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TISSUE DISTRIBUTION WITH TIME AFTER SINGLE INTRAVENOUS ADMINISTRATION OF PENTOTHAL SODIUM (SODIUM ETHYL (1-METHYLBUTYL) AND PENTOTHAL S^{35} THIOBARBITURATE) *

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THE paucity of our knowledge concerning the distribution and physiologic fate of pentothal in the body has been due to the lack of specific and sensitive methods for the determination of the concentration of the drug in tissues and biologic fluids. Recently Jailer and Goldbaum (1) have developed a method which is specific for pentothal and has a high degree of accuracy when applied to analysis of blood and tissues. D. L. Tabern has incorporated S^{35} (produced by the atomic pile at Oak Ridge, Tennessee) in the pentothal sodium molecule. By determination of the radioactivity of the pentothal, after its extraction from tissues, another accurate and specific method for pentothal is available.

We have made a study using these two methods to determine the distribution of pentothal at various times after a single intravenous injection of amounts of the drug which produce deep anesthesia in normal rats. Our observations of the very rapid appearance of high concentrations of pentothal in the lymph of dogs after intravenous injection of this drug emphasize its rapid diffusion from the blood and its immediate distribution throughout the body.

METHODS

The method of extraction of pentothal from blood, lymph and tissues was essentially that described by Jailer and Goldbaum (1) and by

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Dorfman and Goldbaum (2). Plasma or lymph (1.0 cc.) and 0.2 M acetate buffer of pH 5 (5 cc.) were added to redistilled chloroform (10 cc.) in a small separatory funnel and shaken for three minutes. Samples of tissue were removed and immediately frozen in a freezing solution of solid carbon dioxide and alcohol. The frozen tissue was then pulverized between two chilled steel blocks. The powder was weighed and added to the buffer solution (5 cc.) and chloroform was added in volume sufficient to make 10 cc. for 1 Gm. of tissue. The chloroform extract was separated from the aqueous phase by centrifugation and shaken again with an equal volume of 0.5 N sodium hydroxide. The alkaline aqueous layer was then separated and read in a Beckman quartz spectrophotometer at a wave length of 305 millimicrons. The amount of pentothal was calculated from this optical density compared to that of standard amounts of pure pentothal in alkaline solution. In each experiment similar plasma, lymph and tissues obtained from etherized animals without administration of pentothal gave a small blank which was subtracted in the final caluculation without materially affecting the results.

Pentothal containing S^{35} was determined after the alkaline aqueous extract (used for spectrophotometric determination) had been acidified and extracted with an equal volume of chloroform. Aliquots of the chloroform extract were then dried on metal planchets. The radioactivity was determined by the use of a thin mica window Geiger-Müller counter or in a methane flow nucleometer. The counts obtained were compared to the counts obtained from similarly measured pure pentothal S^{35}.

With these methods the recovery of small amounts of pentothal added to blood, lymph or tissues was more than 90 per cent. Almost the same figure was obtained from aliquots of whole rats killed, frozen, ground and mixed immediately after intravenous injection of a measured amount of pentothal.

Male white rats weighing approximately 200 Gm. which had been receiving a stock diet were given 40 mg. of pentothal per kilogram as pentothal sodium in 0.2 cc. of water into the saphenous vein. The injection was timed to take exactly thirty seconds. Exactly thirty seconds later as much blood as possible was withdrawn by direct cardiac puncture and the other organs were excised thereafter as rapidly as possible. The organs and tissues were immediately frozen in a freezing mixture for subsequent weighing. The removal of the blood and tissues was usually accomplished in three minutes. In some animals the withdrawal of blood was not attempted but the heart was excised and the tissues were obtained more rapidly. As a control for the possible degradation of pentothal during the time involved in excising the tissues, 3 rats were bled; the heart was excised one minute after injection of pentothal and the tissues were removed thirty minutes later. The values obtained were similar to those found one minute after in-

jection with the possible exception of perhaps some loss from the liver. Other rats were similarly injected with 40 mg. of pentothal sodium per kilogram and subsequently taken for plasma and tissue analysis three, ten, thirty, sixty or one hunded twenty minutes after injection. An occasional rat diet immediately after receiving 40 mg. of pentothal per kilogram and was not included in this study.

