Metabolism of Clindamycin I: Absorption and Excretion of Clindamycin in Rat and Dog

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Abstract □ Clindamycin hydrochloride, randomly labeled with tritium, was synthesized and used for animal metabolism studies. The drug was administered to rats (oral and intraperitoneal routes) and dogs (oral and intramuscular routes) at a dose of 50–150 mg./kg. In both species, after the oral or parenteral drug administration, the excretion of radioactive materials in the urine (approximately one-third of the dose) and in the feces (approximately two-thirds of the dose) was independent of the route of administration. The initial rate of excretion for the oral dose was significantly faster than the parenteral dose. In the dog, peak plasma radioactivity concentrations were observed at 2 and 4 hr. after oral and intramuscular administration, respectively. The slower rate of absorption and excretion following parenteral compared to oral administration was believed due to precipitation of the drug at the injection site or a difference in transport processes. Based upon the identical areas under the plasma total radioactivity *versus* time curves, plus the fact that the distribution of radioactivity excreted in urine and feces was independent of the route of administration, it was concluded that after oral administration the absorption of this drug into the bloodstream was almost complete and that little appeared to pass through the GI tract for direct elimination.

Keyphrases □ Clindamycin hydrochloride, radiolabeled—absorption and excretion after oral and parenteral administration, rats, dogs □ Absorption, radiolabeled clindamycin hydrochloride—after oral and parenteral administration, rats, dogs □ Excretion, radiolabeled clindamycin hydrochloride—after oral and parenteral administration, rats, dogs

Clindamycin[1] (I), a new antibacterial agent produced by chlorination of lincomycin, exhibits approximately four- to eightfold the *in vitro* antibacterial activity of lincomycin against Gram-positive organisms. *In vitro* clindamycin gave significantly lower CD_{50} values than lincomycin with a number of organisms tested. In addition, this drug has been shown to be a promising antimalarial agent in both mice and monkeys. The chemistry and biological activities were reported previously by Birkenmeyer (1), Magerlein *et al.* (2), and Birkenmeyer and Kagan (3).

Studies on the absorption, excretion, and half-life of clindamycin administered orally (4) or intramuscularly (5) to human subjects were also reported previously. Microbiological assays were used for end-point measurement. It was found that an orally administered dose was absorbed quantitatively and extremely fast in man. The maximal serum activity was achieved within 45 min. postadministration, with a clearance half-life of 2.38 hr. On the other hand, the intramuscularly injected dose was absorbed rather slowly. The maximal serum activity was achieved 2 hr. after administration, with an elimination half-life of 4.76 hr. Local precipitation of the drug at the injection site was believed to be the cause of this absorption delay. Since the bioassay measures only the algebraic sum of the antibacterial activities of the drug and its metabolites, the present study was undertaken to provide an overall understanding of the excretion of this antibiotic.

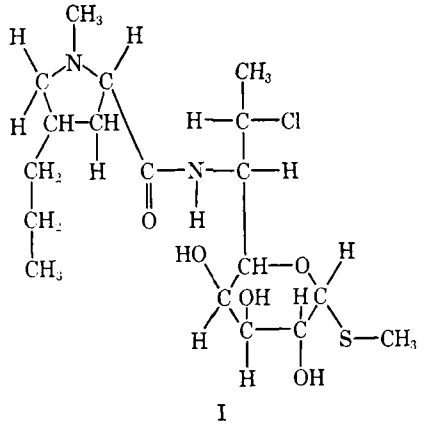
EXPERIMENTAL

Synthesis of Clindamycin-^{3}H Hydrochloride—Since extensive work had already been done on the tritiation of lincomycin hydrochloride (6), it was decided to prepare tritium-labeled lincomycin hydrochloride according to previously described methods and to use it as the starting material for conversion to clindamycin hydrochloride. Although the catalytic gas-exposure tritiation method gives a product of higher radiochemical purity and specific activity, it results in tritiation predominately in the propyl hygric acid portion of the molecule (6). Therefore, to achieve a more random distribution of the tritium label in the molecule, the Wilzbach gas-exposure tritiation method in the absence of catalyst was used.

