SCIENTIFIC SECTION

CAFFEINE AS AN ANTIDOTE FOR HYDRATED CHLORAL.*[1]

BY CHAS. C. HASKELL.

In contrast to most of the common poisons, hydrated chloral produces its fatal effects comparatively slowly. With strychnine, death may occur soon after the administration of the poison, and prevent the employment of any therapeutic measures. After phenol or, especially, mercuric chloride, death may be much delayed, but both of these drugs early produce structural changes in some of the vital organs; thus rendering treatment of no avail if a sufficiently large dose has been absorbed. In the present state of our knowledge, the rule that gastric lavage is the most valuable measure to be employed in the treatment of poisoning from the oral administration of any drug applies as well in the case of chloral as that of any other poison; unfortunately, however, the patient may not come under observation for hours after taking the poison; with such a lapse of time, more or less absorption must have taken place. If the administered dose had been large enough and absorption sufficiently rapid, the patient suffering from strychnine poisoning would have been dead; had the poison been phenol or mercuric chloride, irreparable damage would have been inflicted upon the kidneys and, possibly, other essential structures; but with hydrated chloral, which seldom produces death with the rapidity of strychnine and which is much less likely to cause destructive changes in the kidney or liver; the chance of successfully combatting the systemic action, even after the entrance of an otherwise fatal dose into the circulation, would seem, at least possible.

In toxic doses, chloral affects both the circulation and the respiration. Its deleterious action on the circulation is two-fold; a depression of the vasomotor center, with consequent vascular relaxation; and a direct depression of the heart muscle. In some cases, this cardiac action may be responsible for sudden early death; in the majority of instances, the fatal termination is to be attributed to an effect on the respiratory center. Several physiological antidotes for chloral have been proposed; of these, from theoretical considerations, caffeine would seem best suited for antagonizing the harmful actions of chloral.

Centrally, caffeine stimulates the respiration, manifesting an action apparently diametrically the opposite that of chloral. The effect of caffeine on the vasomotor center is likewise opposed to that of chloral; but the peripheral action of caffeine on the vessel walls tends to neutralize or overshadow this central vasomotor stimulation. On the normal heart muscle, caffeine appears to have a distinctly beneficial effect, increasing both the extent and the rate of the cardiac contractions. There is, however, evidence which would suggest caution in the use of caffeine as an antidote for hydrated chloral. Hale (1) has shown that caffeine actually increases the toxicity of acetanilid and antipyrin; Pilcher (2) found the same to be true of caffeine when used in ethyl alcohol poisoning; and, finally, evidence has been

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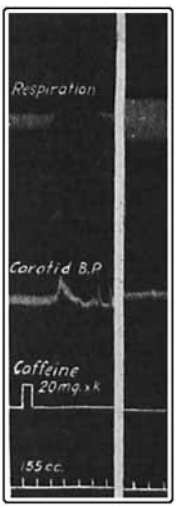
presented (3) which proves that the effect of caffeine in morphine poisoning is definitely harmful.

A demonstration that is frequently used for classes in pharmacology is one illustrating the effects of caffeine administration to an animal that has received a large dose of alcohol, chloral, or similar drug. In tracing No. 1, this effect is shown. The animal, a dog, is etherized for the necessary operative procedures; a tracheal cannula is inserted and connected with a tambour for recording respiration; the carotid artery is connected with a manometer; and a vein exposed for injections of the drugs. The dog is given a dose of hydrated chloral intravenously, in the form of a 10% solution, to bring about a decided permanent depression of both respiration and blood-pressure. A record of the respiration and blood-pressure is now secured, and at the signal, 20 mgm. of caffeine per kilogram body weight are injected intravenously. As a result of this injection, there occurs an abrupt rise in the blood-pressure and a temporary cessation of respiration; very soon, however, the blood-pressure returns to a point only slightly above what it was before the caffeine administration, while the respiration shows a decided increase in depth and rate.



Tracing No. 1.

That caffeine is capable of stimulating the respiration in an animal depressed by chloral is, however, no guarantee that caffeine will effectively antagonize the lethal action of the poison. In order to determine the actual value of caffeine, experiments have been carried out, consisting in the administration of chloral and the subsequent employment of caffeine.

