4. The optimum analgesic structure within this series tested was represented by α-*dl*-2-acetoxy - 1,2 - diphenyl - 3 - methyl - 4 - dimethylaminobutane hydrochloride.

5. Some degree of correlation was shown among the three activities, although exceptions were noted.

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Chlorpromazine and Dextro-amphetamine as Antidotes in Acute Antihistaminic Toxicity in Rats

By I. H. MAEL† and J. F. BESTER

Acutely toxic oral doses of a number of antihistaminics were determined in adult white rats of both sexes. Toxic symptoms included convulsive seizures which lasted some minutes and were periodically repeated, followed by generalized central depression, terminating in unconsciousness and death. Chlorpromazine and dextro-amphetamine were administered in that order, intraperitoneally, in varying quantities and at varying time intervals. It was found that, if chlorpromazine was administered at the onset of convulsions and dextro-amphetamine at the first signs of depression, the recovery rate of animals was quite high.

THERAPEUTICALLY useful antihistaminics were developed well over 20 years ago, and for most of that time their acutely toxic capabilities have been recognized. Just as the various antihistaminics vary in their potencies, so they vary in the frequency and severity of their toxic manifestations. Such variations are largely quantitative, however; and when they occur, the symptoms of acute toxicity are quite similar regardless of the drug used. Typically, drowsiness followed by nervousness, tremors, muscle twitching, delirium, and convulsions are observed along with respiratory depression and cyanosis and followed by unconsciousness and death (1).

Despite the fact that repeated efforts have been made to find satisfactory methods of treatment of acute poisoning with the antihistaminic drugs, methods of treatment continue to be difficult and not overly successful. The need for uniformly adequate antidoting has not lessened with the years; acute antihistaminic poisoning is not uncommon. Each month, for example, several such intoxications are reported in Arizona, totaling 27 for the year 1961 (2). The Poison Information Center in Los Angeles in the first 6 months of 1961 reported 42 acute poisonings from antihistaminics as such, plus an additional 65 due to antihistaminic-containing nonbarbiturate sedatives (3).

The difficulty in preventing poisoning with these drugs and in coping with them when they arise is complicated by the fact that dose effect relationships are inconsistent. For example, the oral LD_{50} of diphenhydramine in rats has been reported as 500 mg./Kg. (4), and of pyrilamine hydrochloride, subcutaneously in rats, as 150 mg./Kg. (5). Yet 400 mg. of diphenhydramine and 1.3 Gm. of pyrilamine, respectively, caused the deaths of two 2-year-old children (1). Connolloy reported serious intoxication of a $5^1/_2$-year-old child following ingestion of 12 mg. of chlorpheniramine (6).

Because antihistaminics typically cause toxic symptoms of mixed characteristics, single antidotes offer little hope of success. Various drugs and drug combinations have been tried and reported. These include histamine, atropine plus epinephrine, phenobarbital, caffeine, dextro-amphetamine (7), ether (8), phenobarbital plus caffeine and ephedrine (9). Results were generally unsatisfactory.

Chlorpromazine reportedly has shown the ability to cause a definite decrease in motor activity without evidence of hypnosis (10). Dextro-amphetamine has long been recognized as an

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TABLE I.– ESTABLISHMENT OF DOSAGE AND ANTIDOTAL SCHEDULES

No. of Rats	Drugs Given	Dosage, mg./Kg.	When Given	Results
5	Diphenhydramine	250	...	Recurring epileptiform convulsions. All dead within 2 hours.
5	Chlorpromazine	50	...	Depression; three deaths.
5	Diphenhydramine Chlorpromazine	250 50	Simultaneously	Severe depression; four deaths.
5	Diphenhydramine	100	...	Excitation only; no convulsions.
5	Diphenhydramine Chlorpromazine	100 25	Simultaneously	Marked depression only.
5	Diphenhydramine Chlorpromazine	250 25	Simultaneously	Depression and death of all.
5	Diphenhydramine Chlorpromazine	250 15	Simultaneously	Depression and death of all.
5	Diphenhydramine Chlorpromazine	250 10	Simultaneously	Depression and death of all.
5	Diphenhydramine Dextro-amphetamine	250 0.15	Simultaneously	Convulsions; all dead in 2 hours.
5	Diphenhydramine Chlorpromazine	250 10	Simultaneously	Depression; all dead in 24 hours.
...	Dextro-amphetamine	0.75	Upon onset of depression	...
5	Diphenhydramine Chlorpromazine Dextro-amphetamine	250 10 1.25	... Simultaneously upon onset of symptoms	No convulsions, but excitation. Later depression with three deaths.
10	Diphenhydramine	250	...	All symptoms well controlled.
...	Chlorpromazine	10	Upon onset of convulsion	...
...	Dextro-amphetamine	0.625	Upon onset of depression	...
...	Dextro-amphetamine	0.3	As needed	...

analeptic. It therefore appeared logical to test their combined abilities in controlling the acute toxic manifestations of antihistaminic agents.

EXPERIMENTAL

White adult Wistar strain rats of both sexes were employed in the study. They were deprived of food and water for 24 hours prior to use. Antihistaminic drug doses were administered in aqueous solution by stomach tube. Concentration of solutions was adjusted so that all doses were of the same volume. Antidotal drugs were administered intraperitoneally, and again volumes were kept constant.