Tritiation of Lincomycin—Three grams of lincomycin free base was submitted[2] for tritiation. The sample was exposed to 15 c. of carrier-free tritium gas for 2 weeks at 27° and 660 mm. Hg pressure. The crude material was twice dissolved in 25 ml. of water and freeze dried to give 2.922 g. of material with a specific activity of 19.26 μc./mg.

Purification of Lincomycin-^{3}H—A 2.8 × 57-cm. column of 200–400-mesh Dowex 50WX8 was washed with water, 2 *N* NH_4OH, water, 2 *N* HCl, and 0.1 *N* HCl in that order. The freeze-dried crude material was loaded onto the column, which was then eluted with 1.4 l. of 0.1 *N* HCl and 1.5 l. of water. Elution was continued with 1.5 l. of 2 *N* NH_4OH, which was collected in 17-ml. fractions at 12 min./fraction. Monitoring the radioactivity of the ammonium hydroxide eluate indicated that the desired product appeared in fractions 34–47. These fractions were combined and concentrated at water-aspirator pressure and 36°. The residue was recrystallized by dissolving in 1 *N* HCl (1 g./ml.) followed by the addition of 10 volumes of acetone. The resulting crystalline material was repeatedly recrystallized until constant specific activity was achieved on successive recrystallizations.

Two final samples were obtained. One sample, weighing 882 mg. with a specific activity of 2.45 μc./mg., was analyzed by paper chromatography with a solvent mixture of *n*-butanol–acetic acid–water (2:1:1). It was also analyzed by TLC on silica gel with the following solvent systems: I, methanol; II, *n*-butanol–acetic acid–water (2:1:1); and III, methyl ethyl ketone–acetone–water (3:1:1). Radioactivity analyses of the papergram and thin-layer plates showed that the material was radiochemically pure.



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[1] Cleocin, The Upjohn Co., Kalamazoo, Mich.

[2] To New England Nuclear Corp., Boston, Mass.

Table I—Recovery of Radioactivity of Clindamycin-^{3}H from Female Rats

	Percent of Administered Dose — Rat Number				
	1	2	3	4	Mean ± *SD*
Oral Administration					
Urine	20.76	33.30	26.93		27.04 ± 5.12
Feces	74.06	62.26	69.10		68.47 ± 4.84
^3H_2O in urine	0.91	1.06	1.63		1.20 ± 0.31
Total	94.96	95.56	96.03		95.51 ± 0.44
Intraperitoneal Injection					
Urine	31.37	21.49	29.30	28.56	27.73 ± 3.7
Feces	66.82	73.95	73.43	66.87	67.76 ± 3.5
^3H_2O in urine	1.20	0.61	0.86	1.42	0.89 ± 0.34
Total	98.40	85.44	102.73	95.43	95.50 ± 6.36

The second sample, weighing 447 mg. with a specific activity of 2.59 μc./mg., was shown to be identical to the first sample by TLC on silica gel with Solvent System III. These two samples were combined for use in the subsequent step.

Preparation of Clindamycin-^{3}H—Twenty milliliters of carbon tetrachloride was added to a stirred slurry of 1.315 g. (2.94 mmoles) of tritiated lincomycin hydrochloride, 3.86 g. (14.72 mmoles) of triphenylphosphine, and 16 ml. of acetonitrile. The mixture was stirred at room temperature under nitrogen for 18 hr. The resulting clear solution was concentrated at reduced pressure, and the residue was dissolved in 20 ml. of water. The insoluble triphenylphosphine oxide was removed by filtration. The filtrate was basified with 6 *N* NaOH solution, and the liberated free base was extracted into 2 × 15 ml. of chloroform. The combined extracts were washed and saturated with sodium chloride solution and concentrated at reduced pressure. The residual oil was dissolved in 20 ml. of methanol, and the solution was refluxed for 1 hr. and concentrated at reduced pressure. The residue was dissolved in about 20 ml. of 0.1 *N* HCl. The insoluble solids were removed by filtration, and the filtrate was extracted with carbon tetrachloride. The aqueous phase was then basified with 6 *N* NaOH and extracted with 2 × 15 ml. of chloroform. The combined chloroform extracts were washed with saturated sodium chloride solution and dried over magnesium sulfate. The dried chloroform solution was concentrated at reduced pressure, and the residual oil was dissolved in a mixture of 2 ml. of ethanol and 7 ml. of ethyl acetate and treated with anhydrous ethanolic hydrochloric acid.

