COMPARATIVE PHYSIOLOGICAL ACTIONS OF SOME ALKANE-DIAMINES

GORDON A. ALLES, CHARLES H. ELLIS AND MILDRED A. REDEMANN

Department of Pharmacology and Experimental Therapeutics, University of California Medical School, San Francisco, and the Laboratories of Gordon A. Alles, Ph.D., Pasadena

Received for publication October 23, 1952

A number of organic bases, on injection into the body, may cause the liberation of histamine. Some aliphatic diamines of simple structure do this, as shown by the studies of MacIntosh and Paton (1949). This study of the relative activities of a series of alkane-diamines was carried out in part for the information on the relations between structure and physiological actions. The study was also carried out to reinvestigate the question as to whether these simpler alkane-diamines do primarily owe their physiological actions to the liberation of histamine.

MacIntosh and Paton (1949) studied the series of α,ω-alkane di-primary-amines up to the C_{16} member of the series, and found the peak of depressor activity to be with the C_{10} and C_{11} compounds. For their proposed verification that these diamines act by liberation of histamine, they carried out a detailed study only with the C_8 compound. It would seem more probable that the characteristic actions of the series would be most clearly defined with the most active compounds. In the present study particular attention was given to the various pharmacological effects of decane-1,10-diamine in order to reveal the most specific actions within this group of compounds.

Studies of mono-amine oxidase and of di-amine oxidase upon diamine substrates, by Blaschko and Hawkins (1950), are of particular interest with regard to the pharmacological actions of such diamines in the body. They found that mono-amine oxidase was particularly active on di-amines when the two amino groups are separated by more than six carbon atoms, as with octane-1,8-diamine and decane-1,10-diamine. Since the duration of the physiological action of these diamines in the body might be expected to be limited because of their destruction by either mono-amine or diamine oxidase systems, it was of interest to study some of their N-alkyl and N-dialkyl derivatives, and of special interest to study their α,ω-di-methyl substituted derivatives. Similar substitution of aliphatic mono-amines has been systematically studied by Alles and Heegaard (1943) for the prevention of action by mono-amine oxidase. A similar structural effect preventing the action of di-amine oxidase has been evidenced by Alles, Wisegarver and Shull (1943) with α-methyl derivatives of imidazolyl-alkylamines.

EXPERIMENTAL. The needed compounds were synthesized in Pasadena by Dr. C. Ernst Redemann and Burnett B. Wisegarver, to whom the present authors owe their best thanks for their work. The identity and purity of the compounds were concluded from the methods of syntheses used and the correspondence of their chloride analyses of the dihydrochloride salts when compared with chloride contents calculated from molecular formulas. Dose comparisons were made on a molecular weight per kilogram basis. The compounds used

were: octane-1,8-diamine dihydrochloride, MW 217; decane-1,10-diamine dihydrochloride, MW 245; dodecane-1,12-diamine dihydrochloride, MW 273; 1,8-dimethyl-octane-1,8-diamine dihydrochloride, MW 245 (decane-2,9-diamine dihydrochloride); 1,10-dimethyl-decane-1,10-diamine dihydrochloride, MW 273 (dodecane-2,11-diamine dihydrochloride); decane-1,10-di(methylamine) dihydrochloride, MW 273; decane-1,10-di(ethylamine) dihydrochloride, MW 301; decane-1,10-di(dimethylamine) dihydrochloride, MW 301; decane-1,10-di(diethylamine) dihydrochloride, MW 357.

Depressor effects in dogs. Effects of the diamines upon arterial pressure following intravenous injection into dogs under sodium pentobarbital anesthesia

