Excretion, Distribution, and Metabolism of Primaquine in Rats

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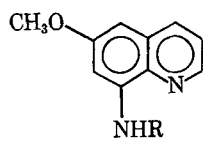
Abstract □ The metabolism of the 8-aminoquinoline antimalarial drug, primaquine (I) was studied using rats. The drug was administered intravenously, intraperitoneally, and orally, and blood samples were collected at various time intervals. Primaquine was metabolized by oxidative deamination to give 8-(3-carboxy-1-methylpropylamino)-6-methoxyquinoline (III). The plasma levels of both primaquine and its metabolite were determined by HPLC. The tissue distributions of radioactive primaquine after intravenous, intraperitoneal, and oral administrations were also determined. Significant concentrations of radioactivity were found in the lungs, adrenal glands, and liver. In addition, a significant portion of the dose was found to be excreted in the feces within 24 h after administration of the drug by either of the three routes.

Keyphrases □ Primaquine—excretion, distribution, and metabolism in rats □ 8-(3-Carboxy-1-methylpropylamino)-6-methoxyquinoline—primaquine metabolite, excretion and distribution in rats □ Metabolism—primaquine in rats, excretion and distribution

Primaquine (I), an 8-amino-6-methoxyquinoline derivative used for the treatment of malaria, is active against the exoerythrocytic forms of *Plasmodium vivax* and *Plasmodium ovale* and against the gametocytes of *Plasmodium falciparum*, thus inhibiting sporogony (1). Primaquine has a low chemotherapeutic index, therefore greatly limiting its prophylactic and therapeutic applications. It is known to induce hemolytic lesions in patients suffering from a deficiency in glucose 6-phosphate dehydrogenase, a genetic condition most common among inhabitants of regions in which malaria is endemic.

Although earlier workers suggested that one or more metabolites of primaquine may be responsible for its toxicity and/or antimalarial activity, very little has actually been accomplished in identifying the metabolite(s) of primaquine. Studies with other 8-aminoquinolines such as pamaquine and pentaquine have indicated that these drugs are metabolized very rapidly (2–6); it was speculated that primaquine might undergo a similar fate. Based on earlier work with pentaquine (6) and pamaquine (7), it was proposed that primaquine underwent metabolic degradation by *O*-demethylation of the 6-methoxy group followed by hydroxylation at the 5-position and oxidation to give a 5,6-quinone derivative. It was further speculated that this product was capable of oxidation–reduction activity and, therefore, may account for the hemolytic activity of primaquine (8). None of these proposed metabolites have actually been characterized from humans or animals; however, 6-methoxy-8-aminoquinoline (II) was identified as a metabolite of primaquine in the urine of humans (9).

We have recently reported the identification of 8-(3-carboxy-1-methylpropylamino)-6-methoxyquinoline (III) as the major metabolite of primaquine in rat plasma after intravenous injection (10); this is also the major metabolite in several species of fungi (11). We report herein further studies on the metabolism and distribution of primaquine after intravenous, intraperitoneal, and oral administrations.



I: R = —$CH(CH_3)CH_2CH_2CH_2NH_2$
II: R = H
III: R = —$CH(CH_3)CH_2CH_2CO_2H$

EXPERIMENTAL

Source of Compounds—Commercially available primaquine diphosphate (I) was used as received[1]. [2,4-^{14}C]Primaquine diphosphate[2] had a specific activity of 1.55 mCi/mmol. 8-(3-Carboxy-1-methylpropylamino)-6-methoxyquinoline (III) was prepared by microbial transformation of primaquine as previously described (11).

Determination of Plasma Levels of Primaquine and Its Metabolite—Male Wistar rats (200–300 g) were anesthetized with sodium pentobarbital (30 mg/kg ip). Primaquine diphosphate was administered either intravenously (10 or 20 mg/kg), intraperitoneally (20 mg/kg), or orally (20 mg/kg) as an aqueous solution in distilled water (40 mg/mL). Multiple blood samples were collected from the intraorbital sinus vein in two 50-μL heparanized capillary tubes at 1, 3, 15, 30 min, and 1, 3, 6, 12, and 24 h after dosing.