Cooling the mixture in a refrigerator overnight gave the crystalline product, which was dried in a vacuum desiccator over phosphorus pentoxide. The product obtained, 488 mg. (37.2% yield), had

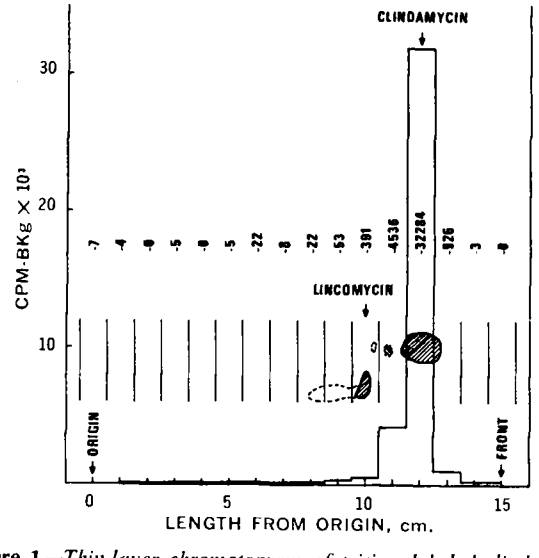

Figure 1—*Thin-layer chromatogram of tritium-labeled clindamycin on silica gel with a solvent system of methyl ethyl ketone–acetone–water (3:1:1).*

Table II—Urinary and Total Excretion Half-Times[a] of Clindamycin-^{3}H Radioactivity in Female Rats

Rat Number	Urine, $t_{1/2}$, hr.	Total, $t_{1/2}$, hr.
Oral Administration		
1	4.1	19.2
2	4.9	25.0
3	4.0	20.6
Average	4.3 ± 0.4	21.60 ± 2.5
Intraperitoneal Injection		
1	7.9	38.0
2	11.0	14.4
3	10.0	42.7
4	8.9	30.0
Average	9.45 ± 1.17	31.28 ± 10.8

[a] Half-times are measured graphically from the plots of $U_\infty - U_t$ *versus* time.

a specific activity of 2.386 μc./mg. This material was chromatographed on a silica gel thin-layer plate with lincomycin hydrochloride and clindamycin hydrochloride standards in Solvent System III (Fig. 1). Analyses of radioactivity on the thin-layer plate indicated that the material was 98.64% radiochemically pure, while 0.90% of the total radioactivity appeared in the same region as lincomycin hydrochloride. Its IR spectrum was identical to form I clindamycin hydrochloride standard.

Anal.—Calc. for $C_{18}H_{34}Cl_2N_2O_5S$ (mol. wt. 461.45): C, 46.85; H, 7.43; Cl, 15.37; N, 6.07; S, 6.95. Found: C, 46.92; H, 7.79; Cl, 14.98; N, 5.68; S, 7.10.

Dosage and Collection of Samples—*Absorption and Excretion Studies in Rats*—Three female Sprague–Dawley (Upjohn strain) rats, with an average weight of 181 g., were used in the oral administration experiments. These rats were fasted for 12 hr. and loaded with 10 ml. of water before dosing. Each rat accepted, through a stomach tube, 1.5 ml. of the solution containing 1.54 mg. of the tritium-labeled clindamycin hydrochloride and 18.7 mg. of the carrier drug. The radioactivity dose was 3.6 μc./rat. The rats were then placed in stainless steel metabolism cages with free access to food and water, and urine and feces samples were collected.

