Relation Between Lipophilicity and Pharmacological Behavior of Minocycline, Doxycycline, Tetracycline, and Oxytetracycline in Dogs

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Four tetracyclines were studied in dogs to determine the relation between their lipophilicity and various other pharmacological characteristics. Lipid solubility correlated inversely with the mean concentration of drug in arterial plasma and renal uptake and excretion, and directly with the biliary concentration gradient (level in bile/level of free drug in serum). Only the more lipophilic congeners minocycline and doxycycline passed the blood-brain and blood-ocular barriers in detectable concentrations. Mean levels of minocycline in the brain exceeded those of doxycycline by almost threefold; the difference was of borderline statistical significance ($P = 0.05$ to 0.1). Lipophilicity correlated inversely with the concentration of antibiotic in renal medulla but not in renal cortex or in the liver. When intestinal loops containing saline, milk, or 10% Gelusil were studied, the only combination exhibiting striking intraluminal accumulation was doxycycline in milk. These results indicate that lipophilicity correlates with many, but not all, of the transport characteristics of tetracycline antibiotics.

Since the discovery of the tetracycline antibiotics over 25 years ago, a number of molecular modifications have been made with a view to improving tissue distribution, prolonging their half-life, augmenting intestinal absorption, and enhancing their antibacterial activity. Many of these objectives have been met in minocycline and doxycycline (6, 9, 10, 25, 26, 34, 41). Of additional interest is the fact that neither of these tetracyclines appears to require a major adjustment in dose in the presence of renal failure (6, 41), suggesting that they are extensively eliminated by nonrenal routes. Doxycycline has been demonstrated to be excreted extensively via the intestine (41). The data relative to minocycline, however, are inconclusive, and biliary excretion (29), intestinal excretion (6), and metabolic degradation (25) have all been considered as possible modes of nonrenal elimination of this agent.

Minocycline and doxycycline are markedly more lipid soluble than is tetracycline or oxytetracycline (Table 1). The lipophilicity of minocycline is particularly striking and appears to endow this agent with a high degree of intestinal absorption and tissue penetration. Although a number of investigators have examined the pharmacological behavior of various tetracyclines in terms of their physicochemical

properties, there have been few comparisons of minocycline and doxycycline in this respect.

The purpose of the present investigation was to compare minocycline, doxycycline, tetracycline, and oxytetracycline with regard to their uptake and excretion by the liver and kidney, and their penetration into ileal contents, brain, cerebrospinal, and ocular fluids. The studies were carried out in a canine model that has been employed in previous investigations in our laboratory (5).

MATERIALS AND METHODS

Surgical preparation. The surgical preparation procedure has been described previously (5). Healthy mongrel dogs weighing 20 to 29 kg were anesthetized. Intravascular cannulas were placed in the femoral artery and vein and left renal, portal, and hepatic veins for aspiration of blood. Clotting was prevented by flushing the cannulas with heparin. Flow probes (Statham Co., Los Angeles, Calif.) were applied to the left renal and portal veins. Mean arterial pressure was recorded with a pressure transducer. Both ureters and the common bile duct were catheterized, and the cystic duct was ligated.

Several additional procedures not performed in previous studies of this model were carried out. The terminal ileum was mobilized, and three contiguous segments were ligated with heavy silk sutures. Care was taken to insure that the blood supply

TABLE 1. *Some physicochemical characteristics of four tetracyclines*

Drug	Chloroform-water partition coefficient at pH 7.4 (36)	Octanol-water partition coefficient at pH 7.5 (8)	Chelation by calcium (35) (%)
Minocycline	30 ^a	1.1 ^b	NK ^c
Doxycycline	0.48	0.60	19
Tetracycline	0.09	0.036	39.5
Oxytetracycline	0.007	0.025	36

^a Data from personal communication, R. G. Kelly, Lederle Laboratories.

^b Value for minocycline inferred from data at other pH values.