After centrifugation in a hematocrit centrifuge for 2 min, the plasma was analyzed using an HPLC procedure shown to be specific for III and primaquine (10). HPLC analyses utilized a C_{18} reverse-phase column[3] (10 μm) with a mobile phase consisting of 6.6 g of K_2HPO_4, 8.4 g of KH_2PO_4, 2.4 L of methanol, 1.6 L of water, and 4 g of *N,N*-dimethyloctylamine (flow rate = 1 mL/min) (10). The sample size consisted of 20 μL of plasma, and detection was accomplished using a dual-wavelength UV detector (254 and 280 nm). For pharmacokinetic studies, the carboxylic acid metabolite (III) was injected at a dosage of 12 mg/kg iv, the molar equivalent to the primaquine diphosphate dosage of 20 mg/kg. Blood samples were collected from the intraorbital sinus vein at 1, 3, 15, 30 min, and 1, 3, 6, 12, and 24 h postadministration. After centrifugation, the plasma samples (20 μL) were analyzed directly by HPLC.

Tissue Distribution of [2,4-^{14}C]Primaquine Diphosphate—Fifty-four male Wistar rats (200–300 g) were anesthetized with sodium pentobarbital (30 mg/kg of body weight ip). An aqueous solution consisting of a 9:1 mixture of primaquine diphosphate and [^{14}C]primaquine diphosphate was administered intravenously (10 mg/kg), intraperitoneally (20 mg/kg), and orally (20

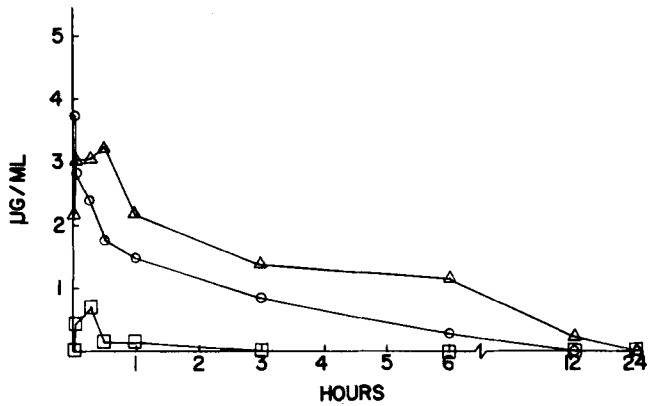


Figure 1—*Plasma concentration of primaquine diphosphate after intravenous (○), intraperitoneal (△), and oral (□) administrations of primaquine diphosphate. Each value represents the average of two animals.*

[1] Aldrich Chemical Co., Milwaukee, Wis.
[2] New England Nuclear, Boston, Mass.
[3] μ-Bondapak; Waters Associates, Milford, Mass.

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Table I—Area Under the Plasma Concentration *versus* Time Curve (AUC) for Primaquine Diphosphate after a 20-mg/kg Dose

Route	Subject	AUC[a], μg/mL·h	Amount Absorbed[b], %
Intravenous	A	9.11	
	B	3.94	
	C	7.98	
	D	4.14	
Mean ± *SD*		6.29 ± 2.6	
Oral	E	3.51	56
	F	0.55	8
	G	0.77	12
Mean ± *SD*		1.61 ± 1.64	25 ± 26

[a] AUC for primaquine diphosphate. [b] Percent absorption as determined from the AUC when primaquine diphosphate was administered orally compared with the AUC when it was administered intravenously.

mg/kg). The rats were sacrificed at 1, 3, 15, 30 min, and 1, 3, 6, 12, and 24 h after administration; two rats were used for the determination of each time point for each route of administration. A blood sample was collected by cardiac puncture and the following organs and tissues were removed: lungs, kidneys, adrenal glands, heart, liver, spleen, pancreas, brain, abdominal muscle, abdominal fat, small intestine, large intestine, testes, and stomach. After the total wet weight of each organ was determined, a portion (100–200 mg) was taken for combustion. The tissue samples were burned in a sample oxidizer[4] and the [^{14}C]carbon dioxide was trapped with a carbon dioxide absorber[5]. The trapped [^{14}C]carbon dioxide was diluted in an organic scintillation cocktail[6], and the radioactivity of each sample was measured in a liquid scintillation counter[7]. Radioactivity in the various tissues was expressed as