In the intraperitoneal injection experiments, four female Sprague–Dawley rats (average weight 190 g.) were used. Each rat was loaded with 5 ml. of water before being injected with 0.5 ml. of an aqueous solution containing 1.85 mg. of the tritium-labeled drug and 28.40 mg. of the cold drug. The radioactivity dose was 4.42 μc./rat. Urine and feces samples were collected for 14 days in the same way as in the oral experiment.

Absorption and Excretion Studies in Dogs—Three male beagle dogs, weighing 11.7, 8.9, and 8.2 kg., respectively, were used. The labeled drug was given orally in hard filled capsules or intramuscularly as a solution. The intramuscular experiment was carried out 8 weeks after the oral experiment to ensure that the dogs retained no residual radioactivity from the first treatment.

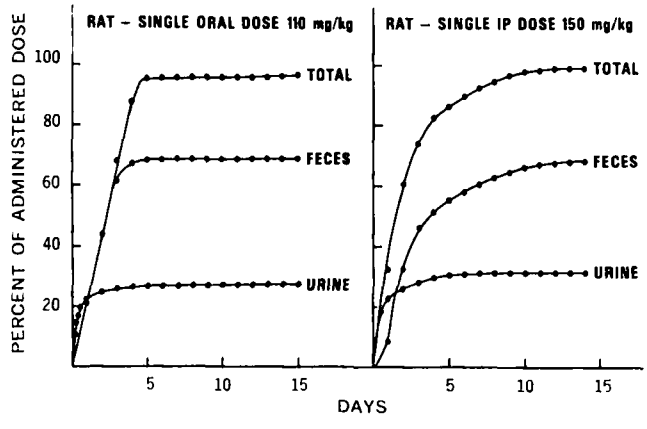

Figure 2—*Cumulative excretion of clindamycin-^{3}H radioactivity by female rat.*

Table III—Recovery of Clindamycin-^{3}H Radioactivity from Male Beagle Dogs

Route of Administration	Mode	Percent of Administered Dose: Dog B67-104 (11.7 kg.)	Dog G67-305 (8.9 kg.)	Dog G67-501 (8.2 kg.)	Mean ± *SD*
Oral administration	Urine	26.70	32.83	31.26	30.29 ± 2.56
	Feces	57.57	53.19	54.42	55.06 ± 1.85
	Total	84.36	86.02	85.67	85.35 ± 0.72
Intramuscular injection	Urine	21.73	27.06	34.42	27.74 ± 5.20
	Feces	71.99	67.50	52.13	63.87 ± 8.50
	Cage Wash	0.10	—	0.64	—
	Total	93.82	94.56	87.19	91.86 ± 3.31

Table IV—Parameters of Urinary and Total Excretion of Clindamycin-^{3}H Radioactivity in Male Beagle Dogs

Parameter	Dog B67-104 Oral	Dog B67-104 Intramuscular	Dog B67-305 Oral	Dog B67-305 Intramuscular	Dog G67-501 Oral	Dog G67-501 Intramuscular	Mean ± *SD* Oral	Mean ± *SD* Intramuscular
Urinary excretion half-time, hr.	4.0	9.12	4.5	8.16	3.8	8.64	4.1 ± 0.29	8.64 ± 0.39
Time required to excrete 90% of the urinary radioactivity, hr.	24	36	24	36	36	36	28	36
Combined urinary and fecal excretion half-time, hr.	7.68	11.04	8.16	10.08	8.16	12.48	8.00 ± 0.23	11.20 ± 0.98
Time required to excrete 90% of the total radioactivity, hr.	24	48	36	48	36	48	32	48

In the oral experiment, both labeled and carrier drugs were weighed into hard-gelatin capsules individually for each dog. Ten milligrams of the labeled drug was also weighed into a volumetric flask for standardization of the radioactivity and correction for decay losses. Dogs were fasted for 18 hr. before dosing and were fed 4 hr. after dosing. Food[3] was given once a day and water was given *ad libitum* throughout the 2-week period. On the 1st and 2nd days, food wetted with water was given to increase the urine output.