^c NK, Not known.

was intact. A cannula was inserted into each loop through a purse-string suture, and 60 ml of normal saline, milk, or 10% Gelusil (Warner/Chilcott, Morris Plains, N. J.) in normal saline was infused into the loops in random order. The contents of calcium, magnesium, and iron in the milk were 1.18, 0.12, and 0.001 mg/ml, respectively. The solution of 10% Gelusil contained no calcium, 2.6 mg of magnesium, and 1.5 mg of aluminum per ml. When the surgical preparation was complete, infusions of antibiotics were started.

Antibiotic infusions. Each of the following tetracyclines was given intravenously to five dogs: minocycline hydrochloride, tetracycline hydrochloride (Lederle Laboratories, Pearl River, N.Y.), doxycycline hyclate, and oxytetracycline hydrochloride (Pfizer Laboratories, New York, N.Y.). A loading dose of 5 mg/kg was given over 2 to 5 min. Minocycline, however, was injected over 10 to 30 min because rapid administration of this agent produced marked hypotension. A continuous infusion of antibiotic was then given at the rate of 1 mg/kg per h with an infusion pump. The drugs were dissolved in normal saline in a concentration such that the hourly quantity was contained in 72 ml.

Collection of specimens. Blood was obtained from the intravascular cannulas at 15-min intervals. Flow rates were measured in the renal and portal veins at the same time. Urine and bile were collected over 30-min periods, and 1 ml of the contents of the ileal loops was aspirated every half hour.

At the end of the 3-h period of infusion, wedge biopsies were obtained from the liver and left kidney; the latter was dissected into cortex and medulla. A section of the wall of each ileal loop was also excised. The aqueous humor of both eyes was aspirated through a 25-gauge needle, and the vitreous was obtained after enucleation of the eye. Cerebrospinal fluid was procured by cisternal puncture. Brain tissue was obtained through a burr hole in the parietal region of the skull. Specimens from the brain, spinal fluid, and eye were generally removed bloodlessly. All tissues and fluids were frozen (-20°C) and assayed within 48 h.

Vital signs, acid-base status, and hematocrit were measured every 15 min and showed no significant

abnormalities, except for the transient hypotension observed with minocycline. Careful attention was paid to hemostasis throughout the studies.

Assays. The techniques used were similar to those described elsewhere (5). Concentrations of the drugs were determined by an agar-diffusion bioassay employing *Bacillus subtilis* spores (ATCC 6633) and antibiotic medium no. 8 (Difco Laboratories, Detroit, Mich.). Tissues were homogenized in a 2.5% solution of trypsin equal in volume to three times the weight of the tissue. Preliminary studies demonstrated that standards dissolved in normal saline produced zones of inhibition of the same size as those resulting from an identical concentration of antibiotics in trypsinized tissue homogenates. For this reason, tissues were assayed using saline standards. Pooled canine serum, bile, milk, and 10% Gelusil were used to prepare standards for assay of the corresponding specimens. Ocular aqueous and vitreous humor and spinal fluids were assayed against standards diluted in saline. For each of these tissues and fluids, the accuracy of the bioassay was $\pm 15\%$.

Studies using ⁵¹Cr-tagged canine erythrocytes indicated that the content of the blood in the biopsies of the liver, kidney, ileum, and brain was approximately 4%.

All statistical analyses were performed using an unpaired *t* test.

RESULTS

Effects of loading dose on blood pressure. The mean arterial blood pressure was not affected by infusion of oxytetracycline or tetracycline. Injection of the initial dose of doxycycline over 2 to 5 min produced a slight (11.4%) rise in mean arterial pressure over base-line values ($P < 0.05$). Infusion of minocycline at the same rate resulted in severe hypotension; thus, loading doses of this agent were administered over 10 to 30 min. Even at this slower rate, minocycline produced a decline in mean arterial blood pressure of 37% (standard error, 11%) compared with values before injection ($P < 0.02$). The effect, however, was transient, with return to base-line levels within 60 min.