RESULTS

The results of these experiments are summarized in figure 1, which shows the amount of pentothal found in the different tissues taken at the times indicated after a single intravenous injection of 40 mg. of pentothal per kilogram. In table 1 the percentage of the total amount of pentothal sodium administered which was found in the organs at the

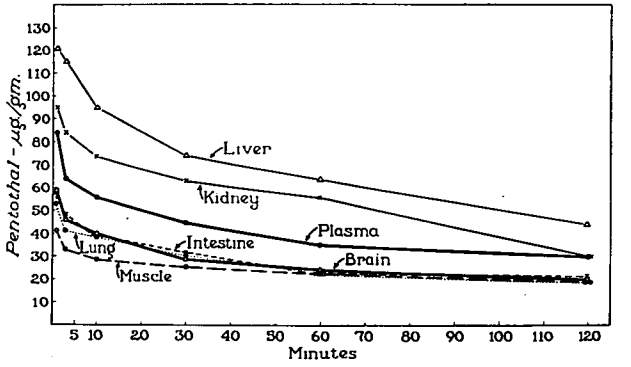

FIG. 1. The concentration of pentothal in tissues at intervals after intravenous administration of 40 mg. of pentothal per kilogram to rats.

times indicated is shown. These figures are based on the weights of the frozen organs after excision. In table 2 the whole tissue was not available; therefore, the percentage of the amount administered is given for each gram of that tissue. It is apparent that pentothal is rapidly distributed throughout the body and that the greatest concentration of pentothal sodium in each tissue is reached within one minute after the beginning of intravenous injection and in these experiments within thirty seconds after completion of injection. Skin, bone and fat take up pentothal somewhat more slowly and do not acquire as high a concentration of the drug as found in other tissues.* There is no evidence of subsequent marked accumulation in any of the tissues studied. It

* These are preliminary findings. Further investigations are being carried out.

TABLE 1

PENTOTHAL DISTRIBUTION IN WHOLE ORGANS (RATS)

Minutes After Beginning of Injection	Percentage of Amount Administered			
	Brain	Liver	Kidneys	Lungs
1	1.2±0.1 (13)*	12.7±0.6 (13)	1.9±0.1 (6)	0.7±0.02 (6)
3	1.0±0.05 (17)	12.3±0.4 (17)	1.7±0.2 (6)	0.6±0.04 (6)
10	0.8±0.04 (16)	10.2±0.4 (17)	1.6±0.03 (6)	0.6±0.04 (6)
30	0.6±0.05 (8)	8.1±0.2 (8)	1.4±0.1 (6)	0.4±0.04 (6)
60	0.5±0.04 (8)	6.4±0.5 (8)	1.1±0.1 (6)	0.3±0.02 (6)
120	0.4 (2)	4.9 (2)	0.6 (2)	0.2 (2)
30†	1.5 (3)	10.3 (3)	1.9 (3)	0.6 (3)

* The figures after the ± indicate the standard errors of the mean. The figures in parentheses indicate the number of animals in each group.

† Circulation stopped at one minute, tissues taken after thirty minutes.

is also evident that the concentration in the major tissues is not markedly different from that of the plasma at any time, the concentration found in the liver and kidneys being somewhat greater than that of the plasma and the concentration in the brain, muscle, lungs and intestine being approximately equal and slightly less than that of the plasma. The skin and retroperitoneal fat do not take pentothal from the blood as readily as do the other tissues.*

TABLE 2

PENTOTHAL DISTRIBUTION IN TISSUES (RATS)

Minutes After Beginning of Injection	Percentage of Amount Administered in Each Gram of Tissue				
	Plasma	Muscle	Intestine	Skin	Fat
1	1.00±0.06 (10)*	0.52±0.04 (6)	0.73±0.09 (6)	0.13 (4)	0.08 (4)
3	0.80±0.04 (10)	0.41±0.01 (7)	0.60±0.03 (10)		
10	0.70±0.03 (10)	0.36±0.01 (7)	0.49±0.01 (10)	0.44 (4)	0.28 (4)
30	0.56±0.02 (8)	0.32±0.02 (8)	0.39±0.03 (8)		
60	0.44±0.02 (8)	0.29±0.03 (8)	0.28±0.02 (8)		
120	0.37 (2)	0.15 (2)	0.28 (2)		
30†	0.77 (3) 1 min.	0.52 (3)	0.65 (3)		

* The figures after the ± indicate the standard errors of the mean. The figures in parentheses indicate the number of rats in each group.

† Circulation stopped at one minute, tissues taken after thirty minutes.

After the immediate distribution of pentothal to the tissues there is a subsequent slow decline of the amount found in each tissue. The loss of pentothal from each tissue is apparently at about the same rate. All of the rats of this series were deeply anesthetized when killed at periods up to thirty minutes. At sixty minutes most were still in deep anesthesia but a few and those taken after one hundred twenty minutes were given ether immediately before the tissues were removed.