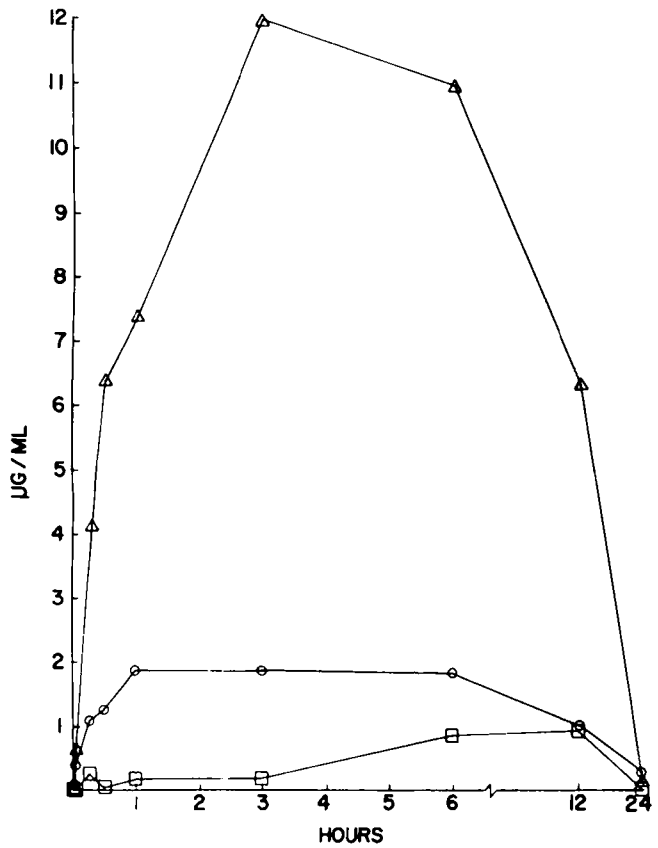

Figure 2—*Plasma concentrations of 8-(3-carboxy-1-methylpropylamino)-6-methoxyquinoline (III) after intravenous (○), intraperitoneal (△), and oral (□) administrations of primaquine diphosphate. Each value represents the average of two animals.*

[4] Packard Tri-Carb Sample Oxidizer Model 306; Packard Instrument Co., Downers Grove, Ill.
[5] Carbosorb; Packard Instrument Co., Downers Grove, Ill.
[6] Perma-Fluor V; Packard Instrument Co., Downers Grove, Ill.
[7] Packard Tri-Carb Liquid Scintillation Spectrometer Model 3255; Packard Instrument Co., Downers Grove, Ill.

Table II—Area Under the Plasma Concentration *versus* Time Curves for 8-(3-Carboxy-1-methylpropylamino)-6-methoxyquinoline (III)

Drug Given	Dose, mg/kg	Subject	AUC[a], μg/mL·h	Conversion to Metabolite[b], %
Primaquine diphosphate	20 iv	H	166	63.6
		I	14.7	5.63
		J	28.5	10.9
		K	22.6	8.67
Mean ± *SD*			57.9 ± 72	22 ± 28
Primaquine diphosphate	10 iv	L	20.2	15.5
		M	25.6	19.6
		N	21.3	16.3
Mean ± *SD*			22.4 ± 2.9	17.1 ± 2.2
Primaquine diphosphate	20 ip	O	56.4	21.6
		P	106.3	40.7
		Q	192.9	73.9
Mean ± *SD*			118.5 ± 69.1	45 ± 26
Primaquine diphosphate	20 po	R	7.08	2.71
		S	7.55	2.89
		T	17.95	6.88
Mean ± *SD*			10.8 ± 6.1	4.2 ± 2.4
Carboxylic acid	12[c] iv	U	216	
		V	298	
		W	270	
Mean ± *SD*			261 ± 42	

[a] Area under the plasma concentration *versus* time curve for metabolite III. [b] Percent conversion as determined from the curve area of III when primaquine diphosphate was administered and curve area when III was administered directly (iv). [c] Molar equivalent to 20 mg/kg of primaquine diphosphate.

the relative concentration (12), defined as (counts of radioactivity in an organ/total radioactivity dose) × (weight of animal/weight of organ).

Determination of Radioactivity in Plasma After Administration of [^{14}C]-Primaquine Diphosphate—[^{14}C]Primaquine diphosphate (1.55 mCi/mmol) was injected intravenously into a single rat at a dose of 10 mg/kg. After 3 h, a blood sample was collected by cardiac puncture, and the rat was sacrificed. The blood was centrifuged, and a portion of the plasma (20 μL) was injected into the HPLC. A total of 16 fractions (1 mL each) were collected, and each fraction was diluted with 15 mL of scintillation cocktail[8]. The radioactivity of each fraction was measured using a liquid scintillation counter[7]. To determine the total radioactivity, a 20-μL portion of the plasma was also diluted with 1 mL of the HPLC mobile phase and 15 mL of scintillation cocktail, and the radioactivity was measured.