Blood samples were collected from the jugular vein immediately before dosing and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, and 48 hr. after dosing. Samples were obtained by using heparinized tubes[4], and plasma was prepared by centrifugation. Urine samples were collected every 4 hr. for the first 12 hr. by catheterization and once a day in stainless steel metabolism cages for the next 2 weeks. Fecal samples were collected as soon as they were seen or at least once a day. They were weighed and homogenized with water to make 20% homogenates. All samples were frozen immediately until analysis for radioactivity.

In the intramuscular experiment, 500 mg. of the drug containing 47.78 μc. of the labeled drug was dissolved in 2 ml. of sterile normal saline and the solution was injected as two split doses of 1 ml. each into the two hindlegs. The dogs were fed 1 hr. after dosing. The rest of the feeding schedules and the collections of blood, urine, and feces were the same as for the oral experiment.

Counting of Radioactivity—A counting medium[5] was used for direct counting of synthetic samples, urine, and tritiated water. A toluene–methanol–4% 2,5-diphenyloxazole/0.04% 1,4-bis-2-(4-methyl-5-phenyloxazolyl)-benzene mixture (9.25:5:0.72) was used for combusted samples. All solvents were reagent grade and were used without further purification.

Radioactivity in all samples was counted by the liquid scintillation technique, with the internal standard method to correct for quenching losses. Synthetic samples were dissolved in appropriate volumes of methanol, and 1.0-ml. aliquots were mixed with 15 ml. of counting solvent. Urine samples were counted directly after mixing 0.5-ml. aliquots with 15 ml. of counting solvent. Blood plasma (0.5-ml.) samples were dried in cellophane bags and combusted by the Schöniger oxygen flask procedure (7). The tritiated water generated from the combustion was collected in 17 ml. of counting solvent, and 15 ml. of the mixture was counted. Aliquots of fecal homogenate were weighed, dried, and combusted in the same way as the plasma samples. Tritiated water in the urine was separated by lyophilization, and 0.5 ml. of the condensate was counted directly as described for the urine samples.

All samples were analyzed in duplicate and counted twice to minimize any error in handling.

[3] Purina dog chow.
[4] Vacutainer.
[5] The Diotol counting solvent used is a mixture of 300 ml. of toluene, 210 ml. of methanol, 350 ml. of 1,4-dioxane, 73 g. of recrystallized naphthalene, and 50 ml. of 4% 2,5-diphenyloxazole and 0.04% 1,4-bis-2-(4-methyl-5-phenyloxazolyl)-benzene.

RESULTS

Absorption and Excretion of Clindamycin-^{3}H Radioactivity in Rats—Table I lists the total recovery from both experiments. When the drug was orally administered, a mean of 27.04% of the total radioactivity was excreted in the urine and 68.47% in the feces. The mean total recovery after 2 weeks was 95.51%. A very small amount of tritiated water was found in the urine (1.2%). Assuming that the same amount of tritiated water was eliminated in the expired air, the total quantity of tritiated water produced would be 2.4% of the dose.

The same excretion pattern was obtained when the drug was injected intraperitoneally. A mean of 27.73% of the total radioactivity was excreted through the kidney and 67.76% in the feces. The mean total recovery was 95.5%. Only 0.89% of the total radioactivity was found in the urine as tritiated water, corresponding to 1.78% if the expired air is included.

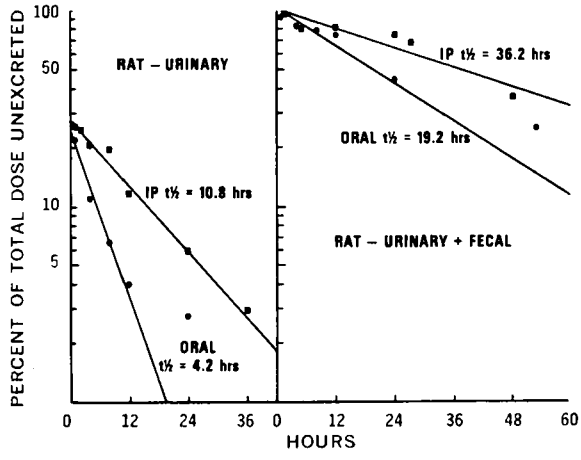

Figure 3—*Urinary and combined urinary and fecal excretion of clindamycin radioactivity by female rat.*