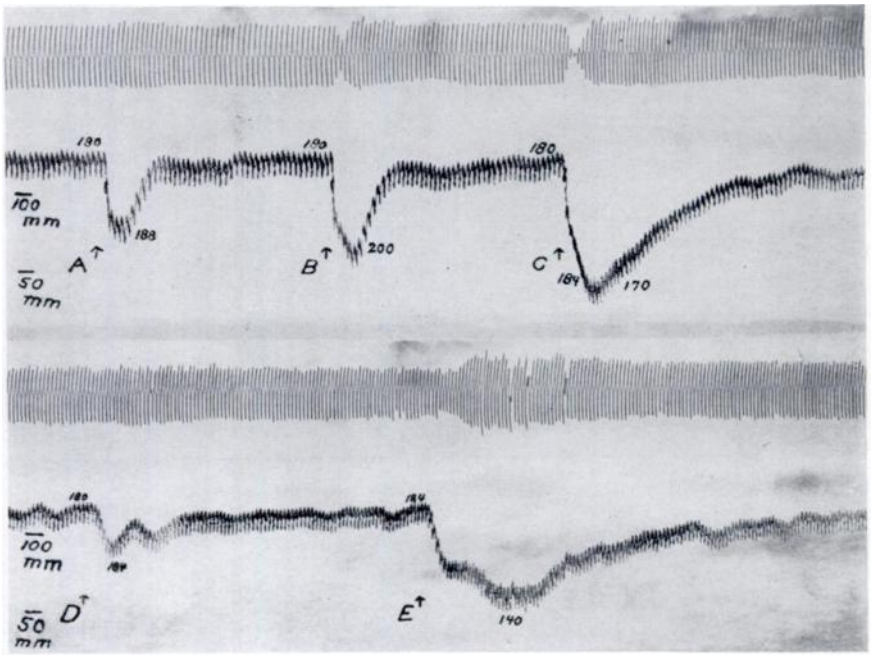

Fig. 1. Dog under pentobarbital anesthesia; tracheal and arterial blood pressure tracings.

A. 10^{-8} moles/kgm. histamine. B. 2×10^{-8} moles/kgm. histamine
C. 5×10^{-8} moles/kgm. histamine. D. 10^{-6} moles/kgm. decane-1,10-diamine
E. 2×10^{-6} moles/kgm. decane-1,10-diamine.
Tracheal tracings above, pulse rates noted on pressure tracings.

were compared. Light levels of anesthesia were used, with an initial 30 mgm. per kgm. dose given intraperitoneally and supplemental 5 or 10 mgm. per kgm. doses given as needed. In no case was a notable latency of effect observed, all falls of carotid blood pressure beginning within 10 seconds after injection into the femoral vein. Rapid repetition of injections of considerably active doses led to a diminished responsiveness of the animal, but with an allowance of 15–30 minutes between successive injections this was not marked. Fairly accurate evaluation of relative effects of any two compounds were made by giving an injection of one compound between two identical injections of the other compound. A comparison

of the extent and time course of the depressor effects in relation to that of histamine is shown in fig. 1.

Several points are noteworthy in the comparisons. First, associated with even pronounced acute falls in blood pressure from histamine, the heart is not usually slowed and may be accelerated, presumably by reflex stimulation resulting from the lowered blood pressure. Second, while small depressor effects of decane-1,10-diamine or closely related compounds occur without notable changes in heart

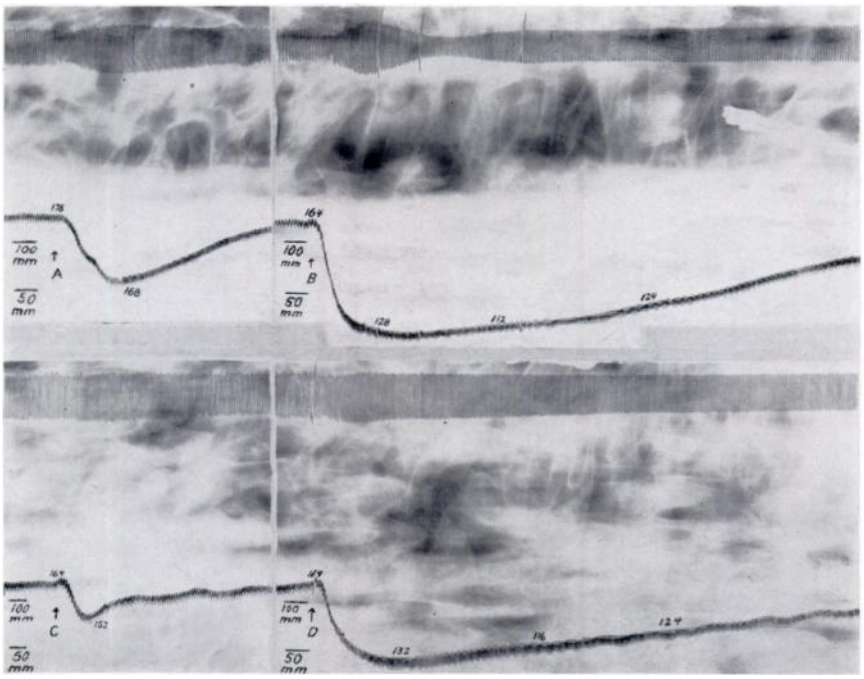

FIG. 2. Dog under pentobarbital anesthesia; tracheal and arterial blood pressure tracings.

