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THE INHIBITORY ACTION OF PALUDRINE ON THE SECRETION OF GASTRIC JUICE

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Because excessive secretion of gastric juice is a common concomitant of chronic peptic ulcers, various workers have looked for substances having an inhibitory action. The secretion of HCl, though partly controlled by the vagus nerves, is peculiar in being stimulated by histamine and in being not greatly affected by atropine. The effect of atropine is described differently by different observers (Polland, 1930 ; Atkinson and Ivy, 1937 ; Gray, 1937 ; King, Comfort, and Osterberg, 1944). It appears to be more effective in abolishing the secretion produced by giving a meal than that produced by injecting histamine. Davenport (1940), and later Rehm and Enelow (1945), investigated the effect of sodium thiocyanate ; when given intravenously to dogs in sufficient amount, it was found to inhibit the secretion of HCl completely.

Recently Babkin and Karp (1947) have observed that the two antimalarial substances quinine and mepacrine (atebrin), when injected intravenously into dogs, depressed the secretion of gastric juice produced by stimulation of the vagus nerves. The doses they used were large in relation to the doses ordinarily given to man ; thus a dog of 10 kg. received 0.2 g. quinine bisulphate or 75 mg. mepacrine. When secretion was produced by the injection of histamine, neither quinine nor mepacrine affected it.

Recently a simple method of examining substances for an inhibitory action on gastric secretion has been developed in this laboratory by Wood (1948) ; cats are used, anaesthetized by cyclopropane or pentobarbitone (nembutal). The only essential point in which the method differs from that proposed by Lim (1923), and modified by Roth and Ivy (1944), is that histamine solution has been infused into the jugular vein at a uniform rate for periods up to 7 hours. In order to obtain a uniform infusion, a pump designed and made by Dr. E. H. J. Schuster has been used, with which a reasonably steady secretion of gastric juice has been obtained. The oesophagus was tied in the neck and not at the cardiac orifice, to avoid the vagi.

The action of paludrine

During the examination of the pharmacological properties of paludrine, its effect on the secretion of gastric juice was tested by this method. When histamine was infused, the rate of secretion rose gradually until at the end of about 1½ hours the amount collected in each 10 min. period became fairly steady. Sometimes 4 hours passed before the flow was steady. At this point, while the histamine infusion continued, the effect of paludrine

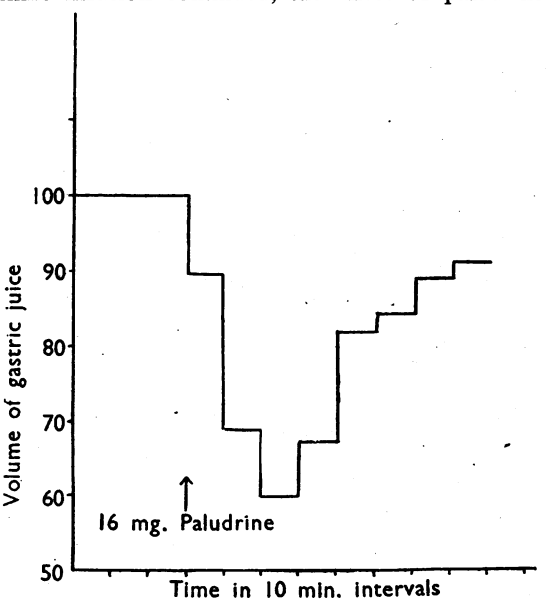


FIG. 1.—To show the fall in the secretion of gastric juice when 16 mg. paludrine were injected. The mean effect on the volume of juice in 9 cats is shown. In each experiment the initial secretion has been given the value 100. Abscissae: time in 10 min. periods.

was examined by making an injection of a single dose intravenously, or else by infusing paludrine intravenously. It was found that paludrine in doses which had only a transient effect on the blood pressure diminished the volume of juice secreted for a period of 60–90 min. The results of nine experiments in which a single injection of 16 mg. paludrine was given were combined so that the mean effect could be determined. This effect is shown graphically in Fig. 1 ; the volume of juice excreted per 10 min. during 30 min. before paludrine was injected is expressed as 100, and the volume fell to 60, after the injection. After reaching a minimum the flow gradually returned to its previous value, and the effect of paludrine could then be observed a second time. Details of one experiment were as follows: Histamine was infused at the rate of 15 μg. per min. into a cat of 3.2 kg. under nembutal anaesthesia (25 mg. per kg.). The rate of flow of gastric juice was 2.6 ml. per 10 min. during 30 min., and after the injection of 16 mg. paludrine it fell to 1.6 ml. during 65 min. The rate then returned to 2.6 ml. for a further 60 min.

In four experiments the injection of 8 mg. paludrine caused a smaller mean reduction in the flow to 75 per cent of the initial value.