RESULTS AND DISCUSSION

Primaquine diphosphate was administered intravenously, intraperitoneally, and orally to male rats, blood was collected at various time intervals, and the plasma was analyzed by HPLC for primaquine (I) and its metabolite (III). After intravenous injection of primaquine diphosphate, the drug disappeared very rapidly from the blood ($t_{1/2} \sim 1$ min). Within 1 min after administration of the dose, the plasma concentration was only 1–5% of the value one would expect if there were an even distribution of the drug in the blood (Fig. 1). This extremely rapid fall in plasma concentration was also observed using ^{14}C-labeled primaquine, where at 1 min after intravenous administration, the relative concentration in blood was 0.22 and in the lung a value of 4.90 was observed. These observations were consistent with the observations of other workers (13, 14) using structurally related drugs, who found that if a given drug contained a basic aliphatic amino group ($pK_a > 8.5$) that was joined to a lipophilic aromatic ring system, the drug would rapidly ($t_{1/2} < 3$ min) accumulate in the lung tissue. Primaquine also contains an aliphatic amine side chain ($pK_a = 10.39$) with a very lipophilic aromatic ring system, which probably accounted for its rapid disappearance from plasma and accumulation in the lung tissue.

After intravenous administration of primaquine diphosphate (20 mg/kg), an initial rapid drop in plasma concentration of primaquine was observed, followed by a considerably slower fall in the plasma level ($t_{1/2} = 2.24 \pm 0.82$ h). When the animals were dosed at a lower level (10 mg/kg), essentially the same half-life was observed ($t_{1/2} = 1.88 \pm 0.35$ h). After intraperitoneal administration of primaquine diphosphate, the plasma levels of primaquine reached a maximum ~30 min (Fig. 1) after administration of the dose, then began to fall at about the same rate that was observed for the intraveneous dose. Following oral administration of primaquine diphosphate (20 mg/kg), the plasma level of primaquine (Fig. 1) never rose above 1.0 μg/mL. From

[8] Insta-gel; Packard Instrument Co., Downers Grove, Ill.

Table III—Relative Concentration of Radioactivity in Tissues after Intravenous Administration of [^{14}C]Primaquine Diphosphate [a]

Tissue	1 min	3 min	15 min	30 min	1 h	3 h	6 h	12 h	24 h	AUC
Lungs	4.90	4.97	4.88	2.69	2.33	1.39	0.28	0.15	0.06	12.12
Adrenal glands	2.39	8.27	3.81	2.15	3.96	1.35	0.87	2.58	0.35	40.23
Liver	1.02	1.55	3.47	1.08	1.92	0.99	0.47	0.20	0.16	11.13
Spleen	0.88	1.10	2.01	0.96	1.01	0.34	0.17	0.58	0.12	9.77
Small intestine[b]	0.50	0.50	0.77	0.68	1.00	4.68	11.23	1.69	0.33	50.88
Large intestine[b]	0.28	0.24	0.26	0.15	0.25	0.09	8.06	7.00	2.07	112.37
Kidney	1.95	3.56	2.56	0.76	0.78	0.57	0.37	0.42	0.37	11.37
Heart	2.43	2.35	1.08	0.40	0.58	0.24	0.17	0.12	0.08	4.36
Stomach[b]	0.11	0.05	0.84	0.55	1.22	0.78	0.18	0.86	0.05	12.73
Blood	0.22	0.19	0.27	0.12	0.28	0.21	0.19	0.08	0.06	2.94
Pancreas	0.77	1.26	0.42	0.56	0.56	0.15	0.12	0.16	0.06	3.88
Abdominal muscle	0.35	0.56	0.62	0.46	0.31	0.08	0.08	0.19	0.05	3.34
Abdominal fat	0.30	0.24	0.29	0.21	0.14	0.18	0.15	0.09	0.05	2.59
Brain	0.13	0.27	0.22	.09	0.24	0.13	0.03	0.05	0.03	1.51
Testes	0.06	0.12	0.16	0.07	0.16	0.17	0.15	0.12	0.06	2.82

[a] Values represent the average obtained from two animals (dosage, 10 mg/kg) per data point. [b] Contents.

Table IV—Relative Concentration of Radioactivity in Tissues after Intraperitoneal Administration of [^{14}C]Primaquine Diphosphate [a]