Intravascular concentrations of tetracyclines. Levels of antibiotic were highest during h 1 of infusion, reflecting the effect of the loading dose. Stable concentrations were attained within 60 to 90 min with each agent. The mean levels of drugs in arterial plasma during h 3 of infusion are shown in Table 2. Although differences among the four agents were small, there was an inverse relation between lipid solubility (Table 1) and the levels of antibiotics in arterial serum. Concentrations of minocycline and doxycycline in the hepatic vein were lower than those in the portal or renal veins ($P < 0.01$). In contrast, concentrations of oxytetracycline were lower in the renal vein than in the portal or hepatic veins ($P < 0.01$).

TABLE 2. Concentrations of tetracyclines in various vessels during h 3 of continuous infusion^a

Vessel	Concn ($\mu\text{g/ml}$)			
	Minocycline	Doxycycline	Tetracycline	Oxytetracycline
Femoral artery	4.1 ± 0.4	5.3 ± 0.7	5.6 ± 0.4	6.8 ± 0.3
Portal vein	3.4 ± 0.3	5.0 ± 0.7	5.1 ± 0.4	6.5 ± 0.3
Hepatic vein	2.8 ± 0.3	4.7 ± 0.6	4.9 ± 0.4	5.9 ± 0.2
Renal vein	3.4 ± 0.4	4.9 ± 0.7	4.8 ± 0.4	5.5 ± 0.2

^a Mean and standard error of four values obtained at 15-min intervals; each drug was administered to five dogs.

Percentage of extraction by liver and kidney. The percentage of extraction value represents the percentage of antibiotic removed from each milliliter of plasma during passage through the organ; the method of calculation has been described previously (5). Stable values were reached during h 2 of infusion. The percent extraction for both the liver and kidney during h 3 ranged from 5 to 18% for all the drugs (Table 3); there was no clear relation to lipid solubility (Table 1).

Absolute extraction by the liver and kidney. The rate of uptake (absolute extraction) of drug by each organ (micrograms per minute) was calculated as the difference in concentration between efferent and afferent vessels multiplied by the flow rate of plasma (5). The mean renal plasma flow rates during h 3 of infusion ranged from 70 to 90 ml/min for all animals, except those receiving minocycline (44 ml/min). Portal flow rates ranged from 120 to 180 ml/min, except in dogs receiving doxycycline (237 ml/min). Values for absolute renal extraction were stable by 2 h, whereas those for hepatic extraction fluctuated throughout the study.

During h 3 of infusion (Table 3), extraction by the kidneys was significantly higher for tetracycline and oxytetracycline than for the two more lipophilic agents ($P < 0.01$ in each instance). In contrast, no relation to lipid solubility was evident for hepatic extraction.

Excretion in urine and bile. The concentrations and rates of excretion in urine and bile became stable during h 2 (Fig. 1). The four congeners differed significantly from one another with respect to their levels and rates of excretion in urine ($P < 0.02$ in each instance), and both of these measurements correlated inversely with their relative lipophilicity (Table 1). Most striking was the low urinary concentration of minocycline (mean, $3 \mu\text{g/ml}$) during h 3. The pH of urine varied from 6.2 to 8.5.

In contrast to the findings in urine, there were only minor disparities among the antibiotics in their biliary excretion. There were no

significant differences in either concentration or rate of excretion in bile among the four agents during the first 2 h. By 3 h (Fig. 1), the biliary level of tetracycline was significantly lower than that of minocycline ($P < 0.05$), and its rate of excretion was less than that of doxycycline ($P < 0.05$). The pH of bile ranged from 7.0 to 7.6 (median, 7.4) for each tetracycline.

Concentrations in various tissues and fluids. The concentrations of minocycline and doxycycline were significantly higher than those of either oxytetracycline or tetracycline in the cerebrospinal fluid, brain, and ocular aqueous and vitreous humor ($P < 0.05$ in each instance) (Fig. 2). The mean levels of minocycline or doxycycline in all of these sites ranged from 0.7 to $2.9 \mu\text{g/ml}$, whereas tetracycline and oxytetracycline were undetectable ($<0.3 \mu\text{g/ml}$). The concentrations of minocycline were similar to those of doxycycline, except in the brain where the difference was of borderline statistical significance ($P = 0.05$ to 0.1).