Diphenhydramine was used initially because its action and side effects seemed most typically representative of the group (11).

After antidoting, the animals were kept under observation for 72 hours.

Initial experimental procedures were designed to establish appropriate doses, dosage schedules, and sequence of drug administration. The results of this testing are shown in Table I.

Symptoms exhibited by those animals receiving only diphenhydramine followed closely the pattern described for humans. The time between drug administration and first symptoms varied from 8 minutes to 65 minutes. Excitation increased, particularly to such stimuli as noise and touch. Respiratory depression developed. Spontaneous movements increased, but gait became unsteady. A Straub reaction occurred in some animals. Muscle twitching steadily increased in intensity until full epileptiform convulsions ensued. Cyanosis was quite evident. Short periods of collapse separated convulsive episodes. Unconsciousness, accompanied by decreasing convulsions and increasing cyanosis, led ultimately to death.

Those animals receiving diphenhydramine plus chlorpromazine showed only the signs of depression; those receiving diphenhydramine plus dextro-amphetamine developed the signs of excitation more rapidly and more severely.

Because the last procedure shown in Table I appeared to be most effective, a total of 32 additional animals were treated by this routine. Diphenhydramine (250 mg./Kg.), was administered orally. As soon as convulsions became evident, chlorpromazine (10 mg./Kg.), was given intraperitoneally and as depression developed, dextro-amphetamine (0.625 mg./Kg.), was given intraperitoneally. If depression continued or returned, further doses of dextro-amphetamine (0.3 mg./Kg.), were given. In no instance was it necessary to administer more than three such additional doses.

DISCUSSION

All 32 animals showed the initial symptoms of toxicity, but only 22 developed convulsive seizures and only these were treated. The remaining ten animals recovered without treatment. Of the 22 treated, three failed to respond to chlorpromazine

and died during convulsions. Of the 19 whose convulsions ceased following chlorpromazine administration only one died during the ensuing depression while 18 recovered. Thus, of a total of 42 animals receiving 250 mg./Kg. of diphenhydramine, 32 developed symptoms requiring treatment and 28 of these recovered.

Limited studies of the effectiveness of this regimen in combating acutely toxic doses of several other antihistaminics were conducted. The protocol was unchanged, except that challenging doses of antihistaminics were altered to parallel potency. The results are reported below.

Tripelennamine.—Doses of 100, 150, 200, and 250 mg./Kg., respectively, were administered to eight rats. Chlorpromazine (4 mg./Kg. for each 100 mg./Kg. of tripelennamine), and dextro-amphetamine (0.25 mg./Kg. for each 100 mg./Kg. tripelennamine), served as antidotes. Only at the largest challenging dosage level was it necessary to give more than one dose of dextro-amphetamine. At this level one animal died. All others recovered.

Thenylpyramine.—Dosage and antidotal procedures were identical with those for tripelennamine. However, in all cases three doses of dextro-amphetamine were given. At each of the 200 and 250 mg./Kg. levels of thenylpyramine one animal died. All others recovered.

Chlorphenamine.—Challenging doses were 10, 15, 20, and 25 mg./Kg., respectively. Antidoting doses were 4 mg./Kg. of chlorpromazine and 0.25 mg./Kg. of dextro-amphetamine for each 10 mg./Kg. of chlorphenamine. A single administration of dextro-amphetamine sufficed in all cases and all animals recovered.

At the present time, these studies are continuing. Because current antidotal procedures against antihistaminic acute toxicity leave much to be desired, any improvement in method warrants further study. It is hoped that the combination of drugs herein described, or closely related drugs to be tested in our laboratory, will continue to show promise.

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Solubility of Carbon Dioxide, Krypton, and Xenon in Lipids

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The solubility of carbon dioxide, krypton, and xenon has been measured at one atmospheric pressure and at temperatures of 25, 30, 37, and 45° in olive oil, dog fat, human fats, and rat-pooled fat. The solubility of the gases studied in the oil and fats was found to decrease as the temperatures increased. Heats and entropies of solution have been calculated from linear dependencies of logarithm of the solubility with reciprocal absolute temperature. There seems to be a linear relationship between solubility, surface tension, and viscosity of the lipids.

THE PRIMARY objective of this study is to obtain some precise data on the solubility of krypton and xenon in lipids for calculation of body fat in a living body. Carbon dioxide was also included in this study because of the paucity of such data in lipids.

The solubilities of carbon dioxide, air, oxygen, nitrogen, and hydrogen in corn oil, in both unhydrogenated and hydrogenated lard, and in cottonseed oil have been measured at various temperatures by several investigators (1–3). They found that all the gases, with the exception of carbon dioxide, are increasingly soluble in the fat as the temperature rises. The solubility of carbon dioxide in human fat, dog fat, and rat fat at 38° was reported by Nichols (4). The solubility of xenon in olive oil and other aromatic oils, and of radioactive krypton and xenon in olive oil has been measured at 20, 22, and 37° by Steinberg and Manowitz (5), and Lawrence, *et al.* (6), respectively. Steinberg and Manowitz claimed their data, which are identical with Lawrence, *et al.*'s, to be accurate within 10%. It is obvious that these data are not sufficiently precise for calculating body fat in a living body.

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EXPERIMENTAL

Materials Employed.—Research grade carbon dioxide, krypton, and xenon were purchased from Matheson Co. According to their specifications,