THE ABSORPTION, DISTRIBUTION AND URINARY EXCRETION OF MESCALINE IN THE DOG[1, 2, 3]

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The isolation and elucidation of the structure of mescaline, 3,4,5-trimethoxyphenylethylamine, by Späth (1921), made its synthesis possible and permitted intensive studies of its pharmacological and psychological effects. Early investigations on the fate of mescaline in the dog and in the human were necessarily limited to studies of urinary excretion because of lack of specificity or low sensitivity of the analytical methods employed. In a study of excretion of mescaline in the human, Moller (1935) was able to recover 94 per cent of the administered drug from his own urine whereas recovery in psychopathic patients was significantly lower. These results have never been confirmed. Slotta and Müller (1936) could detect no free mescaline in the 24 hour urine of dogs that had been given large doses of the compound orally, but were able to isolate 40–50 per cent of the administered amine, as the 3,4,5-trimethoxyphenylacetic acid, and found some free amine in the feces. These workers were unable to find either the free amine or the acid in human urine after ingestion of 400 mgm. of mescaline. Richter (1938) using a microestimation of amines based on the color of amine picrates, recovered 53 per cent of an intravenous dose and 58 per cent of an oral dose of mescaline given to humans. More recently Salomon (1949), using a method based on the determination of the methoxyl groups in the urine, has shown that from 9–39 per cent of the ingested mescaline was excreted in eighteen hours. He found no difference in the rate of excretion in normal and abnormal subjects.

Using a method of estimation of organic amines described recently (Woods *et al.*, 1951), plasma levels, tissue distribution and urinary excretion of mescaline were studied in the dog. The results are reported in this paper.

METHOD. Mescaline was administered in doses of 20 mgm./kgm.[4] by the oral (stomach tube), intramuscular, and intravenous routes to four female mongrel dogs weighing between 17 and 28 kgm. Following an experiment each dog was allowed to recuperate at least ten to fourteen days before being subjected to another experiment. The animals received a liter of water on the night before an experiment and another liter an hour before receiving the drug. All plasma samples were obtained from oxalated venous blood. Urine samples were collected

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[3] We are indebted to Dr. E. L. Sevringhaus for arranging with Basle Laboratories of Hoffman-La Roche, Inc., for the preparation of the mescaline sulfate and for furnishing several synthetic derivatives.

[4] Dosages were calculated as mgm./kgm. of free amine but administered as the sulfate.

at frequent intervals from a Foley-bag indwelling catheter for from eighteen to twenty-four hours after mescaline was given. Because of the high blank values obtained from cage collected urine, only catheter specimens were analyzed and this necessarily limited the time during which mescaline excretion was followed. In all cases, control plasma and urine samples were obtained just before administration of mescaline.

For the tissue distribution studies, doses of 25 mgm./kgm.[4] of mescaline were given intravenously and the dogs were sacrificed by exsanguination under ether anesthesia, one hour and four hours after the administration of the drug. One gram of each organ or tissue to be studied was homogenized and extracted in the usual manner. Control values were obtained by sacrificing an animal to whom mescaline had not been given, and extracting the tissues in a similar manner.