Levels of oxytetracycline in the liver were significantly higher than those of tetracycline ($P < 0.05$) or minocycline ($P < 0.01$).

TABLE 3. Percentage of extraction and absolute extraction of tetracyclines by the kidney and liver during h 3 of infusion^a

Antibiotic	Extraction (%)		Absolute extraction ($\mu\text{g/min}$)	
	Left kidney	Liver	Left kidney $\times 2$	Liver
Minocycline	18 ± 2	16 ± 4	60 ± 8	80 ± 17
Doxycycline	10 ± 2	8 ± 3	68 ± 16	95 ± 34
Tetracycline	15 ± 2	5 ± 2	139 ± 20	55 ± 22
Oxytetracycline	18 ± 1	10 ± 1	174 ± 16	137 ± 23

^a Mean and standard error of four values in each dog; each drug was administered to five animals.

FIG. 1. Concentrations and rates of excretion of antibiotics in urine and bile; mean and standard error of values during h 3 of infusion. Urinary concentrations are from the left ureter; urinary excretion represents the sum of the values from both ureters.

FIG. 2. Concentrations (mean and standard error) of antibiotics at various sites after 3 h of infusion. Note the difference in scale of the two graphs. Asterisks indicate locations in which no antibiotic could be detected ($<0.3 \mu\text{g/ml}$).

Minocycline was present in lower concentrations than the other three agents in renal cortex ($P < 0.02$). There was an inverse correlation between lipophilicity and the levels of drugs in the renal medulla; however, the only differences of statistical significance in this tissue were between minocycline and oxytetracycline ($P < 0.05$).

The concentration of the tetracyclines in various tissues and fluids was calculated as a concentration gradient, that is, as a percentage of the level of free drug in the serum (Table 4). The latter value was derived by multiplying the concentration of drug in arterial serum (Table 2) by the unbound fraction, using the protein binding data shown in Table 5. The resultant mean levels of free antibiotics were (micrograms per milliliter): minocycline, 1.02; doxycycline, 0.95; tetracycline, 1.12; and oxytetracycline, 4.96. Thus, the concentrations of free drug were approximately fivefold as high for oxytetracycline as for the other agents. For comparative purposes, data reported by other investigators are also shown in Table 4. There was no distinct relation between lipophilicity and the concentration gradient for renal or hepatic tissue. In contrast, there was a direct correlation between lipid solubility and the concentration gradient in bile, and an inverse correlation in urine. The two more lipophilic agents exhibited much higher concentration gradients in the brain, cerebrospinal fluid, and aqueous and vitreous humor than did tetracycline and oxytetracycline.

In no instance were we able to show a strictly linear relation between the lipid-water partition coefficient (Table 1) or its logarithm and the concentrations or concentration gradients of the antibiotics (36).

Concentration in wall and contents of ileal loops. There were no significant differences among the antibiotics with respect to their concentrations in the wall of saline-containing loops (Fig. 2). The levels of antibiotics in the walls of loops containing milk or Gelusil were similar to those in segments filled with saline. The concentrations of drugs in the contents of ileal loops showed a progressive increase during the course of infusions (Table 6). A striking accumulation of doxycycline was observed in segments containing milk; these exceeded the levels encountered with any other combination of antibiotic and type of ileal fluid ($P < 0.05$).

DISCUSSION

The transport of antibiotics from serum into interstitial fluid and tissues is influenced by a number of factors, including serum protein binding and lipid solubility of the compound (16, 18). The capillary bed of most tissues contains small fenestrations that permit ready passage of substances of molecular weight up to about 1,000. Thus, that portion of most antibiotics not bound to protein penetrates the interstitial fluid with relative ease. In contrast, diffusion across the blood-brain and blood-ocular barriers, intestinal epithelium, and cell membranes depends upon movement through a lipid barrier. In general, lipid solubility facilitates transport in these circumstances. These correlates, however, are relative, and the pharmacological behavior of the tetracyclines is influenced markedly by their pK_a , degree of chelation by metals, and binding to other cellular constituents (36, 39). Furthermore, the concentrations of these agents in the major organs of excretion, such as the liver and kidney, have been said to correlate poorly with their relative lipophilicity (36).