Tissue	1 min	3 min	15 min	30 min	1 h	3 h	6 h	12 h	24 h	AUC
Lungs	2.21	1.89	5.45	4.08	4.24	3.80	0.53	0.75	0.07	27.37
Adrenal glands	1.16	1.93	5.70	3.19	5.48	2.03	0.74	0.29	0.31	21.77
Liver	3.07	3.38	5.73	1.94	3.06	1.26	0.65	0.24	0.12	15.24
Spleen	3.52	1.30	1.47	1.92	3.45	1.50	0.29	0.14	0.10	12.49
Small intestine[b]	2.22	2.20	0.75	1.07	1.13	1.65	17.25	0.90	0.23	93.51
Large intestine[b]	2.43	1.00	0.31	0.29	0.37	0.22	7.71	1.35	1.56	57.55
Kidney	0.58	1.48	1.90	1.54	1.43	1.12	0.45	0.25	0.14	10.89
Heart	0.59	0.38	0.44	0.61	0.59	0.48	0.21	0.14	0.06	4.88
Stomach[b]	0.28	0.36	0.18	1.04	0.76	1.59	0.81	0.04	0.02	9.53
Blood	0.22	0.10	0.18	0.18	0.33	0.34	0.36	0.08	0.05	4.03
Pancreas	2.75	2.77	0.72	2.18	1.27	0.69	0.22	0.18	0.06	7.63
Abdominal muscle	3.42	0.29	1.61	0.32	0.31	0.34	0.18	0.04	0.04	3.22
Abdominal fat	2.61	0.56	0.30	0.48	0.37	0.31	0.27	0.13	0.08	4.46
Brain	0.06	0.05	0.04	0.05	0.11	0.10	0.05	0.04	0.02	1.13
Testes	0.20	0.05	0.20	0.07	0.14	0.15	0.15	0.13	0.02	2.60

[a] Values represent the average obtained from two animals (dosage, 20 mg/kg) per data point. [b] Contents.

Table V—Relative Concentration of Radioactivity in Tissues after Oral Administration of [^{14}C]Primaquine Diphosphate [a]

Tissue	1 min	3 min	15 min	30 min	1 h	3 h	6 h	12 h	24 h	AUC
Lungs	0.46	0.16	0.40	0.51	0.24	1.20	0.19	0.23	0.04	6.772
Adrenal glands	0.11	0.32	1.32	0.50	0.37	0.98	0.54	0.98	0.41	17.15
Liver	0.03	0.04	0.14	0.71	0.73	1.15	0.43	0.39	0.06	9.90
Spleen	0.06	0.19	0.09	0.29	0.14	0.51	0.08	0.16	0.03	3.582
Small intestine[b]	0.04	0.03	0.06	0.11	1.35	13.44	4.87	0.87	0.08	65.571
Large intestine[b]	0.04	0.02	0.02	0.04	0.03	0.48	0.84	2.15	0.30	26.190
Kidney	0.03	0.04	0.14	0.20	0.15	0.55	0.16	0.17	0.07	4.344
Heart	0.06	0.05	0.16	0.12	0.09	0.21	0.06	0.07	0.03	1.81
Stomach[b]	0.57	11.98	41.30	53.17	19.14	13.71	8.40	2.48	0.04	149.20
Blood	0.02	0.03	0.02	0.04	0.04	0.08	0.04	0.05	0.03	1.08
Pancreas	0.47	0.11	0.05	0.33	0.13	0.26	0.08	0.08	0.03	2.23
Abdominal muscle	0.14	0.04	0.13	0.10	0.09	0.10	0.07	0.06	0.06	1.651
Abdominal fat	0.19	0.08	0.07	0.05	0.06	0.18	0.03	0.09	0.10	2.12
Brain	0.03	0.02	0.02	0.03	0.02	0.05	0.02	0.05	0.02	0.83
Testes	0.04	0.01	0.03	0.04	0.02	0.06	0.03	0.09	0.02	1.26

[a] Values represent the average obtained from two animals (dosage, 20 mg/kg) per data point. [b] Contents.

a comparison of the area under the primaquine concentration *versus* time curves of the oral and intravenous routes of administration (Table I), it was found that only 25% (range 8–56%) of the primaquine diphosphate was available to the central compartment.

Following intravenous or intraperitoneal administration of primaquine diphosphate (20 mg/kg), the plasma level of the carboxylic acid metabolite (III) was found to increase very rapidly, and after 1 h the concentration of metabolite III was far greater than that of primaquine (Fig. 2). When a pure sample of III was given at a dose equivalent on a molar basis to 20 mg/kg of primaquine diphosphate, the initial concentration of III was much greater (Fig. 3) than had been observed for primaquine. Therefore, it would appear that once the basic amino group is metabolically removed from the side chain of primaquine, the metabolite no longer has a high affinity for the lung and other tissues. In addition, the half-life of III ($t_{1/2} = 4.38 \pm 0.26$ h) was found to be twice as long as that of primaquine itself. The very high plasma concentration of the metabolite compared with primaquine (Figs. 1 and 2) could be a result of the much lower tissue affinity and longer half-life of the metabolite compared with that of the parent drug.