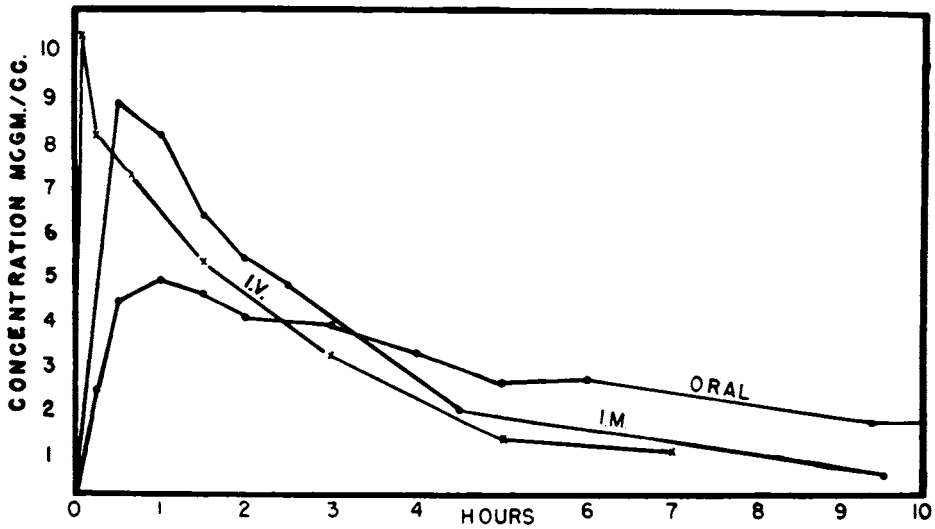

FIG. 1. Plasma concentrations in microgm. per ml. of mescaline at various times after the oral, intramuscular, and intravenous administration of 20 mgm./kgm. to the dog.

Plasma levels. Figure 1 shows the results of representative experiments in which mescaline was given intravenously, intramuscularly and orally to the same dog. After intravenous administration of 20 mgm./kgm. of mescaline there is a rapid decrease from a high initial level in the plasma to concentrations of from 6–10 microgm. per ml. in two to thirty minutes. This rapid fall, probably due to redistribution of the drug from the plasma to the tissues, is followed by a more gradual disappearance of mescaline from the blood stream, being complete in six to eight hours. Intramuscular injection of mescaline in the dog produces the same general type of plasma decay curve as does intravenous administration, with the exception that after the former the peak plasma levels are somewhat lower.

Following oral administration, plasma levels reach a peak more slowly, but even so the maximum plasma levels are attained within an hour. The peak levels after oral administration are moderately lower than those obtained after parenteral administration but significant amounts of mescaline are found in the

plasma for periods up to ten hours. The plasma concentration, after reaching peak levels, remains relatively constant for two to four hours after ingestion of the drug.

Immediately after intravenous administration, more slowly after intramuscular and oral administration, the usual autonomic and central nervous system signs of mescaline intoxication appeared. Nausea, vomiting, mydriasis, injected conjunctivae, and hyperreflexia were seen in various degrees in most of the animals. Nausea and mydriasis were present in all; the other signs were noted in some animals, but were absent in others. A peculiar chewing motion of the jaws, hitherto not described, was seen in every animal. Profound depression was noted in some dogs in from three minutes to half an hour after administration of the drugs, depending on the route of entry. This depression lasted six to ten hours.

There were, however, some dogs that showed excitement rather than depression, disorientation in space, and inability to localize sounds. Dogs receiving 25 mgm./kgm. for tissue distribution studies showed marked catatonia, as described by De Jong (1932).

TABLE 1

Recoveries of mescaline in the urine of the dog after administration of 20 mgm./kgm. by the indicated route

ROUTE	PER CENT RECOVERY OF ADMINISTERED DOSE	
	Dog M-3	Dog M-4
Oral	39	44
IV	39	28
IM	46	35

Although the time of onset of the various signs and effects of mescaline intoxication varied with the route of administration, the severity of the toxic state seemed to be the same no matter what the route of entry. In a general way the intensity of the signs of intoxication parallels the plasma levels of mescaline.

Urinary excretion. Significant amounts of mescaline have been recovered from the urine of dogs given 20 mgm./kgm. by the three above-mentioned routes of administration. Recoveries range from 28–46 per cent of the administered dose,[5] with no apparent difference in recovery no matter what the route of administration (table 1). Positive identification of the material recovered as mescaline was made by the preparation of the crystalline picrate derivative and comparison of the melting point and mixed melting point with synthetic mescaline picrate.

Figure 2 shows a typical cumulative recovery curve correlated with concomitant plasma levels after intramuscular administration of 20 mgm./kgm. of

[5] Investigations being carried out in cooperation with the Public Health Service Hospital, Lexington, Ky., indicate that the percentage of administered mescaline found in the urine of the human is of the same order of magnitude as that found in the dog.

mescaline. It can be seen that mescaline appears in the urine in detectable amounts as early as thirty minutes after administration with the maximum rate of excretion in about two to four hours.