A. 2×10^{-6} moles/kgm. decane-1,10-diamine
B. 5×10^{-6} moles/kgm. decane-1,10-diamine
C. 5×10^{-6} moles/kgm. 1,10-dimethyl-decane-1,10-diamine
D. 10^{-5} moles/kgm. 1,10-dimethyl-decane-1,10-diamine

rate, larger depressor effects are accompanied by a notable decrease in heart rate and increase in pulse pressure, as registered by membrane manometer tracings. Third, where the depressor effect of histamine amounts to 50 mm. Hg or more, the respiratory tracings usually showed evidence of some bronchoconstriction. With decane-1,10-diamine slight decreases of respiratory amplitude were observed on occasion, but usually there was a transient or lasting increase in respiratory amplitude or rate, or both. As shown in fig. 2, respiratory amplitude or rate, or both, may be increased even with very profound and lasting falls in blood pressure, and no evidences of bronchoconstriction were noted. Fig. 2 also shows the lesser activity of the 1,10-dimethyl substituted decane-1,10-diamine, and, particularly in comparison of the effects of the smaller dosages, it is not apparent

that this methyl-substituted compound has any greater duration of action. The depressor effects of either compound in the larger doses illustrated last between 10 and 20 minutes, and pressures as low as 20 mm. Hg may be reached and may be persistent for some time, with apparently complete and subsequently uneventful recovery after 20 to 30 minutes.

Any attempts at precise comparative valuation of the intensity of depressor activities of the compounds studied were complicated by the dose-effect relationship. Once a threshold dosage for minimal depressor effect has been exceeded, there is a rather sharp increase in depressor effect with increased dosage. Thus, comparisons of doses of two compounds for minimal depressor effects may give results which are distinctly different than from comparisons made at doses which give substantial depressor effects. As shown in fig. 1, the increased effect of a twofold increase in dose of decane-1,10-diamine is disproportionately large. In fig. 2, the response to 2×10^{-6} moles per kgm. of decane-1,10-diamine is considerably greater than the response to 5×10^{-6} of its 1,10-dimethyl derivative. Furthermore, the response of 5×10^{-6} moles per kgm. decane-1,10-diamine is more comparable to that of 10^{-5} of its 1,10-dimethyl derivatives, although in prior sequence it appeared that the threshold effect of 10^{-6} moles per kgm. decane-1,10-diamine was between that of 10^{-6} and 2×10^{-6} of its 1,10-dimethyl derivative.

The compounds were found to have the following comparative activities for threshold depressor effects (falls of 10–20 mm. Hg): histamine, 100–200; octane-1,8-diamine, 0.5; decane-1,10-diamine, 1.0; dodecane-1,12-diamine, 0.5; 1,8-dimethyl-octane-1,8-diamine, 0.5; 1,10-dimethyl-decane-1,10-diamine, 0.5; decane-1,10-di(methylamine), 0.5; decane-1,10-di(ethylamine), 0.2–0.25; decane-1,10-di(dimethylamine), 0.1; decane-1,10-di(diethylamine), 0.1. Each of these valuations represents a rough averaging of studies made in three or four animals for each compound, in comparisons for which decane-1,10-diamine was used as a reference standard.

Depressor effects in rabbits. In a dose range of 5×10^{-7} to 2×10^{-6} moles per kgm. histamine consistently caused a pressor response in rabbits under light pentobarbital anesthesia, followed only in the case of the highest dosage by a fall in blood pressure associated with circulatory collapse. On the other hand, decane-1,10-diamine at no time showed any trace of pressor action under the same conditions. For example, 5×10^{-6} moles per kgm. given intravenously was without any notable action, but 10^{-5}, 2×10^{-5} and 4×10^{-5} moles per kgm. doses of the diamine resulted in increasingly pronounced depressor actions followed by complete recovery to the initial blood pressure levels. With the depressor doses a moderate acceleration of the heart occurred during the period of depressor action. This acceleration was subsequently followed by some slowing of the heart rate. Atropine had no notable action on either the depressor response or pulse rate changes induced by the decane-1,10-diamine.

In rabbits, as in dogs and later in guinea-pigs, the "delayed depressor response" reported by MacIntosh and Paton (1949) for cats has not been apparent, i.e. there has been no marked latent period before hypotensive responses occur.

Depressor effects in guinea pigs. Since these animals are generally more

sensitive to histamine than are dogs, cats or rabbits, the action of the alkanediamines on arterial pressure was studied extensively in them.

A carotid artery was cannulated with a short piece of 22 to 26 gauge hypodermic tubing connected by polyethylene tubing to a Sanborn Electromanometer. To the 0.9 per cent solution of sodium chloride in the reservoir was added heparin sodium in a concentration of 1 per cent. Animals weighing from 400 to 500 gm. were suitable, and intraperitoneal injections of 40 mgm. per kgm. or more as needed, of pentobarbital sodium were used for anesthesia. Injections were made into the jugular or superficial circumflex iliac veins through some polyethylene tubing connected to a cannula of hypodermic tubing lying in the vein.