Following intravenous administration of primaquine diphosphate (20 mg/kg, Table II) it was found that 22% (range 5.63–63.6%) of the dose was converted to the metabolite (III). When the dose was reduced by half, essentially the same extent of conversion was observed (mean 17.1%; range 15.5–19.6%). When the primaquine diphosphate was administered intraperitoneally, the percent conversion to the metabolite was slightly higher (mean 45%, range 21.6–73.9%); however, the difference was not statistically significant at the 95% level.

Following oral administration of primaquine diphosphate (20 mg/kg, Table II), it was found that the percent of metabolite III that ultimately reached the plasma (mean 4.2%, range 2.71–6.88%) was significantly lower than that seen in the other routes of administration. Since only 25% of the primaquine that was administered orally actually reached the plasma, it would also be anticipated that the amount of the metabolite formed would be correspondingly lower if the primaquine was poorly absorbed or if the primaquine was being excreted in the bile following a first pass through the liver.

From a comparison of the HPLC analyses of the plasma of primaquine-treated animals and plasma blanks, only metabolite III and primaquine were

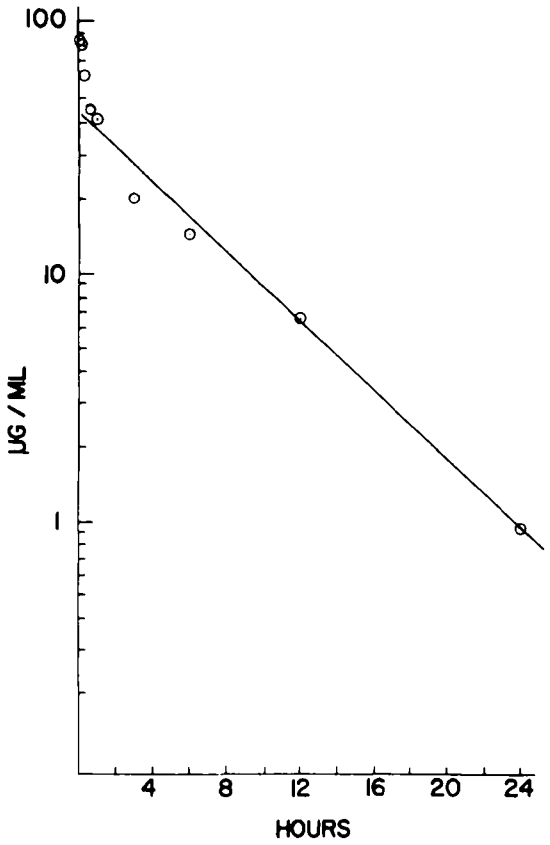

Figure 3—*Plasma concentration of 8-(3-carboxy-1-methylpropylamino)-6-methoxyquinoline (III) after an intravenous injection of III. Each value represents the average of three animals. Metabolite III showed a half-life of 4.38 ± 0.26 h.*

detected. To determine if other metabolites might have gone undetected in the plasma, a rat was administered [^{14}C]primaquine diphosphate (10 mg/kg iv; 1.55 mCi/mmol). The rat was sacrificed 3 h after administration of the labeled primaquine, and a blood sample was taken by cardiac puncture. A portion of the plasma was injected into the HPLC, and 1-mL fractions were collected. Each of the fractions was diluted with scintillation cocktail and the radioactivity was measured. It was found that 59% of the total radioactivity in the plasma could be accounted for in fractions containing the carboxylic acid metabolite (III) and 5% as unchanged primaquine.

An investigation of the tissue distribution of primaquine in rats was undertaken using ^{14}C-labeled primaquine diphosphate. While this work was in progress, Holbrook *et al.* reported on the tissue distribution of labeled primaquine in rats using [6-*O*-methyl-^{3}H]primaquine (15). In that report, the distribution of primaquine was measured in seven rat tissues (lung, liver, kidney, spleen, heart, brain, and blood) at 15–180 min after intraperitoneal administration (15). We report herein the distribution of primaquine in 15

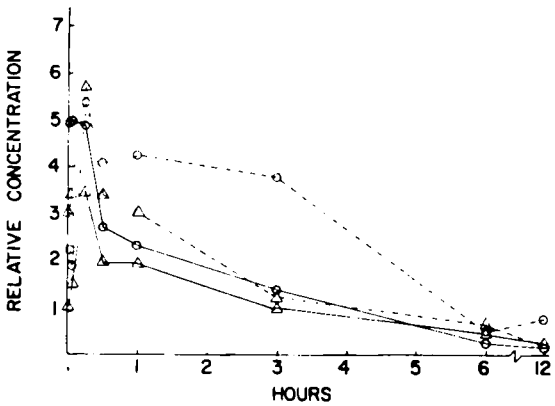

Figure 4—*Relative concentration of radioactivity in the lung (○) and liver (△) after intravenous (—) and intraperitoneal (---) administrations of [^{14}C]primaquine diphosphate. Each value represents the average of two animals.*

