost entirely unmetabolized drug [5]. In our anephric patients an additional 6% of the radioactive label, approximately one-half of which represented tritiated water, was removed by hemodialysis 72 hours following administration of the compound, thereby giving an overall average recovery of some 83% of the administered drug. This represents a high rate of recovery for single dose pharmacokinetic studies.

In our studies most of the doxycycline eliminated with feces probably was not secreted with bile. Although relatively high concentrations in that fluid have been observed, the total quantity of drug eliminated by such a route as measured by microbiologic methods in humans with biliary fistulae in the studies of Mahon, Wittenberg and Tuffnel [10] and Fabre et al [7] have shown that less than 5% of the totally administered compound is excreted via the bile. In addition, the studies of Schach von Wittenau and his associates [5, 14] have shown in an experimental dog model that when using both a microbiologic and radioactive assay system for doxycycline analysis less than 5% of the totally administered drug is eliminated in the bile.

We may gain a better understanding of the fate of doxycycline in our anephric patient studies by correlating our results with the physicochemical properties of the drug and with data derived from observations made during animal experiments. Doxycycline compared to earlier tetracyclines is more lipophilic and, consequently, penetrates lipid membranes with

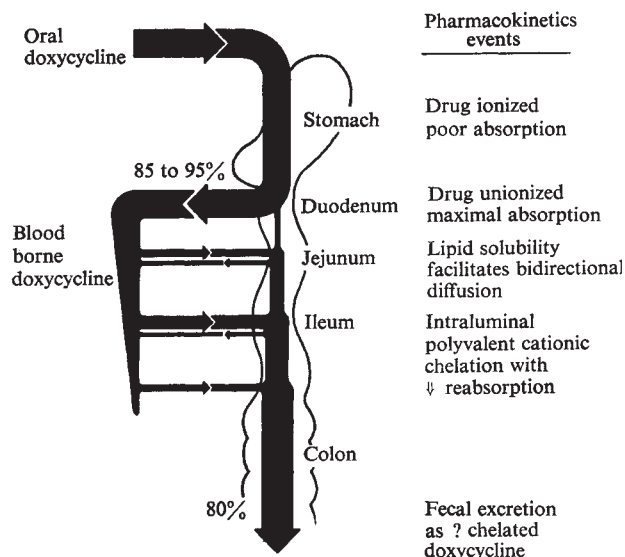


Fig. 4. Suggested pharmacokinetic characteristics of doxycycline in the intestinal tract of anephric humans, derived from a correlation of the results noted in anephric patients, the physicochemical properties of the drug and observations made during animal experiments.

greater ease. Like most tetracyclines it reaches its maximum degree of lipophilicity at about pH 5.5 [14], and animal experiments suggest that the duodenum is the primary site of absorption [6, 15]. All tetracyclines form complexes with metal ions [16, 17]. In the case of doxycycline, it has been demonstrated that such complexes are unstable in the acid contents of the stomach, thus allowing free drug to enter the duodenum [6] and accounting for the fact that the simultaneous ingestion of food and doxycycline does not inhibit the absorption of this tetracycline from the upper gastrointestinal tract [11]. However, when a metal complex of the drug is formed in (or directly introduced into) the alkaline contents of the small intestine, it remains stable and in such form cannot easily be absorbed [6]. In animal experiments it has been shown that bidirectional diffusion of doxycycline can occur across the mucosa of gastrointestinal tract throughout the length of the small bowel and that the net direction of such diffusion is from the serosal to the mucosal side of the small bowel wall provided normal intraluminal contents are present within the lumen of the bowel [6].

Therefore, in anephric patients (Fig. 4) it is possible to speculate that following oral administration of doxycycline high duodenal concentrations of free drug are achieved which allow almost complete absorption of the compound to take place. Blood-borne doxy-

cycline is then presented to the serosal surface of the small intestine and diffusion of drug into the intestinal lumen takes place. In the lumen cationic chelation occurs and in such form doxycycline cannot be reabsorbed. The capacity of the intraluminal contents to bind successive amounts of doxycycline is not readily superseded since the daily doses of the drug are small and new intraluminal contents are constantly added to the small bowel by gastric emptying and biliary, pancreatic and succus entericus secretions. Minor additional contributions to fecal elimination of the drug are made by biliary secretion.

Thus, absorption followed by transmucosal diffusion and intraluminal chelation of the compound such that it cannot be reabsorbed appears to be a plausible mechanism to resolve the somewhat contradictory facts of sequential intestinal absorption followed by excretion.

Specific information detailing the cationic binding constants of doxycycline is not available, but it may be assumed that doxycycline behaves qualitatively in a manner similar to other tetracyclines [16, 17]. If these other tetracyclines passed through the bowel wall as easily as does doxycycline, one might expect them to be excreted in a similar fashion. Therefore, it does not appear to be a unique complexing ability which causes doxycycline to be excreted with feces, but rather its marked lipid solubility which allows sufficiently rapid movement of the drug across the bowel wall into the luminal contents, and the quantitatively small daily dosages which require elimination.

Our studies indicate that the extension of the drug's biologic plasma $t_{1/2}$ is minimal in otherwise stable anephric patients maintained on intermittent dialysis. The $t_{1/2}$ of radioactivity was, however, extended to a value of $32\frac{1}{2}$ hours (Fig. 2), indicating the presence of nonbioactive compounds in small concentration in the plasma. Whether these trace amounts of nonbiologically active metabolites represent tritiated water alone or tritiated water in addition to nonbiologically active metabolites of doxycycline cannot be resolved at present since it is not possible to calculate the absolute quantity of nonbioactive material as its volume of distribution and identity are unknown. One of the risks inherent in the use of tritiated drugs for drug metabolism studies is the possibility of generating radioactive compounds not related to the original drug. This may occur by the transfer of the ^3H label to plasma water or by enzymatic transfer of the tritium label to natural body constituents without generating extracellular tritiated water [18, 19]. In the case of doxycycline, the formation of small quantities of tritiated water has been established [5]. The quantities of nonbioactive materials involved in these studies

were minimal and the experience to date following repetitive administration of the compound suggests that they are of no clinical significance.

In the patients with impaired renal function, the plasma $t_{1/2}$ of bioactive drug (Table 3) was similar to that noted in the anephric patients, and the renal clearance of the drug was directly correlated with the degree of reduction in the patient's glomerular filtration rate.

As yet there are no clinical reports of doxycycline inducing prerenal azotemia by the mechanisms common to other tetracyclines [21, 21].

In conclusion, these studies demonstrate that in the anephric state or in the presence of renal impairment, the extension of the drug's biologic plasma $t_{1/2}$ is not clinically significant. This finding in association with the results of repetitive dosing studies as reported by other investigators [9, 10] suggests that no alteration in the usual therapeutic drug regimen is necessary when this compound is used in the absence of renal function. Removal rate of the drug by hemodialysis is not of therapeutic significance. In addition, our investigations more clearly identify in humans the nonrenal, nonhepatic, gastrointestinal pathway of doxycycline excretion. This drug therefore appears to be unique among the tetracyclines in that when renal failure complicates the clinical picture doxycycline may be used as a drug of choice if a tetracycline is indicated for the therapy of systemic infection.

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