As in the dog studies, no marked differences in latency between the alkanediamines and histamine were observed. The depressor responses of the compounds studied were qualitatively similar, but it was clear that, quantitatively, decane-1,10-diamine is the most active depressor agent. In guinea pigs, as in dogs, certain compounds were found to be markedly less effective than others at threshold dosage levels, yet were equally active at dosage levels above the threshold amount. However, for approximate screening, it was more convenient to compare the magnitude of response to a fixed dose of each compound. At 5×10^{-6} moles per kgm. the compounds can be rated with regard to the magnitude of depressor response in order of decreasing activity as follows: for the primary diamines, decane-1,10-diamine, 1,10-dimethyl-decane-1,10-diamine, 1,8-dimethyl-octane-1,8-diamine, dodecane-1,12-diamine, octane-1,8-diamine. For the N-alkyl substituted diamines, decane-1,10-di(methylamine) was more active than decane-1,10-di(ethylamine), but was less active than decane-1,10-diamine. Likewise the di(dimethylamine) was more active than the di(diethylamine), but was less active than the di(methylamine), and was less active than the corresponding diamine.

It was evident that decane-1,10-diamine represents the maximum depressor activity in the group, although 1,10-dimethyl-decane-1,10-diamine and 1,8-dimethyl-octane-1,8-diamine were almost as effective. Fig. 3 shows that the durations of action of 1,8-dimethyl-octane-1,8-diamine and 1,10-dimethyl-decane-1,10-diamine were not notably longer than that of the compound with α-methyl substitutions, nor were the secondary and tertiary diamine derivatives appreciably different in duration of action when corresponding intensity of action was produced.

In comparing decane-1,10-diamine with histamine at threshold depressor levels, histamine was found to be about 500 times more active than the diamine (10^{-6} moles per kgm. for the diamine, 2×10^{-9} for histamine). At higher dosage, however, the diamine compared more favorably, 2×10^{-6} moles per kgm. giving a depressor response equivalent to that resulting from 10^{-8} histamine, or a ratio of 200:1, and in some instances ratios as low as 50:1 were observed. Uncertainty arises in trying to evaluate the diamine depressor actions in terms of histamine depressor action with any great degree of accuracy, since the durations of their actions differ so greatly.

MacIntosh and Paton (1949) reported that Neo-Antergan markedly reduced

the amplitude of the depressor response to octane-1,8-diamine. They concluded that "anti-histamine drugs can antagonize the circulatory effects of histamine liberators, but the antagonism is a limited one." Some studies of antagonism of the depressor response of decane-1,10-diamine in the guinea pig have led us to find a fairly definite molal ratio required between diamine and antagonist, and between histamine and antagonist. Benadryl, at 10^{-5} moles per kgm. reduced the depressor response to 2×10^{-6} moles per kgm. decane-1,10-diamine to one-half

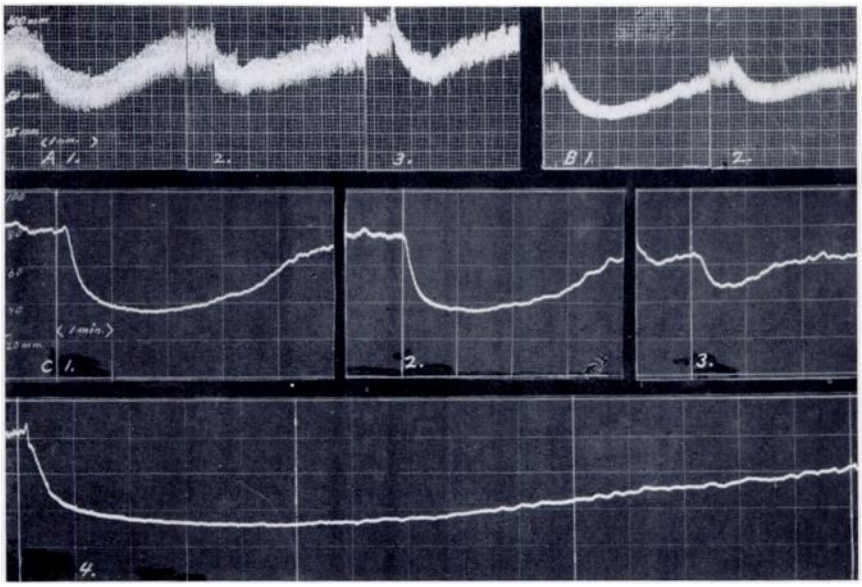

FIG. 3. Carotid blood pressure effects in guinea pigs.