Dogs and cats were the animals used in this study. It was first necessary to determine the minimal fatal dose of chloral for dogs; using the intraperitoneal method of administration of a solution of hydrated chloral, 25% in strength, it was found that these animals showed considerable individual variations in resistance. Thus, two dogs out of nine receiving a dose of 0.45 Gm. per kilogram body weight succumbed; all five died after a dose of 0.55 Gm. per kilogram; but one out of seven that were given 0.6 Gm. per kilogram survived. The results of these experiments are given in condensed form in Table I.

TABLE I.—RESULTS FROM INTRAPERITONEAL INJECTION OF HYDRATED CHLORAL INTO DOGS.

Chloral Gm. × Kg.	No. dogs used.	Mortality.
0.40	2	000.0%
0.45	9	22.2%
0.50	12	83.3%
0.55	5	100.0%
0.60	7	85.7%

Having determined approximately the toxicity of the poison for dogs by this method of administration, other dogs were given similar doses of chloral intraperitoneally and immediately afterward received subcutaneous injections of from 20 to 40 mgm. caffeine per kilogram. The results of these experiments are given in Table II.

The results obtained from the hydrated chloral alone and those following the

TABLE II.—RESULTS FROM INTRAPERITONEAL INJECTION OF HYDRATED CHLORAL AND SUBCUTANEOUS INJECTION OF CAFFEINE INTO DOGS.

Chloral Gm. × Kg.	No. dogs used.	Mortality.
0.40	2	00.0%
0.45	2	00.0%
0.50	13	76.9%
0.55	9	88.8%
0.60	4	100.0%

TABLE III.—MORTALITY OF CONTROL AND OF TREATED DOGS COMPARED.

Controls.	Chloral, Gm. × Kg.	Treated.
00.0%	0.40	00.0%
22.2%	0.45	00.0%
83.3%	0.50	76.9%
100.0%	0.55	88.8%
85.7%	0.60	100.0%

injection of the chloral and treatment with caffeine are compared in Table III.

At first glance, these figures might be taken as lending support to the view that caffeine is of value in the treatment of poisoning by hydrated chloral. In the untreated controls, the dose of 0.45 Gm. hydrated chloral per kilogram was responsible for a mortality of 22.2%; where caffeine was used as an antidote, there were no deaths. Inspection of Tables I and II show, however, that there were nine control dogs that received this dose of chloral; of these, seven survived. Only two dogs were given this dose of chloral and subsequent caffeine treatment; it is quite possible that a larger series of treated animals would have given a mortality figure fully as high as observed in the controls. Where a dose of 0.5 Gm. of chloral was used, ten of twelve controls succumbed; with this dose of chloral and caffeine treatment, ten of thirteen animals succumbed; a difference which is extremely slight. Only five dogs were used as controls for the dose of 0.55 Gm. chloral per kilogram, all succumbing; while, of a series of nine dogs given this dose of chloral and injections of caffeine, only one survived. That this lone survival was the result of unusually high natural resistance to the chloral is rendered probable by the fact that an untreated control survived a dose 20% larger; while all of the treated animals, four in number, died from this larger dose. It would seem, therefore, from the results of the experiments on dogs that doses of caffeine up to 40 mgm. per kilogram had no effect on the course of poisoning by hydrated chloral.

Sollmann (4) states that the average minimal fatal dose of hydrated chloral for cats by oral administration is 0.42 to 0.45 Gm. per kilogram. As in the case of the dogs, the intraperitoneal method of administering chloral was adopted in the present investigation; partly because of its greater ease and partly because, by it, was avoided the danger of a loss of part of the administered dose through vomiting. It was found that the fatal dose by intraperitoneal injection was decidedly lower than when the drug was given by mouth; all the cats receiving a dose of 0.23 Gm. per kilogram intraperitoneally succumbing. As with the dogs, the chloral was injected in the form of a 25% solution. The results of the injection of chloral alone are given in Table IV.

Apparently, individual differences in resistance were much less in evidence with the cats than with the dogs; three cats receiving a dose of 0.2 gram per kilogram surviving while all died from a dose of 0.23 Gm. per kilogram.

TABLE IV.—RESULTS FROM INTRAPERITONEAL INJECTION OF HYDRATED CHLORAL INTO CATS.

Chloral Gm. × Kg.	No. cats used.	Mortality.
0.20	3	00.0%
0.22	7	42.9%
0.23	7	100.0%
0.25	3	100.0%
0.30	3	100.0%

Another series of cats was injected with varying doses of chloral intraperitoneally and, immediately afterward, received subcutaneous injections of 40 mgm. of caffeine per kilogram. The results in these treated animals are given in Table V.

