STUDIES ON PARALDEHYDE. I. THE MEDIAN LETHAL DOSE, LD_{50}, OF PARALDEHYDE FOR GUINEA PIGS *†

FRANK A. KAY, M.D., EMMETT B. CARMICHAEL, M.D., PH.D., AND GRADY W. PHILLIPS, B.S.

Tuscaloosa, Alabama
University, Alabama

WIEDENBUSCH discovered paraldehyde in 1829, but it was Vincenzo Cervello (2) who introduced it as a hypnotic in animals and then, on February 13, 1882, took four 0.5 Gm. doses of the drug which produced a deep sleep with a resulting decrease in the pulse rate. The results of his researches were published in 1882 (2), and the next year Enrico Morselli (3) introduced the drug therapeutically at the Royal Asylum of Turin. The use of the drug was reported by Berger (4) in Germany, March 24, 1883; by two Americans, Dana (5) August 25, 1883, and Wilson (6) December 8, 1883; by Dujardin-Beaumetz (7) in France, January 30, 1884; and by Strahan (8) in Great Britain, January 1885.

Paraldehyde has been used extensively, both as a hypnotic and sedative, and only eleven reported fatalities (9–18) have been found in the literature. Either idiosyncrasy to the drug or concurrent disease appears to have been a contributing factor in the death of some of these patients. Dr. H. M. Goodman (10), of Louisville, Kentucky, recorded a fatal case of paraldehyde poisoning in a paper published November 8, 1890. This case was reported a year previously to Dr. Goodman in a private communication by Dr. S. Brzozowski, of the same city. The patient, an adult male, suffering from insomnia with no evidence of any former acute or chronic trouble, had been taking 2 ounces of the elixir of paraldehyde every hour or two when first seen by Dr. Brzozowski. Although the urine contained a large amount of albumin, the patient continued to take the drug and died soon afterward. Dr. Brzozowski attributed his death to paraldehyde. Although Dr. Goodman's paper did not appear until eleven weeks after the *Lancet* anonymously reported the Bridget O'Brien case (9), we believe that Dr. Brzozowski noted the first human fatality due to paraldehyde. Miss Bridget O'Brien (9), an adult, entered the Fever Hospital, attached to the Cork Workhouse, suffering from typhoid fever, and little hope was entertained for her recovery. A nurse gave her 6 to 7 teaspoonfuls of paraldehyde and the patient died four hours later.

* From the Bryce Hospital, Tuscaloosa, and the Department of Physiological Chemistry, School of Medicine, University of Alabama, University, Alabama.

† A preliminary report of this work was presented at the meeting of the American Physiological Society, 1942 (1).

Later case reports seem to indicate that if there is no recognized disease, patients can tolerate several times the above-mentioned dose of paraldehyde even though the sleep and hypnosis might persist two to three days. Mackenkie (19), in 1891, reported that a woman recovered after taking 3.5 ounces of paraldehyde and could answer questions in fifty-one hours. Leschke (20), in 1934, stated that patients have recovered from as much as 150 Gm. of the drug. Hanson (21), in 1937, gave 120 cc. of the drug to a patient in labor, with recovery. In 1941, Kay (22) observed a psychoneurotic white woman, age 49 years, who took 120 cc. of the drug by error. She recovered after fifty-nine hours of unconsciousness and stupor.

Because of the general acceptance of paraldehyde as a safe drug, it seemed wise to make further observations on its effect on laboratory animals. The present paper deals with the determination of the median lethal dose, LD_{50} (23), of the drug for guinea pigs.

TABLE 1

STUDIES ON THE TOXICITY OF PARALDEHYDE, 1 : 10 SOLUTION, FOR DIFFERENT WEIGHT GROUPS OF GUINEA PIGS

Weights of guinea pigs	11.00* cc.		11.25 cc.		11.50 cc.		11.75 cc.		12.00 cc.		12.25 cc.		12.50 cc.		12.75 cc.		13.00 cc.		13.25 cc.		13.50 cc.		13.75 cc.		14.00 cc.		Total	
	I	D	I	D	I	D	I	D	I	D	I	D	I	D	I	D	I	D	I	D	I	D	I	D	I	D	I	D
grams																												
280–499	10	2	6	0	10	3	8	4	11	8	8	4	11	6	8	6	12	7	7	6	9	7	4	3	4	4	108	60
500–1130	7	3	4	2	9	6	5	1	25	13	26	8	24	8	20	8	19	12	18	10	16	12	18	14	17	12	208	109
280–1130	17	5	10	2	19	9	13	5	36	21	34	12	35	14	28	14	31	19	25	16	25	19	22	17	21	16	316	169

* cc. of 1 : 10 solution of paraldehyde per kilogram body weight of guinea pig.