A. 1. 5×10^{-6} moles/kgm. decane-1,10-diamine. 2. 5×10^{-6} 1,8-dimethyl-octane-1,8-diamine. 3. 5×10^{-6} 1,10-dimethyl-decane-1,10-diamine

B. Using smaller bore cannula 1. 5×10^{-6} moles/kgm. decane-1,10-diamine. 2. 5×10^{-6} 1,10-dimethyldecane-1,10-diamine

C. Using Integrating Circuit on Electromanometer 1. 2×10^{-5} moles/kgm. decane-1,10-diamine. 2. 2×10^{-5} decane-1,10-di(methylamine). 3. 2×10^{-5} decane-1,10-di(dimethylamine). 4. 8×10^{-5} decane-1,10-diamine

the unantagonized level, while only 2×10^{-7} moles per kgm. Benadryl was required to reduce the equivalent depressor response of 2×10^{-8} moles per kgm. histamine to one-half. Neo-Antergan showed about the same degree of activity against histamine, since 2×10^{-7} moles per kgm. Neo-Antergan also half-blocked 2×10^{-8} moles per kgm. histamine, while 10^{-5} moles per kgm. half-blocked 4 or even 8×10^{-6} moles per kgm. decane-1,10-diamine.

Our studies also included Neohetramine, which was found to be only about one-fifth or two-fifths as active against histamine as the above two antihistaminics, but a 1:1 ratio was found in its antagonism of decane-1,10-diamine, i.e., although distinctly less active against histamine, it was more active than Benadryl or Neo-Antergan against the diamine. The relative effectiveness of certain

antihistaminics may be quite different with respect to histamine and diamine antagonism.

Attempts were made to find a change in histamine-like activity in the plasma of guinea pigs receiving large doses of decane-1,10-diamine, similar to the experiments of MacIntosh and Paton (1949) in which cats were used. Doses of 10^{-5} to 10^{-4} moles per kgm. (2.45 to 24.5 mgm. per kgm. of dihydrochloride) of decane-1,10-diamine were used, and, because of the depressing effect of the compound on respiration at the highest doses, artificial respiration was maintained. Blood samples were collected from an inlying carotid cannula immediately before, 1, 5 and 30 minutes after injecting the dose of decane-1,10-diamine sufficient to cause a profound fall of arterial pressure. The samples were heparinized then centrifuged and tested on isolated guinea-pig ileum for "histamine-activity." While some activity was found even with control samples, no evidence of a change in such activity was found following the injection of the diamine, even though a dose of 10^{-4} moles per kgm. was given in three of the eight experiments carried through. Such a dose is about twice that of octane-1,8-diamine reported by MacIntosh and Paton (1949) to be effective in causing the appearance of histamine-like activity in the blood plasma of cats.

EFFECTS ON ISOLATED GUINEA PIG ILEUM. Strips suspended in a 37°C. bath of oxygenated Locke solution were not sensitive to concentrations of the diamines in comparison with histamine. MacIntosh and Paton (1949) reported octane-1,8-diamine to be inactive in concentrations of 10^{-4} (presumably 10^{-4} gm. dihydrochloride per ml. or 4.6×10^{-4} molal), but that it caused a contraction with 10 times this concentration in some experiments. In our studies, while 10^{-4} molal octane-1,8-diamine had little effect, 5×10^{-4} and 10^{-3} caused relaxation.

Decane-1,10- and dodecane-1,12-diamines caused relaxation at 10^{-4} molal, but at 5×10^{-4}, while the decane compound was still relaxant, the dodecane compound caused an initial contraction. At 10^{-3} molal both compounds caused contraction, the dodecane most notably. Similarly, the 1,8-dimethyl-octane-1,8- and 1,10-dimethyl-decane-1,10-diamines usually caused some relaxation at lower concentrations but differed at 10^{-3} molal in that, although the first compound had little effect or caused relaxation, the second compound caused contraction.

The decane-1,10-di(methylamine) and -di(ethylamine) also caused relaxations at lower concentrations but both caused some contraction at 10^{-3} molal. The decane-1,10-di(dimethylamine) and -di(diethylamine) caused contractions at 10^{-4} and 5×10^{-4} molal as well as at 10^{-3} concentrations.

EFFECTS IN INTRADERMAL TESTS IN MAN. The intradermal injection of histamine in sufficient concentrations results in the triple response reaction of Lewis (1926) in the skin. MacIntosh and Paton (1949) reported octane-1,8-diamine as showing a +++ reaction from 10^{-2} (presumably 10^{-2} gm. dihydrochloride per ml. or 4.6×10^{-2} molal), a ++ or + reaction to 5×10^{-4}. Our studies were made on five persons, and intradermal injections were made into the skin along the volar surface of the forearm. Both decane-1,10-diamine and its 1,10-dimethyl-derivative were tested, and these compounds as dihydrochlorides were made up

in dilutions of 10^{-4} and 10^{-5} molal with a sterile isotonic sodium chloride solution. With both compounds a flare and wheal response of notable extent was observed after 10^{-5} molal injections, and greater responses were observed after 10^{-4} molal injections. The responses to the 10^{-5} and 10^{-4} molal injections were roughly comparable quantitatively to those of 10^{-7} and 10^{-6} molal histamine in the same persons under the same conditions. We also noted that, as MacIntosh and Paton (1949) reported for octane-1,8-diamine, no persistent inflammation or necrosis was caused by either the decane-1,10- or 1,10-dimethyl-decane-1,10-diamines when used in concentrations up to and including 10^{-3} molal.