TABLE V.—RESULTS FROM INTRAPERITONEAL INJECTION OF HYDRATED CHLORAL AND SUBCUTANEOUS INJECTION OF CAFFEINE INTO CATS.

Chloral Gm. × Kg.	No. cats used.	Mortality.
0.22	6	83.3%
0.23	7	100.0%

A comparison of the results obtained on cats where the doses of 0.22 and 0.23 Gm. hydrated chloral per kilogram were given alone and in conjunction with 40 mgm. caffeine per kilogram is presented in Table VI.

TABLE VI.—MORTALITY OF CONTROL AND TREATED CATS COMPARED.

Controls.	Chloral, Gm. × Kg.	Treated.
42.9%	0.22	83.3%
100.0%	0.23	100.0%

Certainly, the conclusion would be justified in the case of cats that caffeine, in what might be considered a moderate dose, is of no benefit in the treatment of chloral poisoning; indeed, so far as the evidence presented is to be relied upon, it exerts an unfavorable influence. Salant and Rieger (5) place the average minimal fatal dose of caffeine for cats by oral administration at 150 mgm. per kilogram; Pilcher (2) states that death has occurred after 60 mg. per kilogram, but, evidently, he considers this exceptional, placing the minimal fatal dose at 120 mgm. per kilogram. Sollmann (4) places the M.F.D. for cats by hypodermic injection at 150 mgm. per kilogram. In view of the somewhat questionable influence of the comparatively small dose of caffeine that was employed in the treatment of the animals poisoned by chloral, three more cats were given the dose of 0.22 Gm. chloral per kilogram and then were injected subcutaneously with 100 mgm. caffeine per kilogram. All of these animals succumbed quite promptly.

CONCLUSIONS.

1. The determination of the M.F.D. of hydrated chloral for dogs by intraperitoneal injection appears to be difficult of accomplishment; it is in the neighborhood of 0.5 to 0.7 Gm. per kilogram body weight.

2. The M.F.D. of hydrated chloral for cats can be fixed with considerable accuracy when the drug is injected intraperitoneally, being very close to 0.23 Gm. per kilogram.

3. Caffeine was not found to be of any benefit in the treatment of poisoning by hydrated chloral.

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THE BIO ASSAY OF ACONITE.*

BY L. W. ROWE.

A few years ago all aconite preparations were being standardized chemically by determining the amount of alkaloid contained in them. A comparison of clinical activity with the chemical showed many discrepancies and a search was begun for a more satisfactory means of determining aconite activity. A physiological method was adopted—M.L.D. guinea-pig method (1)—which has proved to be reasonably accurate and its results are really proportional to the therapeutic value. From a theoretical standpoint the present method is satisfactory and the work of Swanson (2), (3) on this subject has done much to standardize the technique of the test and to render the results obtained in different laboratories correspondingly more uniform.

When considered from the practical viewpoint of a commercial laboratory, however, the guinea-pig method has one disadvantage, namely, that it is more expensive to conduct than the importance of small lots of the drug really warrants. To be reasonably certain of results, from 8 to 15 healthy, normal adult guinea-pigs must be used and the pigs alone are worth usually $10 or more for a test. Sometimes an assay requires an even larger number of pigs.

The high initial cost for test animals alone, led to a desire to reduce it in some way without decreasing the accuracy of the results and experiments were begun using the white mouse as the test animal. The cost of white mice is only about one-tenth that of normal adult guinea-pigs. A technique was developed similar to that using guinea-pigs except that the mice are injected intraperitoneally instead of subcutaneously. This method of injecting gives more rapid and satisfactory results. The volume of the dose injected should never be over 1 cc. with 0.5 cc. as the average volume. The absorption following intraperitoneal injection is certainly more uniform from a quantitative standpoint than is true with subcutaneous administration and the work of Zeigler (4) is corroborative of these facts. Also, the possibility of leakage is negligible, if a fine needle is used; subcutaneous injection into so small an animal as a mouse being often attended by an appreciable loss through leakage at the site of injection.

The following table gives a summary of about twenty tests and presents comparative data for analysis:

* Scientific Section, A. PH. A., Des Moines meeting, 1925.