Table V—Parameters of Plasma Clindamycin-^{3}H Radioactivity in Male Beagle Dogs

	Dog B67-104		Dog G67-305		Dog G67-501		Mean ± *SD*	
	Oral	Intramuscular	Oral	Intramuscular	Oral	Intramuscular	Oral	Intramuscular
Maximum concentration (uncorrected), mg./ml.	43.577	18.70	61.245	43.26	63.178	41.01	56.00	34.32
Maximum concentration (corrected for dose level), (mcg./ml.)/(mg./kg.)	0.861	0.438	0.921	0.770	0.875	0.672	0.886 ± 0.026	0.627 ± 0.140
Time of maximum, hr.	2	5	2	5	3	4	2.33 ± 0.47	4.67 ± 0.47
Disappearance half-time, hr.	4.00	5.65	4.40	5.37	3.20	5.50	3.87 ± 0.50	5.55 ± 0.39
Area under the curve (uncorrected), mcg.-hr./ml.	292.48	250.91	521.80	473.75	482.83	564.69	432.30	429.78
Area under the curve (corrected for dose level), (mcg.-hr./ml.)/(mg./kg.)	5.78	5.87	7.84	8.43	6.68	9.26	6.77 ± 0.85	7.85 ± 1.44
Relative absorption efficiency, %	98.45	100	93.03	100	72.21	100	87.90 ± 11.3	100

Since the intraperitoneally injected dose was presumably absorbed quantitatively, the identical distribution of radioactivity excreted after the two routes of administration suggested that oral absorption was also quantitative.

Figure 2 shows cumulative urinary, fecal, and total excretion of radioactivity after both routes of administration. Excretion was rapid in the urine but slow in the feces. Eighty-six percent of the radioactivity excreted in the urine was excreted in the first 48 hr. Fecal excretion was relatively slow and irregular. With both routes of administration, it took 120 hr. before 90% of the total fecal radioactivity was recovered.

During the first 24 hr. after administration, the percent urinary excretion of radioactivity from the oral (22.40 ± 4.0) and intraperitoneal (22.20 ± 2.37) doses was equivalent. During the same period, fecal excretion eliminated 29.68 ± 8.86% of the oral dose but only 8.79 ± 6.0% of the intraperitoneal dose. The difference apparently indicated that the transport of this drug to the bile was substantially slower after intraperitoneal than oral administration.

Although the different routes of drug administration did not appear to affect the distribution of total radioactivity in urine and feces, they did affect the initial rate of excretion (Fig. 3). The semilogarithmic plots clearly show that the initial rate of urinary excretion of the orally administered clindamycin radioactivity was twice as fast as the intraperitoneally injected dose. Table II lists the estimated half-lives for appearance of radioactivity in the excretions of each rat in this experiment. The average half-time for urinary excretion was 4.3 hr. for the oral dose in contrast to 9.45 hr. for the intraperitoneal dose. The half-times for the total elimination of the drug, as obtained by combining the urinary and fecal excretions of radioactivity at each time interval, also showed that the orally administered dose was excreted faster than the injected dose.

Absorption and Excretion of Clindamycin-^{3}H Radioactivity in Dogs—Two weeks after the administration of clindamycin-^{3}H, the average recoveries of radioactivity from three dogs in the oral experiment were 30.29 ± 2.56% from urine, 55.06 ± 1.85% from feces, and 85.35 ± 0.72% total. On the other hand, 27.74 ± 5.2% of the intramuscular dose appeared in the urine and 63.85 ± 8.5% in the feces. The total recovery in this case was 91.86 ± 3.31%. Recovery data for each individual dog are listed in Table III.

Figure 4 shows cumulative urinary, fecal, and total excretion of radioactivity after each route of administration. The identical distribution of radioactivity between urine and feces again suggested quantitative oral absorption. In all cases, only trace amounts of tritiated water were found in the urine. This indicated good stability of the radioisotope label in the drug during metabolic transformations.