ACUTE LETHAL TOXICITY. Studies were made with white mice using intraperitoneal injections of 0.1 or 0.5 molal solutions as needed. When rapid death occurred, it was preceded by convulsions and labored breathing. Immediate autopsy showed the heart to be beating after respiration had stopped. In some

TABLE 1

Dosage-mortality data following intraperitoneal injection of various diamines into mice

COMPOUND	DOSE MILLIMOLES PER KGM.	DOSE MGM. PER KGM.	MORTALITY RATIO	APPROXIMATE LD_{50} MILLIMOLES PER KGM.
Octane-1,8-diamine	3.0	651	0/10	3.5
dihydrochloride	4.0	868	9/10	
Decane-1,10-diamine	0.6	147	2/10	0.7
dihydrochloride	0.8	196	9/10	
Dodecane-1,12-diamine	0.6	164	0/10	0.7
dihydrochloride	0.8	218	7/10	
1,8-Dimethyl-octane-	1.0	245	2/10	1.3
1,8-diamine dihydrochloride	1.5	368	10/10	
1,10-Dimethyl-decane-	0.6	164	1/10	0.7
1,10-diamine dihydrochloride	0.8	218	8/10	

animals constriction of the intestines was noted, and occasionally unusual peristalsis was evident. With delayed deaths, cyanosis was evident, respiration becoming increasingly slower until death ensued. Table 1 gives the lethal frequency data for the compounds studied.

The toxicity of decane-1,10-diamine and its 1,10-dimethyl derivative was approximated in white rats following intraperitoneal injection, and found to be 0.5–0.7 millimoles per kgm. for LD_{50}.

Since histamine is far more toxic for guinea pigs than for mice or rats, the toxicity in these animals was also approximately determined. The LD_{50} was about 0.4–0.5 millimoles per kgm. for both decane-1,10-diamine and its 1,10-dimethyl derivative on intraperitoneal injection.

In guinea pigs that died from receiving a lethal dose of either compound, pronounced effects on the gastric mucosa were apparent on prompt autopsy. The stomach lining showed eroded and hemorrhagic areas and red blotches of grossly dilated vascular bed were often notable in the walls of the intestine. In some cases the erosion of the stomach had proceeded to perforation and extrusion of

gastric contents into the peritoneal cavity. Animals not dying as a result of approximately an LD_{50} dose were autopsied 72 hours after injection, but none showed gross gastrointestinal pathology. A marked dilation of the heart was often noted in guinea pigs that died from receiving a lethal dose of these diamines.

Because of the notable effects on the gastric mucosa, further study was given to this effect as produced by decane-1,10-diamine. On the basis of 0.5 millimols per kgm. being the acute LD_{50} dose, a study of the effects of $\frac{1}{2}$, $\frac{1}{4}$ and $\frac{1}{8}$ of this dose, repeated daily intraperitoneally for two weeks, was made on groups of five animals for each dose. A control group receiving injections of 0.9 per cent sodium chloride was included. Of the twenty animals used only five died within the two weeks, and all of these were receiving $\frac{1}{2}$ LD_{50} dose. Two of these showed gastric erosion. The animals receiving only $\frac{1}{4}$ and $\frac{1}{8}$ LD_{50} and the control group were sacrificed at the end of the two-week period, and two of the five receiving the $\frac{1}{4}$ LD_{50} dose showed evidence of intestinal congestion and the intestines had adhered to the abdominal wall at sites of an intraperitoneal injection. None of the other animals showed any gross gastrointestinal pathology.

ABSENCE OF EFFECT ON GASTRIC SECRETION. In view of the gastric erosion produced by lethal doses of the diamines in guinea pigs, it was of interest to see if these compounds were active in producing an increase in gastric secretion. This would be expected if the compounds liberated notable amounts of histamine in the body. MacIntosh and Paton (1949) reported a single experiment in which licheniformin seemed to cause increased gastric secretion in the cat, but made no such study with any of the other compounds listed by them as histamine liberator substances.

Single intravenous doses of histamine as large as 10^{-7} to 10^{-6} moles per kgm. were not found active in increasing gastric juice in either the guinea pig or rabbit. However, repeated intravenous doses of but 5×10^{-9} to 5×10^{-8} moles per kgm. each minute for 15 minutes caused the gastric acid output to be consistently and considerably increased. Rabbits were found more generally suitable for this work than guinea pigs.