We have examined four tetracyclines of markedly different lipophilicity to compare their pharmacokinetic behavior in the major organs of excretion and their penetration into sites of notoriously poor access. As shown in data from other studies (Table 5), the extent of protein binding of minocycline by canine serum is similar to that of doxycycline and tetracycline, despite their disparate lipid solubilities. This fact simplified the interpretation of our own data since it eliminated the influence of this variable. There is no correlation between the pK_a values of the various tetracyclines and their partition coefficients; indeed, the apparent dissociation constants of the four agents are quite similar, except for minocycline, which displays a second dimethylamino group with a

TABLE 4. Concentration gradients of tetracyclines in various canine tissues and body fluids^a

Tissue or body fluid	Concn gradient: ^b			
	Minocycline	Doxycycline	Tetracycline	Oxytetracycline
Kidney				
Present study ^c	<i>14</i>	<i>36</i>	<i>32</i>	<i>7</i>
Other studies	10 (21)	22 (36)	10-50 (20)	4 (36)
Urine				
Present study	<i>2.5</i>	<i>21</i>	<i>84</i>	<i>41</i>
Liver				
Present study	<i>15</i>	<i>25</i>	<i>18</i>	<i>9</i>
Other studies	16 (21)	16 (36)	10 (20)	3 (36)
Bile				
Present study	<i>96</i>	<i>95</i>	<i>32</i>	<i>15</i>
Other studies	120-150 ^d (21)		75 ^d (20)	4 (39)
Ileum				
Present study	<i>8</i>	<i>16</i>	<i>14</i>	<i>4</i>
Other studies	8 (21)		1-1.5 (12, 20)	
Cerebrospinal fluid				
Present study	<i>0.98</i>	<i>1.15</i>	<i><0.27</i>	<i><0.06</i>
Other studies	0.4 (21)		0.4 (20, 22)	
Brain				
Present study	<i>2.8</i>	<i>1.26</i>	<i><0.27</i>	<i><0.06</i>
Other studies	2.6 (21)		0.2 (20)	
Aqueous humor				
Present study	<i>0.7</i>	<i>1.42</i>	<i><0.27</i>	<i><0.06</i>
Other studies	0.4 (21)		0.6-2.5 (20)	
Vitreous humor				
Present study	<i>0.7</i>	<i>2.0</i>	<i><0.27</i>	<i><0.06</i>
Other studies	0.6 (21)		0.5 (20)	

^a Numbers in parentheses indicate references; data in italics are those obtained in the present study.

^b Level of drug in indicated site (micrograms per gram or micrograms per milliliter)/level of free (unbound) drug in serum (micrograms per milliliter). This latter value has been determined by multiplying the concentration of total drug in serum by: minocycline, 0.25; doxycycline, 0.18; tetracycline, 0.20; and oxytetracycline, 0.73.

^c Data are for renal cortex. Values for medulla were: minocycline, 11; doxycycline, 25; tetracycline, 26; oxytetracycline, 9.

^d Gall bladder bile.

TABLE 5. Selected aspects of the canine pharmacology of four tetracyclines^a

Tetracycline	Serum protein binding (%)	Parenteral dose (%) excreted in:		
		Urine	Feces	Bile
Minocycline	75 ^b	6-15 (21, 28)	80-90 ^c (21)	
Doxycycline	82 (39)	16-22 (37, 39)	75 (37)	3 (37)
Tetracycline	80 (39)	56 (28)		
Oxytetracycline	27 (39)	53 (39)		1.8 (39)

^a Numbers in parentheses indicate references.