Semilogarithmic plots for excretion of clindamycin-^{3}H radioactivity are presented in Fig. 5. The patterns in both urinary and overall excretion appear to be similar to that of the rat (Table IV). Both plots show that the dose of orally administered clindamycin was eliminated faster than the intramuscularly injected dose.

In the initial phase of the urinary excretion, the average elimination half-life after intramuscular administration was 8.64 ± 0.39 hr. compared with 4.10 ± 0.29 hr. after oral administration, which indicated that the drug and metabolites were eliminated 2.1 times more rapidly through the kidney after oral dosing. On the other hand, in the initial phase of the total excretion, the average elimination half-life after intramuscular administration was 11.20 ± 0.98 hr. compared to 8.0 ± 0.23 hr. *via* the oral route. This implies that the drug was eliminated 1.4 times more rapidly following oral than intramuscular administration. The delayed excretion following intramuscular administration was believed due to drug precipitation at the injection site or a difference in the transport process.

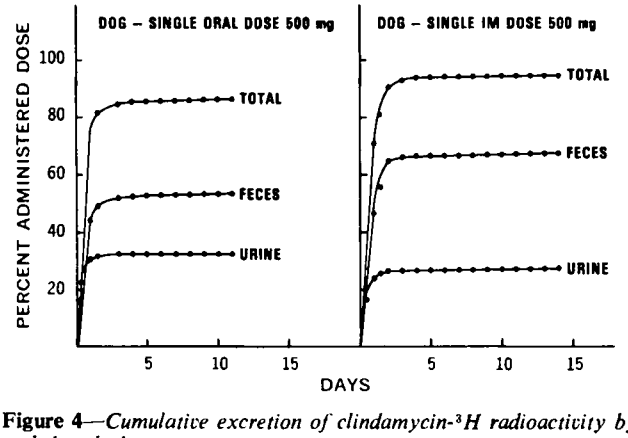

Figure 4—*Cumulative excretion of clindamycin-^{3}H radioactivity by male beagle dog.*

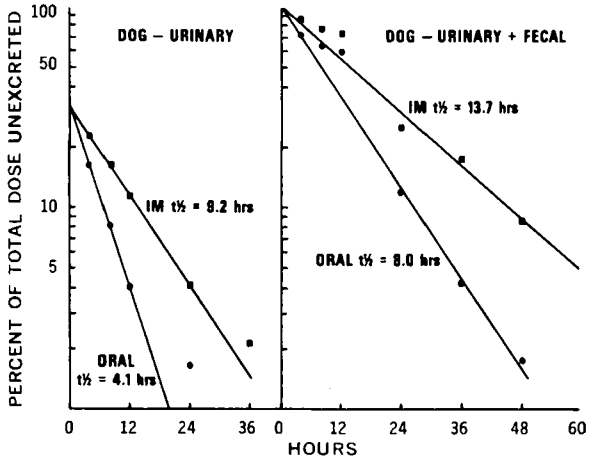

Figure 5—*Urinary and combined urinary and fecal excretion of clindamycin radioactivity by male beagle dog.*

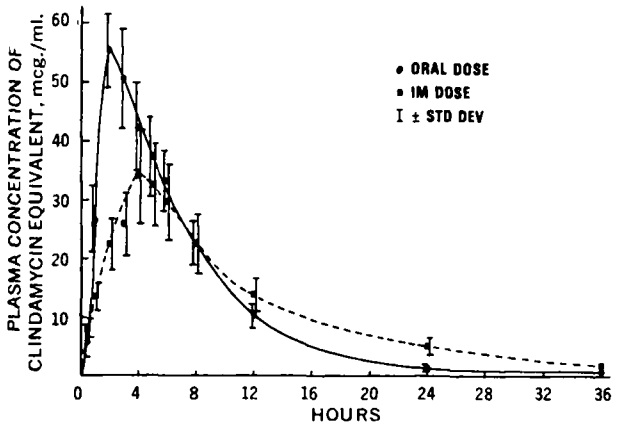

Figure 6—*Plasma concentration of clindamycin and metabolites (expressed as micrograms of clindamycin equivalent per milliliter of plasma) in dogs after oral (●) or intramuscular (■) administration of tritium-labeled clindamycin hydrochloride.*