In an animal under pentobarbital anesthesia, a tracheal cannula was tied in place in case artificial respiration became necessary. The esophagus was ligated in the neck, an incision made into the abdominal wall, and the duodenum ligated. A catheter was introduced into the stomach through the pylorus and tied securely by a second ligature around the duodenum.

After flushing out the stomach with successive 25 ml. portions of warm 0.9 per cent sodium chloride solution until free of undigested materials, a 30-minute period for equilibration was used. Then 25 ml. of saline were introduced and allowed to drain. Gastric secretion was then collected at 30-minute intervals using a 25 ml. saline rinse when collecting each sample.

Injections of 0.2 ml. were made at one-minute intervals for 15 minutes through an inlying venous cannula. The 30-minute gastric samples were titrated with 0.02 N NaOH to pH 3.0 (free acid) and to pH 8.5 (total acidity) using a Beckman pH meter.

The effect of histamine in both guinea pigs and rabbits was to notably increase the total acidity and particularly the free acid (titration to pH 3.0). However, the injection of 10^{-6} to 5×10^{-6} moles per kgm. per minute of decane-1,10-diam-

ine was without any effect in animals that were responsive to histamine at 10^{-8} to 5×10^{-8} moles per kgm. per minute (fig. 4). On the basis that the comparative activities of the two compounds are as 1:100, as indicated by depressor activities or by the intradermal wheal response in man, it appears that the activity of the diamine with respect to histamine is considerably less than 1:100 in any possible stimulation of gastric acid secretion.

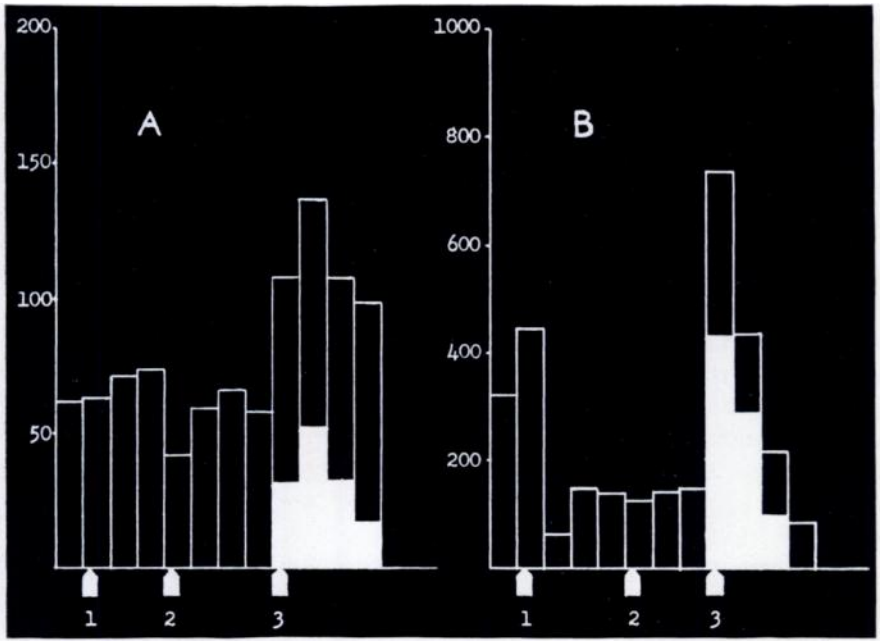

FIG. 4. Gastric acid following decane-1,10-diamine and histamine.

Blocks represent 30-minute period, with height proportional to micromoles HCl total acidity. Filled-in blocks represent free acidity in same unit. Injection periods show an interval of 15 minutes.

A. Guinea-Pig. 1. 0.2 ml./min. 0.9% NaCl. 2. 5×10^{-6} moles/kgm./min. decane-1,10-diamine. 3. 5×10^{-8} moles/kgm./min. histamine.

B. Rabbit 1. 0.2 ml./min. 0.9% NaCl. 2. 10^{-6} moles/kgm./min. decane-1,10-diamine. 3. 10^{-8} moles/kgm./min. histamine.

DISCUSSION. The more active alkane-diamines are depressor in their action on the circulation in the dog, cat, rabbit and guinea pig. While MacIntosh and Paton (1949) apparently quite regularly observed a significant delay in the onset of the depressor action in the cat, and on occasion in the dog, we have not observed this latency in any of our experiments with the dog, rabbit or guinea pig. The depressor responses that have been observed appeared to be of about the same magnitude in relation to dosage as those reported by MacIntosh and Paton (1949), and were also found to be maximal with respect to decane-1,10-diamine as compared with octane-1,8 and dodecane-1,12-diamines.