Slotta and Müller (1936) recovered 38 per cent of the administered mescaline in the form of 3,4,5-trimethoxyphenylacetic acid in dog urine by the use of a procedure involving repeated and complex manipulations. Whereas we have not been able to confirm their results, only traces of the acid having been found using their method, we are not yet willing to exclude oxidative deamination to 3,4,5-

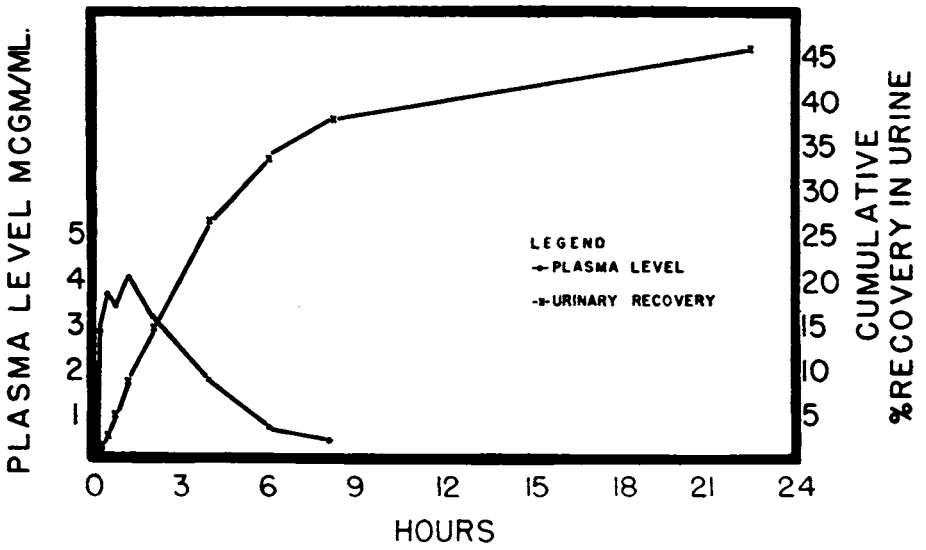

FIG. 2. Plasma concentrations in microgm. per ml. and cumulative urinary recovery in per cent of administered dose of mescaline at various times after intramuscular administration of 20 mgm./kgm. to the dog.

TABLE 2

Recovery of mescaline in microgm. per gm. of tissue or ml. of plasma

Each figure represents an average of duplicate determinations

	KIDNEY	LIVER	SPLEEN	SKELETAL MUSCLE	OMENTAL FAT	VENTRICULAR MUSCLE	CEREBRAL CORTEX	PLASMA
1 hour after administration of 25 mgm./kgm.	57	50	48	14	5.2	34	12	10
4 hours after administration of 25 mgm./kgm.	46	31	26	15	<5.0	12	13	7.1

trimethoxyphenylacetic acid as a major path of metabolism of mescaline in the dog.

Tissue distribution. Studies of the distribution of mescaline in the tissues of dogs were carried out as described above. Table 2 shows the distribution of the amine in the tissues at one hour and four hours after the intravenous adminis-

tration of 25 mgm./kgm. of mescaline. There seems to be a selective deposition in the parenchymatous organs studied, liver, spleen, and kidney, where the concentrations of mescaline are three to six times those in the plasma. After three hours, the amounts in the spleen and liver are significantly lower than those found in the kidney, but this is to be expected since the peak excretion of mescaline is from two to four hours after administration. The fact that brain and blood levels are of the same order of magnitude confirms the work of Vogt (1935), who also found much higher levels in liver and kidney than in blood or brain.

The erythrocyte-plasma ratio of mescaline has been found to be 1.2–1.4 to 1.

SUMMARY

1. The plasma levels of mescaline in dog plasma have been determined following intravenous, intramuscular, and oral administration of 20 mgm./kgm. of mescaline sulfate. The decay curves follow the characteristic slope usually related to differences in the route of administration. The intensity of the signs of the pharmacological action of mescaline parallels the plasma levels.

2. Renal elimination of unaltered mescaline in the dog accounts for 28 to 46 per cent of an administered dose, the larger portion of the eliminated fraction being excreted within four and one-half hours and the remainder within twenty-four hours. Only traces of 3,4,5-trimethoxyphenylacetic acid could be detected in the urine.

3. During the first four hours after intravenous administration the concentration of mescaline in the kidney, liver, or spleen is three to six fold higher than in plasma or brain.

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