^b Personal communication, R. R. Roepke, Lederle Laboratories, Pearl River, N. Y.

^c Includes biliary excretion.

pK_a of about 5 (4, 24). This peculiarity may contribute to the greater lipophilicity of minocycline at neutral pH (4).

The results of the present investigation indicate that certain pharmacological properties of the tetracyclines correlate closely with their relative lipophilicity. Among the most striking was the inverse relation of lipid solubility with urinary excretion and absolute renal extraction of the tetracyclines. The reason for this correlation is not clear since elimination of these agents by the kidney is believed to occur solely by glomerular filtration (29, 30), and differences in protein binding cannot account for the findings. One explanation might be back diffusion of the more lipophilic congeners from the tubular lumen (40), a possibility that is supported in part by the fact that the disparity in the levels of antibiotic in the renal cortex was much less than that in the urine.

The levels of total drug in arterial plasma also showed a striking correlation with lipophilicity. We are reluctant, however, to infer a direct relation from this observation since these concentrations are the result of a number of factors that were not examined in the present study, including the extent of serum protein binding, rate of elimination, and volume of distribution of the antibiotic. Indeed, the calculated levels of free minocycline, doxycycline, and tetracycline in the serum were virtually identical.

Biliary excretion of the four tetracyclines, when expressed as the concentration gradient (Table 4), showed an excellent correlation with lipid solubility. The relation between lipophilicity of a compound and its biliary excretion is by no means clear (33); in fact, in one study of penicillins in a rodent model, an inverse relation between the two functions was noted (31).

A marked permissive effect of lipophilicity was evident in the penetration of antibiotics across the blood-brain and blood-ocular barriers. Minocycline and doxycycline achieved concentrations 0.7 to 2.8 times the level of free drug in the serum, whereas oxytetracycline and tetracycline were undetectable.

Levels of drugs or their concentration gradients in the hepatic parenchyma and in renal cortex correlated poorly with lipophilicity. In contrast, the levels of antibiotics in the renal medulla (Fig. 2) exhibited an excellent inverse correlation with lipid solubility of the drug. It is not possible to determine the extent to which urinary antibiotic, within the collecting ducts of the medulla, contributed to this finding. With the exception of absolute renal extraction, there was no correlation between lipophilicity and

TABLE 6. Concentrations of tetracyclines ($\mu\text{g/ml}$) in contents of ileal loops^a

Tetracycline	Solution in ileal loop		
	Saline	Gelusil (10%)	Milk
Minocycline	0.6 ± 0.3	0.3 ± 0.2	3.0 ± 1.0
Doxycycline	5.5 ± 1.7	4.4 ± 2.2	36 ± 11
Tetracycline	2.4 ± 1.4	0.7 ± 0.7	1.8 ± 0.9
Oxytetracycline	4.2 ± 1.8	1.9 ± 1.5	3.7 ± 1.6

^a Mean and standard error of concentrations during the last half of h 3 of infusion of antibiotic; each drug was administered to five dogs.

percent extraction or absolute extraction by the liver or kidney.

Doxycycline displayed a marked propensity to accumulate intraluminally in ileal segments containing milk. Such accumulation presumably is the result of the relatively high lipophilicity of doxycycline, permitting its passage across the intestinal mucosa, and its tendency to form complexes with polyvalent cations of metals (41); moreover, the observation is in accord with the finding that substantial amounts of doxycycline may be passively transported from the serum into the intestinal lumen of dogs (37), rats (38), and humans (41). Although the data of Table 1 suggest that doxycycline is somewhat less readily chelated by calcium than is oxytetracycline or tetracycline, other work indicates that at approximately neutral pH, the tetracyclines are almost completely chelated by all polyvalent metallic cations studied (1, 2, 4). Of interest is the observation that the calcium chelation product of doxycycline but not of minocycline or tetracycline forms an insoluble precipitate at antibiotic concentrations of 5 and 20 $\mu\text{g/ml}$ (J. Krueger, Lederle Laboratories, personal communication). This may explain the unique propensity of doxycycline to accumulate intraluminally in milk-containing loops of ileum. The reason for the failure of doxycycline to become concentrated in loops filled with 10% Gelusil is not clear. One partial explanation is the fact that aluminum hydroxide, at neutral pH, presents virtually no free aluminum to bind the antibiotic. Since the tetracyclines are not metabolized to any important extent in dogs (19, 21, 37), our data leave unanswered the question of the nonrenal routes of elimination of minocycline.