Figure 6 shows the plasma levels of clindamycin radioactivity in dogs after two different routes of drug administration. When drug was administered orally, a peak concentration of 56-mcg. drug equivalents/ml. was observed at 2–3 hr. with a disappearance half-time of 3.8 hr. When drug was given intramuscularly, a peak concentration of 34-mcg. drug equivalents/ml. was observed at 4–5 hr. The disappearance half-time was estimated to be 5.5 hr.

Table V lists the parameters of plasma clindamycin concentration curves obtained for the three dogs. After the dosage levels were corrected to account for the slight differences in body weight, the mean areas under the plasma concentration curve per milligram dose per kilogram body weight were 6.77 ± 0.85 and 7.85 ± 1.44 mcg./hr./ml. for the oral and intramuscular doses, respectively. The ratio of the areas indicated that an average of 87.9 ± 11.3% of the drug was absorbed orally.

The plasma drug disappearance half-times were estimated graphically to be 3.87 ± 0.50 hr. for the orally administered dose and 5.55 ± 0.39 hr. for the intramuscularly injected dose. These values only represent the initial drug and/or metabolite disappearance in the first 12-hr. period since the curves deviate from the first-order kinetics after that period. A small secondary peak occurred after the animals were fed, strongly suggesting enterohepatic recirculation of drug and/or metabolites.

DISCUSSION

Based upon the described data it appears that orally administered clindamycin hydrochloride is rapidly and nearly quantitatively absorbed by rats and dogs. The drug is also rapidly excreted through both kidney and bile. However, the injected dose is absorbed and excreted much slower than the oral dose. These observations are consistent with the results of Novak *et al.* (5) in their study of absorption and excretion of intramuscularly administered clindamycin in man.

The absorption efficiencies of orally administered drug for each individual dog, as estimated by urinary excretion and areas under the plasma concentration curve, were not identical but were consistent. Both estimations show that orally administered drug was absorbed nearly quantitatively in Dogs B67-104 and G67-305 but only 70–90% in Dog G67-501. The difference is not considered significant.

The delayed absorption of the injected dose was suggested by Novak *et al.* (5) as being caused by the precipitation of the drug at the injection site. Since most of the drug at pH 7.4 (extracellular fluid pH) exists as the free base with low aqueous solubility and since the fluid volume in the injection site is limited, it is possible that the injected dose acts as if the drug were given in aqueous suspension. In addition, local swelling and irritation were observed at the injection site and persisted for 5–6 hr. This finding would be inconsistent with this postulation.

The lower plasma level and the slower initial rate of excretion of clindamycin radioactivity after intramuscular administration than after oral administration in dogs could also be caused by a difference in transport processes. The oral dose was absorbed and went through the portal system to the liver, where the entire dose was exposed to metabolism. On the other hand, the parenterally administered dose was absorbed into the venous system and delivered to the heart. Only a fraction of the cardiac output passes through the liver in each circulation.

However, the same argument cannot be used to explain the delayed excretion of the intraperitoneally administered clindamycin in the rat. Lukas *et al.* (8) recently showed that drugs administered intraperitoneally are absorbed primarily through the portal circulation and pass through the liver before reaching other organs. Therefore, the delay of excretion must be related to the slow absorption process through the peritoneal membrane, either due to local precipitation of the drug or other unknown reasons.

A similar case was reported by Burns *et al.* (9) in their study of phenylbutazone absorption. This drug was rapidly and completely absorbed from the GI tract in man but very slowly absorbed after intramuscular injection. The peak plasma concentration was reached 2 hr. after oral administration; but if an intramuscular dose was given, the peak was not observed until 6–10 hr. afterward. In this case, however, Burns *et al.* (9) proved that the cause of the delayed absorption was drug precipitation at the site of injection.

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