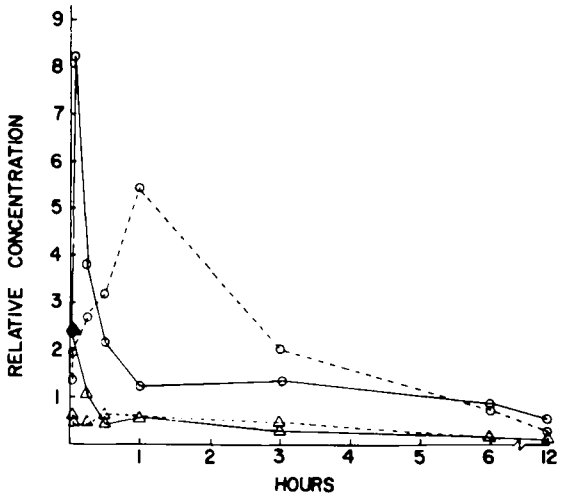

Figure 5—*Relative concentration of radioactivity in the adrenal gland (○) and heart (△) after intravenous (—) and intraperitoneal (---) administrations of [^{14}C]primaquine diphosphate. Each value represents the average of two animals.*

tissues at nine intervals from 1 min to 24 h after intravenous, intraperitoneal, and oral administration using ring-labeled [^{14}C]primaquine rather than the methyl-labeled [^{3}H]primaquine previously used. Although there appears to be wide distribution of primaquine throughout the body tissues, it is apparent that the radioactivity is concentrated in certain tissues, as determined by relative concentration (12).

At 1 min after intravenous administration of [^{14}C]primaquine diphosphate, the lungs contained the highest concentration of radioactivity (relative concentration = 4.90; Table III). Radioactivity was also concentrated in the heart, adrenal glands, kidneys, and liver. The adrenal glands and lungs contained the highest concentrations of radioactivity until 3 h after injection, when the contents of the small intestine showed the highest concentration of radioactivity. The contents of both the small and large intestines continued to contain the highest relative amount of radioactivity at 6, 12, and 24 h after injection. It appears, therefore, that there is extensive recirculation of radiolabeled material through the intestinal system after intravenous injection.

Following intraperitoneal administration of labeled primaquine, a number of tissues showed a selective concentration of the radioactivity (Table IV). Significant uptake was observed for the lung (Fig. 4), liver (Fig. 4), adrenal (Fig. 5), and spleen (Fig. 6) tissues. Large quantities of the radioactivity were also found in the contents of the large and small intestines in the later time periods following the intraperitoneal dosage (Fig. 7). Although the time course of the intraperitoneal and intravenous routes were different, there were no significant differences in the tissue distribution.

Following oral administration of labeled primaquine, a significantly different distribution of the radioactivity was observed (Table V). The areas under the curves (AUC) for the lung, adrenal, spleen, kidney, heart, blood, and pancreas tissues were found to be only 22 ± 4% (range 19–29%) of the dose-adjusted AUC values obtained after intravenous administration. However, the AUC for the liver was found to be 45% of that obtained after intravenous administration. These findings suggest that a major portion of the primaquine reaches the liver; however, metabolism and excretion into the bile prevents the major portion of the dose from reaching the plasma and other tissues.

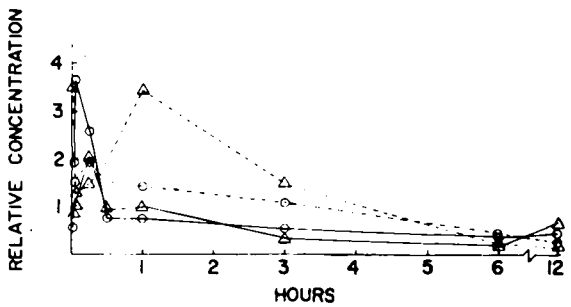

Figure 6—*Relative concentration of radioactivity in kidney (○) and spleen (△) after intravenous (—) and intraperitoneal (---) administrations of [^{14}C]primaquine diphosphate. Each value represents the average of two animals.*