Although minocycline is strikingly more lipid soluble than doxycycline, especially in terms of its chloroform-water partition coefficient (Table 1), the only respects in which the two compounds exhibited pharmacological differences were in their urinary excretion, levels in renal

TABLE 7. *Selected aspects of human pharmacology of four tetracyclines^a*

Tetracycline	Serum protein binding (%)	Parenteral dose excreted in urine (%)	Concn gradient ^b	
			Bile	Cerebrospinal fluid
Minocycline	76 (25)	6-9 (7, 10, 25)	150 (25)	0.5-1.0 (6, 25)
Doxycycline	82-93 (10)	35 (3, 10)	30-80 (11)	0.5-1.0 (25, 26)
Tetracycline	55-64 (10)	60 (23)	12-25 (11)	0.07-0.3 (14, 32, 42)
Oxytetracycline	27-35 (10)	70 (23)	10-15 (11)	0.14-0.24 (15, 17, 42)

^a Numbers in parentheses indicate references.

^b Concentration of drug in various sites (micrograms per milliliter)/concentration of free (unbound) drug in serum (micrograms per milliliter). The following fractions were used to compute the serum level of unbound drug: minocycline, 0.24; doxycycline, 0.18; tetracycline, 0.40; oxytetracycline, 0.70.

cortex, and accumulation in the lumen of ileal segments containing milk. In addition, levels of minocycline in the brain were almost three-fold those of doxycycline, although the differences were not quite significant ($P = 0.05$ to 0.1). This finding is of interest in view of the apparent capacity of minocycline to produce vestibular disturbances (27).

The octanol-water partition coefficient appeared to correlate somewhat better than the chloroform-water partition coefficient with the in vivo behavior of minocycline and doxycycline. Although the octanol-water system has been regarded as a good model for the study of passage across membranes, the relations involved are exceedingly complex and are best expressed logarithmically (13). We are, therefore, reluctant to draw any conclusion as to which type of partition coefficient correlates best with the pharmacological behavior of these agents.

Even though a loading dose of antibiotic was administered in these studies, it is possible that distribution equilibrium was incomplete at the end of the 3-h period of infusion. The fact that most indices were stable by 3 h suggests that the differences noted among the agents would probably persist at full equilibrium. The validity of our findings is further supported by the general agreement of the results with those of others (Table 4), despite differences in experimental techniques.

In Table 7, data concerning selected aspects of the pharmacology of tetracyclines in humans have been compiled. The results are similar to those in dogs, with a marked inverse correlation between lipophilicity and urinary excretion of the tetracyclines and a direct correlation between the concentration gradients in bile and cerebrospinal fluid.

The results of these studies support the notion that lipophilicity correlates well with certain properties of tetracyclines. Although we were unable to show a strictly linear correla-

tion between the lipid-water partition coefficient (or its logarithm) and any of the pharmacological measurements observed with these antibiotics, it seems likely that such a relation would hold for certain nonspecialized tissues, such as muscle (36). There is an inverse relation of lipophilicity with renal extraction, excretion, and medullary concentration of the antibiotics and a direct one with the biliary concentration gradient and penetration of the blood-brain and blood-ocular barriers. In contrast, the hepatic uptake of the drugs and the concentrations of antibiotic in the liver and in renal cortex show little relation to lipid solubility. The capacity of doxycycline to accumulate in segments of ileum containing milk suggests that this route of elimination may be peculiar to this congener and may be strongly influenced by the nature of the chelating substance present intraluminally.

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