When larger amounts of paludrine were given by slow infusion instead of by single injection, the periods of reduced gastric secretion lasted until the termination of the experiment. Fig. 2 shows the mean effect of infusing 60 mg. paludrine during 30 min. into 6 cats. The graph records the change in the total free acid excreted. The volume of juice per 10 min. was measured ; 1 ml. of this juice was then titrated against $N/50$ NaOH using thymol blue as the indicator. The total secretion of free acid per 10 min. was then calculated. The initial rise in secretion shown in Fig. 2 occurred in two of the six experiments for 20 min. ; thereafter there was a prolonged fall. In these experiments, both the volume of juice secreted and the concentration of free acid in the juice were reduced. The only effect the paludrine infusion had on the blood pressure was to cause an occasional initial rise. In four other experiments, doses of paludrine from 120 mg. to 180 mg. were infused. Table I shows these results. It can be seen that there was an initial stimulation of the secretion in Exp. 1. In these experiments, as in those recorded in Fig. 2, the volume of juice secreted did not recover from its low value.

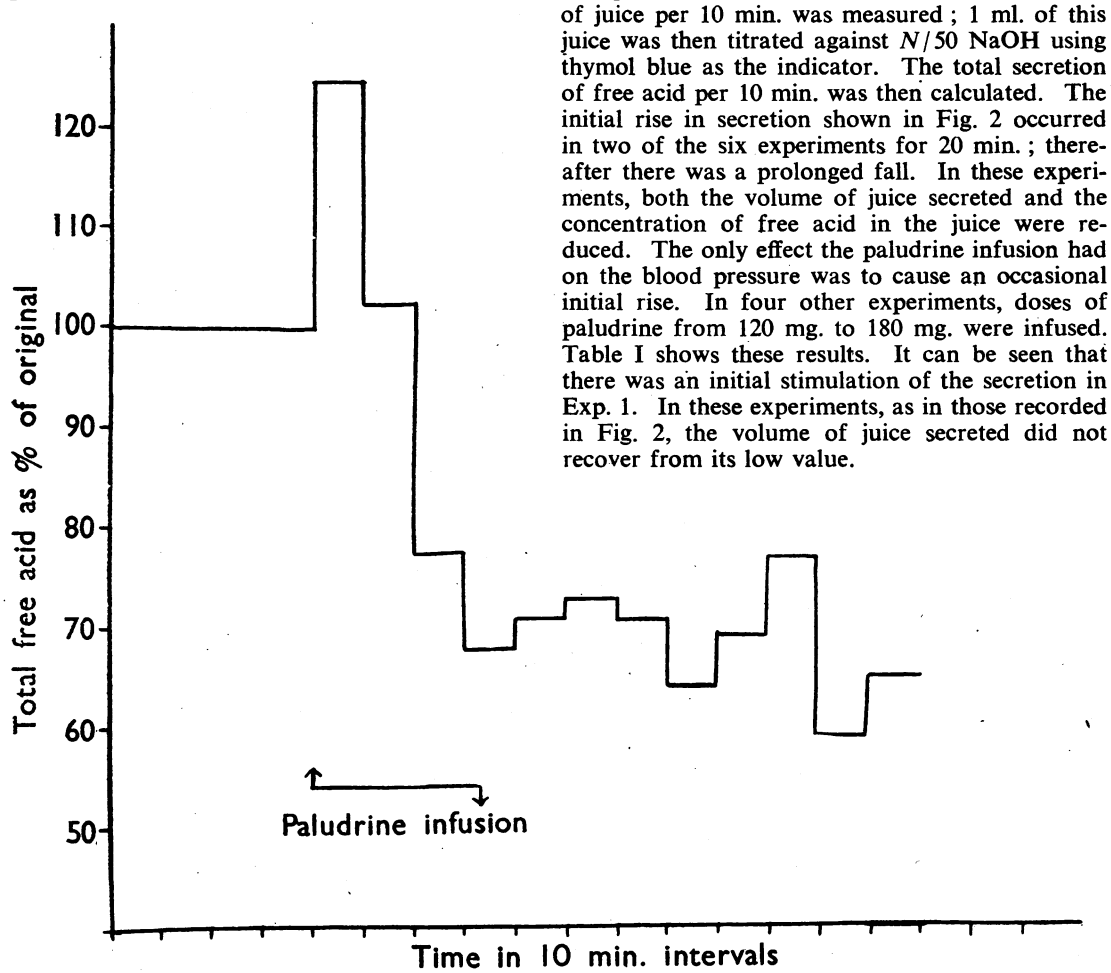


FIG. 2.—To show the mean fall in total free acid in gastric juice caused by intravenous infusion of 60 mg. paludrine into 6 cats. In 2 experiments there was an initial increase in secretion.