I, number of animals injected.

D, number of animals that died following the corresponding injection of paraldehyde, 1 : 10 solution.

The paraldehyde was diluted with water, one volume of the drug being made up to ten volumes. It was necessary to cool both the solution and the syringe below 18 C. to prevent the drug from coming out of solution. The dose of this solution varied by increments of 0.25 cc. from 11 to 14 cc. per kilogram, and was injected intraperitoneally.

Three hundred and sixteen normal, well-fed guinea pigs were used on this series of experiments. They were divided into two weight groups: (*a*) 280 to 499 Gm., and (*b*) 500 to 1,130 Gm., as indicated in table 1. There were 108 animals in the first group and 208 in the second group. These experiments have extended over eighteen months and some animals were injected during each season.

From table 1 it can be seen that there is a wide range of doses that killed about 50 per cent of the animals. Although only a few animals were given the small doses, it seems that those animals in the second group were more susceptible to the toxic effects of the drug than those

animals in the first group. If the results are summarized as indicated in the lower line in the table, we find that the LD_{50} lies between 11.75 and 13 cc. of the 1:10 solution of paraldehyde per kilogram.

To study the effects of the drug on these animals, the periods of time required for the development of three stages in the hypnotic state were selected (24): (*a*) the time from the injection until the animal could not support and propel itself after stimulation either by gently pulling the hair on the hips or by pinching; (*b*) the time from the injection until the animal could be aroused sufficiently to walk or propel itself forward after stimulation; and (*c*) the time from the injection until the animal could walk with a steady gait for a distance of about a meter. The onset of sleep began at the conclusion of the first stage and the end of sleep was coincident with the termination of the second stage. The time from the injection until the animal had awakened and was able to walk with a steady gait was considered as the maximal hypnotic time. The animal was considered to be awake at the end of the third stage and would eat if given green food at that time. The time of injection and the onset of sleep were recorded for all of the animals. If the animal survived, the duration of sleep and the maximal hypnotic time were recorded in many instances. In case an animal did not survive, the time that the heart ceased to beat was recorded and this was accepted as the time of death.

The onset of sleep varied from one to two minutes, but there seemed to be no constant findings with either dose used or with either weight group of animals. The duration of sleep varied from about three to six hours, while the maximal hypnotic time varied from five to ten hours.

The animals that died usually stopped breathing within a few minutes after receiving the paraldehyde and their hearts ceased to beat within about ten to fifteen minutes from the time of the injection.

Summary

1. A 1:10 dilution of paraldehyde was injected intraperitoneally into 316 normal guinea pigs to determine the median lethal dose, LD_{50}.

2. The doses used varied by increments of 0.25 cc. from 11 to 14 cc. per kilogram.

3. The animals weighed from 280 to 1130 Gm. and they were divided into two weight groups: (*a*) 280 to 499 Gm., and (*b*) 500 to 1130 Gm.

4. The median lethal dose, LD_{50}, lies between 11.75 and 13 cc. of the 1:10 solution of paraldehyde per kilogram, if the results are summarized of all of the animals on each dose. However, animals of the first weight group (young animals) did not seem as susceptible to the toxic effects of the paraldehyde as those in the second weight group. The LD_{50} for the former group was 11.75 to 12.25 cc. of the drug per kilogram, while the LD_{50} for the latter group was 11.25 to 12 cc. per kilogram.

5. Respiratory failure seemed to be the primary cause of death in those animals that were killed by the paraldehyde.

6. There seems to be a wide variation in the individual resistance of guinea pigs to paraldehyde.

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