Two dogs were given 23.5 mg. of pentothal per kilogram intravenously. The dogs had been prepared three days previously when the major lymphatic from the small intestine had been cannulated, with the animal under ether anesthesia and with aseptic technic, with a small plastic tube which was then passed through the abdominal wall and drained lymph continuously. At the time of the injection of pentothal the animals were in excellent condition. The two experiments were similar. The results of one are shown in figure 2. Lymph collected before the pentothal was given was used for blank determination. The flow of lymph was such that approximately the volume contained in the plastic tube would be emptied in five minutes. Lymph was collected for the period from five to fifteen minutes after injection of

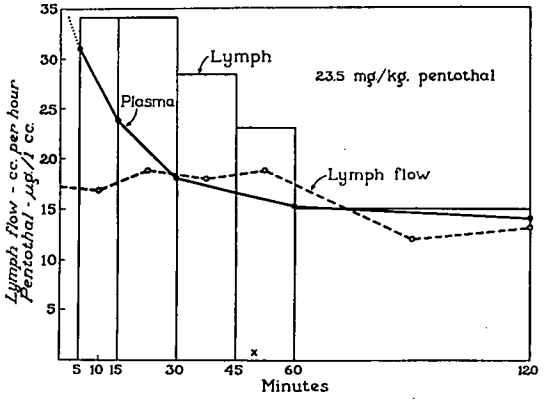

FIG. 2. The concentration of pentothal in plasma and intestinal lymph of a dog after intravenous administration of 23.5 mg. of pentothal per kilogram.

pentothal and subsequently to thirty, forty-five, sixty and one hundred twenty minutes. Blood specimens were obtained at five, fifteen, thirty, sixty and one hundred twenty minutes. In each period the concentration of pentothal in the lymph was slightly greater than that of the plasma at the beginning and end of the period taken. Because of the volume of lymph contained in the plastic tube and in the lymphatics it was not possible to compare lymph and plasma simultaneously and the higher figures obtained for lymph are in part due to the lymph drained having been formed at some time before. It is apparent, however, that the lymph acquired a high concentration of pentothal immediately after intravenous injection of the drug and that subsequently the concentration declined to that of the declining concentration of the

plasma. Both dogs began to show signs of recovery from the anesthetic about fifty minutes after the pentothal had been given.

COMMENT

The results obtained by the use of the spectrophotometric and radioactive determinations of pentothal in the tissues in these experiments were similar. This is another indication of the specificity of the spectrophotometric method for pentothal and indicates that degradation products are not included in these determinations of pentothal. Sulfates formed from the sulfur liberated by degradation of pentothal are not determined in the fraction extracted for radioactive determinations. Because of the large amounts of pentothal determined in these experiments the spectrophotometric method was simpler and somewhat more accurate than the radioactive measurements. If smaller amounts of pentothal are to be measured the radioactive method would be more accurate.

The values obtained thirty seconds after the completion of injection indicate the very rapid and fairly even distribution of pentothal through the major tissues of the body. No tissue examined continued to abstract pentothal from the blood to produce a higher concentration of the drug in any one organ. The fact that the decline in the concentration of pentothal is very similar in each organ does not, however, indicate that each participates equally in the degradation of the drug. The data are quite consistent with the possibility that degradation takes place in one location but that the rapid redistribution of pentothal immediately replaces the amount that could be destroyed in any single location.

In the few rats in which the circulation was stopped and the tissue was taken thirty minutes later, there was no evidence of any degradation of pentothal during the period of thirty minutes, as each tissue had the concentration of pentothal almost equal to those found when the tissues were taken at one minute. All tissues other than the liver showed less than 10 per cent breakdown of pentothal, but a 20 per cent loss of pentothal in the liver was indicated in the 3 rats used, a result which is of questionable significance. Richards (3) found that about 50 per cent of the pentothal that he added to heparinized blood was inactivated with thirty minutes' incubation, while plasma had little effect. Shideman, Kelly and Adams (4) found 12 per cent breakdown of pentothal by liver slices in one hour. Dorfman and Goldbaum (2) found that in three hours' incubation liver slices destroyed 40 to 50 per cent of added pentothal while liver brei and liver homogenate destroyed only 13 and 6 per cent. Kidney slices and kidney brei destroyed 30 and 21 per cent in the same time. Beiler, Juhasz and Cerecedo (5) using *in vitro* methods, presented data to indicate that pentothal was destroyed by diaphragmatic or intestinal tissue but not by liver.

SUMMARY

Pentothal injected intravenously is rapidly distributed to all the tissues of the body. Within thirty seconds after completion of injection most of the pentothal is out of the blood and is found with few exceptions fairly evenly distributed in the various organs. The concentration in the brain, muscle, intestine and lungs is only slightly less than that of the plasma at that time and the concentration of the drug in the liver and kidneys is higher. Subsequently no tissue accumulates additional pentothal in significant amounts and the concentration decreases gradually in each tissue. Approximately half of the original concentration of pentothal is present in each tissue one hour after administration of 40 mg. per kilogram to the adult white rat.

Our observations give no indication of a possible site for the destruction of pentothal by a specific organ.

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