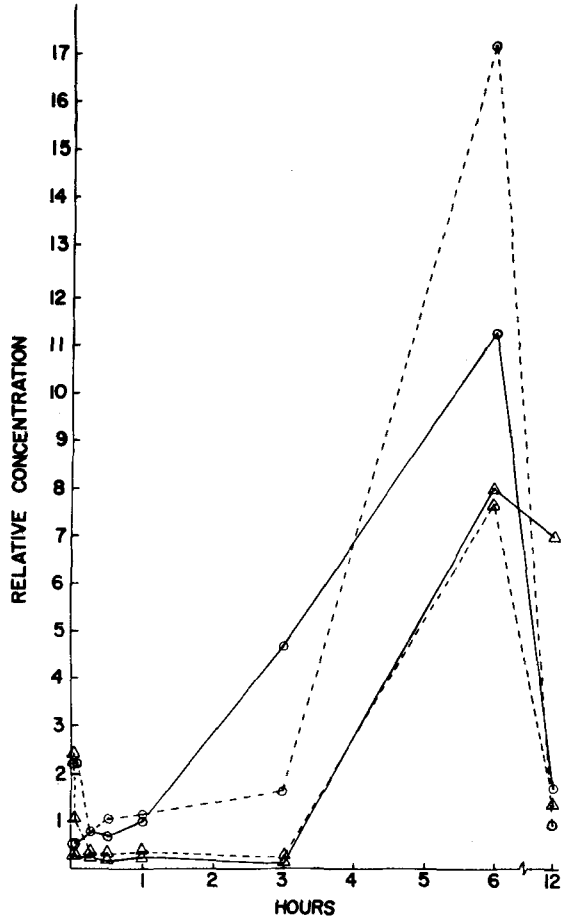

Figure 7—*Relative concentration of radioactivity in the contents of the small intestine (○) and large intestine (△) after intravenous (—) and intraperitoneal (---) administrations of [^{14}C]primaquine diphosphate. Each value represents the average of two animals.*

Consistent with these findings was the observation that a significant portion of the radioactivity was found in the feces following intravenous or intraperitoneal administrations (Table VI). Since the percentages of the dose found in the feces after intravenous, intraperitoneal, and oral administrations are all nearly the same, it would appear that primaquine is fairly well absorbed when given orally, but that only a small portion (25% by HPLC analysis) of the primaquine actually reaches the plasma because of first-pass metabolism and enterohepatic circulation.

CONCLUSIONS

The results of these studies show that primaquine was rapidly metabolized after intravenous and intraperitoneal injection and a major metabolite (mean 28%, range 5.6–74%) was found to be the carboxylic acid product (III) resulting from oxidative deamination. At 3 h after administration of the dose, this metabolite accounted for almost 60% of the total radioactivity in rat plasma, as shown by HPLC fractionation of radioactive blood samples. These findings were consistent with those of Holbrook *et al.* (15), which indicated that the majority of the radioactivity in the blood samples was not extractable into heptane under alkaline conditions.

A significant finding of the current distribution studies was that a large portion of the carbon-14 was found in the intestinal tract and feces following intravenous or intraperitoneal administration. Of the label excreted during the first 24 h following intravenous or intraperitoneal administration, approximately one-third was found in the feces, which would suggest that enterohepatic circulation may be involved in the distribution and metabolism of primaquine.

When primaquine was given orally, only 25% (range 5–56%) of the dose ultimately reached the plasma, while 18% of the dose was excreted in the feces during the first 24 h. These observations would suggest that first-pass metabolism and enterohepatic circulation may be involved in the systemic availability of primaquine following oral dosing. When labeled primaquine was administered intravenously, the major portion of the dose was found in highly perfused tissues such as the lungs, adrenal glands, liver, spleen, and heart, while little remained in the plasma. This rapid uptake by lung tissue has also been reported for similar aromatic compounds containing a very basic aliphatic amino group (13, 14).

When the labeled primaquine was administered orally, the tissue distribution was found to be significantly different because of enterohepatic recirculation and first-pass metabolism. Following oral administration, the amount of label reaching most tissues was reduced to 22% of that obtained after intravenous administration. However, the amount reaching the liver remained fairly high following oral administration, which was significant considering that primaquine is normally administered orally to suppress the malaria organisms residing in the liver.

Table VI—Percentage of Radioactive Dose Excreted in Urine and Feces after Intravenous, Intraperitoneal, and Oral Administrations of [^{14}C]-Primaquine Diphosphate [a]

Route of Administration	Radioactive Dose Recovered, %	
	Urine (0–24 h)	Feces (0–24 h)
Intravenous	26%	18%
Intraperitoneal	37%	14%
Oral	11% (17%)[b]	16% (20%)[b]

[a] Each value represents the average from two animals. [b] Values reported by Ryer *et al.* (16).

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