TABLE I

EFFECT OF INFUSED PALUDRINE ON VOLUME OF GASTRIC JUICE IN CATS

Exp.	Rate of histamine infusion μg./min.	Paludrine mg.	Duration of infusion min.	Gastric juice per 10 min. ml.	Period of observation min.	Mean percentage to which volume of juice fell
1	15	140	52	6.3 8.7	60 20	138
		,,	,,	4.3	110	68
2	15	120	100	4.6 3.8	30 140	82
3	15	180	90	4.7 2.2	60 160	47
4	15	120	60	1.7 0.5	40 170	29

In all experiments the rate of histamine infusion was usually 15 μg. per min., or more, throughout. Only in two experiments was it 10 μg. per min. This is a high rate of histamine infusion, providing a powerful stimulus to secretion and a severe test for an inhibitory substance.

Paludrine consists of the biguanide molecule, substituted at one end with the *p*-chlorophenyl radical, and at the other with the *iso*propyl radical. Compounds structurally related to paludrine were also tested to see if they would inhibit gastric secretion. The first three compounds tested were biguanide, *iso*propyl biguanide, and di-*iso*propyl biguanide. All were found to be inactive as shown by the results in Table II. These results were obtained by expressing the total secretion for an hour after the drug was given as a percentage of the total secretion of the hour previous to the administration.

In an effort to obtain a more quantitative estimation of the inhibitory power, the principle of the method recently described by Howat and Schofield (1948) was adopted. The main difference between this method and that previously used was that, instead of giving the test substance during a constant infusion of histamine, it was given between two periods of histamine infusion, each of 48 min. duration. The second response was expressed as a percentage of the first, the

TABLE II

NON-INHIBITORY BIGUANIDES

Substance	Dose in mg.	Total free acid for 1 hr. after drug as % of that for 1 hr. before drug	Average
Biguanide ..	60 60 60	133 91 84	106
*Iso*propyl-biguanide	60 60 60 60	140 106 103 57	102
	120	89	
Di-*iso*propyl-biguanide	60 60	120 93	107

TABLE III

PALUDRINE AND RELATED COMPOUNDS

Substance	Dose infused mg.	Total free acid expressed as % of original value	Average
Paludrine .. .. (N_1-*p*-chlorophenyl-N_5-*iso*propyl-biguanide)	60 60 60	75 71 17	54
N_1-*p*-chlorophenyl-N_5-methyl-biguanide	60 60 32	66 32 68	49
N_1-*p*-chlorophenyl-biguanide	80 60 60	92 33 155	93
N_1-*p*-methoxyphenyl-biguanide	60 60	78 64	71
N_1-*p*-chlorophenyl-N_3-methyl-guanidine	60 60 60	141 70 23	78

TABLE IV

SUMMARY OF RESULTS

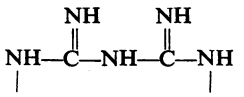
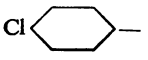
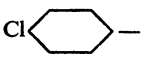
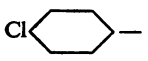
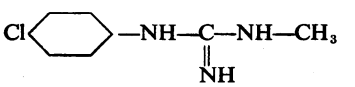
	Amount (mg.) administered	No. of expts.	Approximate percentage to which secretion was reduced
	60	9	60
	60	2	50
	60	2	70
	60	3	90
C_3H_7— —H	60	4	no reduction
C_3H_7— —C_3H_7	60	2	" "
H— —H	60	3	" "
	60	3	80

figure being a measure of the inhibitory power of the test substance.

By this method, five more compounds were tested (including paludrine as a standard). The results of these experiments are shown in Table III. The mean secretion of acid in three experiments in which paludrine was infused was reduced to 54 per cent of the original value; by the first method, six experiments gave a mean value of 64 per cent. The results shown in Tables II and III have been combined and arranged in order of activity, to give Table IV.

Discussion and Summary

Extensive trials of paludrine in men have been made in testing its value against malaria, and it is known to be a well-tolerated substance. A large dose produces gastro-intestinal symptoms in some individuals, and Hughes, Schmidt, and Smith (1947) have described how dogs fed on a diet containing paludrine become disinclined to eat. It seems probable that these observations are related to our finding that paludrine exerts an inhibitory action on the volume and acidity of gastric juice evoked by histamine. A similar compound in which the *iso*propyl group of paludrine was replaced by a methyl group was found to exert a similar effect. Other related substances had less or no effect. We have observed an initial stimulating action in a few experiments, preceding the inhibition. This is probably an example of a preliminary stimulant action preceding inhibition, which is commonly met in inhibitory drugs. Thus the first effect of taking atropine by mouth is to slow the pulse rate and cause the hands to become moist in most people; the later effect is of course the opposite. Atropine appears first to stimulate and later to paralyse the cholinergic nerve endings in the heart and sweat glands.

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