In our experiments in the guinea pig, large and prolonged falls in blood pres-

sure were unaccompanied by the appearance of increased "histamine-like" activity in the plasma, and there was no concomitant manifestation of histamine-like activity on the bronchi. It would seem possible that the observations of "histamine-like" substances appearing in the blood in cats and dogs with the alkane-diamines may have been related to particular conditions of circulation at the time of injection of the diamines. MacIntosh and Paton (1949) noted that in the dog, a change from an immediate to a delayed response could be effected on occasion by an intravenous infusion of epinephrine.

Certainly, the diamines studied can produce marked depressor effects without any apparent implication of histamine as part of the mechanism of action. The mechanism of action may involve the same or similar receptor sites as are involved in the action of histamine. Atropine is relatively ineffective against the depressor actions of both the diamines and histamine. However, the sharing of a common mechanism generally in the body is not apparent in the lack of bronchoconstrictor effects by the diamines, the marked difference in the effectiveness of the diamines and histamine on the ileum, and in the failure of the most active diamines to show any pressor effect like histamine in the rabbit. The absence of notable toxicity differences for the diamines between guinea pigs and mice or rats, in contrast to the greater sensitivity of guinea pigs to histamine, also indicates different mechanisms of action.

The causation of gastric lesions and erosions from acute or chronic lethal doses of the two diamines studied as to this effect, is somewhat suggestive that in such response histamine might play a part. Histamine administered by intramuscular injection in beeswax preparations (Hay, Varco, Code and Wangensteen, 1942), or in near lethal doses by subcutaneous injection (Van Meter and Oleson, 1949), does cause a similar result. However, the primary effect of the diamines may simply be a serious impairment of circulation in the gastric and intestinal blood vessels. Histamine liberation may also occur from such stasis and in turn contribute toward the production of the gastric erosion.

The depressor activity of the di-N-methyl derivative of decane-1,10-diamine is almost as great as the primary amine, while the di-N-ethyl derivative was clearly less active. This structural relationship is similar to that found with the more active sympathomimetic amines. The lesser activity of the di-N-dimethyl derivative similarly corresponds with the effect of such structural change upon the sympathomimetic activities of phenalkylamines. Comparable situations also exist with regard to the N-methyl and N-dimethyl derivatives of histamine and their relative activities as reported by Vartiainen (1935).

SUMMARY

1. Decane-1,10-diamine and a number of closely related alkane-diamines were studied and compared to histamine. Doses 100 to 1000 times greater on a molal basis were required to produce a comparable intensity of depressor effect in dogs and guinea pigs.

2. Unlike histamine, the most active of these diamines, decane-1,10-diamine, does not cause any pressor effect in the rabbit.

3. On a molal ratio basis the depressor activities of decane-1,10-diamine are not as effectively blocked as those of histamine by anti-histamine agents. Blocking effectiveness towards decane-1,10-diamine as compared with that towards histamine is not the same for different antihistamine compounds.

4. No changes of histamine-like activity in the plasma of guinea pigs could be demonstrated following doses of decane-1,10-diamine which produce marked depressor responses.

5. On isolated ileum the alkane-diamines caused slight relaxations with minimally active bath concentrations, and contractions with higher concentrations. They are much less active than histamine in producing a contraction of the ileum.

6. Intradermal injections of the most active alkane-diamines into the skin in man cause a flare and wheal response similar to that of histamine, but they are only 1/100 as active.

7. Acute lethal toxicity of the most active alkane-diamines is about the same for intraperitoneal injection into mice, rats or guinea pigs. Gastric lesions and erosions were noted in guinea pigs receiving lethal doses. Decane-1,10-diamine, which showed such effects with lethal doses, is not an effective stimulant of gastric acid secretion.

REFERENCES

ALLES, G. A., AND HEEGAARD, E. V.: J. Biol. Chem., **147:** 487, 1943.

ALLES, G. A., WISEGARVER, B. B., AND SHULL, M. A.: THIS JOURNAL, **77:** 54, 1943.

BLASCHKO, H., AND HAWKINS, J.: Brit. J. Pharmacol., **5:** 625, 1950.

HAY, L. H., VARCO, R. L., CODE, C. F., AND WANGENSTEEN, O. H.: Surg. Gynec. and Obst., **75:** 170, 1942.

LEWIS, T.: "Blood Vessels of the Human Skin and Their Responses", Shaw, London, 1926.

MACINTOSH, F. C., AND PATON, W. D. M.: J. Physiol., **109:** 190, 1949.

VAN METER, J. C., AND OLESON, J. J.: Proc. Soc. Exp. Biol. and Med., **71:** 163, 1949.

VARTIAINEN, A.: THIS JOURNAL, **54:** 259, 1935.