EFFECT OF RESERPINE ON GASTRIC ACIDITY

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Reserpine is reported to cause increased acid gastric secretion in cats and dogs. Clark and Schneider (1955) have shown increased gastric acidity in patients treated with oral and parenteral administration of reserpine. It is, therefore, advised that reserpine should be given with caution in cases of peptic ulcer. While investigating the effect of intraventricular reserpine on gastric acidity in cats, it was noted by Gaitonde *et al.* (1960) that there was a rise in blood histamine in a few animals following intravenous reserpine. Since the mechanism of action of reserpine on acid gastric secretion is not very clear, it was decided to investigate its action on gastric secretion in animals. Preliminary observations are presented in this report.

METHODS AND MATERIAL

Thirteen cats (nine intact and four spinal, excluding control animals) and three dogs were used in this study. Animals were starved for twenty-four hours before anaesthesia. Cats were anaesthetised with ether and anaesthesia was maintained with chloralose i.v. 80 mg/kg. A polythene tube (diameter 1 mm.) was introduced via femoral vein into inferior vena cava. This served to administer drugs as well as to draw blood samples. Abdomen was opened by a midline incision extending downwards from xiphisternum. A glass cannula (eight cms. long and half cm. diameter) was inserted in the stomach through a niche in the most avascular part in the anterior wall opposite incisura angularis and was fixed in a position by a purse-string suture. Abdomen was closed by interrupted sutures and position of cats was adjusted to effect a complete drainage of gastric contents. Samples were collected in a ten ml. measuring cylinder every fifteen minutes. The contents were aspirated to avoid incomplete drainage. At the end of most of the experiments stomach was opened to look for any evidence of pooling of secretions due to defective drainage.

Free acidity of each sample was estimated by titrating against N/100 NaOH, using methyl red as indicator and expressed as mEq HCl/litre. Reserpine was administered intravenously in a dose of 500 μg irrespective of the weight of the animal.

Seven ml. of blood were removed from inferior vena cava initially and at the time of maximum acid gastric response following the administration of

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the drug, as observed from the titration against N/100 NaOH. Equivalent amount of saline was administered to minimize changes in circulating blood volume.

Spinal preparation: Cats were anaesthetised with intratracheal ether, spinal cord was transected at the level of second cervical vertebra as described by Burn (1954) and the spinal preparation was maintained on artificial respiration. Drugs were administered through femoral vein half an hour after transection of the cord. Cats were given 2 mg/kg of atropine sulfate intravenously.

Four cats, three intact and one spinal were followed up for 5 hours after administration of requisite amount of solvent (pH 4) to exclude the possibility of an effect due to solvent as well as spontaneous changes in acid gastric response.

Dogs were anaesthetised by intraperitoneal pentobarbitone 40 mg/kg. Ryle's tube was passed in stomach and the basal collection was aspirated at intervals by introducing ten ml. of saline and aspirating the contents. The aspirated material was then titrated against N/100 NaOH using methyl red as indicator and results expressed as before.

Estimation of histamine: Histamine was extracted from five ml. of blood by Code's (1952) modified method. Blood histamine was estimated in seven cats using atropinized guinea-pig ileum mounted in 5 ml. bath at 36°C. Values of histamine are expressed in terms of histamine base.

Estimation of 5-hydroxytryptamine: Serum was separated from the remaining 2 ml. of blood and used for 5-HT assay. Serum 5-HT was estimated directly on atropinized rats colon mounted in a special nutrient fluid at 20°C as described by Dalgleish *et al.* (1953). Preparations responding to 0.005 μg of 5-HT in 2 ml. bath were used for assay. It was previously ascertained in each case that such a preparation did not respond to 100 μg of histamine base and 2 μg of Ach in the bath. Values of 5-HT in serum are expressed in terms of 5-HT base.

RESULTS

Effect of reserpine on gastric acidity of intact cats: Table I shows an effect of reserpine given intravenously on acid gastric secretion in nine cats expressed as mEq HCl/litre. The initial figure in each case is an average of three consecutive readings taken before administration of the drug. The final figure is a peak response obtained following 500 μg of i.v. reserpine.

Thus it can be seen that on an average there has been a rise in gastric acidity of 213% over the basal reading, the minimum being 54.8% and the

maximum being as high as 500%. It takes on average 35 minutes for the action to manifest itself. The peak effect is reached in about an hour. In a few cats we have observed a peak effect in 30 min. whereas in one it was as late as 150 min. from the time of administration. In most of these animals there was slight initial fall in acidity followed by a sustained rise.

TABLE I

Effect of 500 μg of reserpine i.v. on acid gastric secretion in cats.

S. No.	*Acid gastric secretion* mEq. HCl/litre Initial	Final	%age rise or fall over initial.		Time in minutes for Onset	Peak.
1.	1.46	2.36	60.86	Rise	30	45
2.	0.730	1.46	100	,,	15	60
3.	0.54	0.27	50	Fall	15	45
4.	1.12	4.065	275	Rise	30	45
5.	0.730	4.2	470	,,	60	150
6.	1.82	2.8	54.8	,,	60	75
7.	0.62	3.12	420	,,	45	60
8.	1.59	3.05	92.2	,,	30	30
9.	0.62	3.65	500	,,	30	60
Aver.	1.06	2.77	213.3		35	63.6
S.D.	1.497	1.16				
S. E.	0.53	0.41				

Fig. 1 shows a typical acid gastric response observed after administration of 500 μg reserpine i.v. It can be seen from this figure that reserpine action manifested in 15 minutes and the peak effect was observed in 45 min. while acidity failed to come to basal value even after 135 minutes.

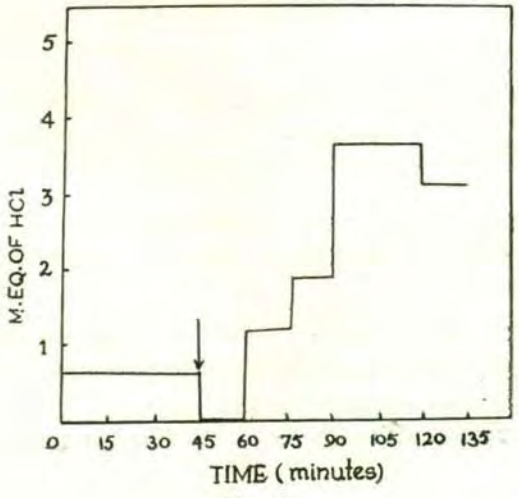

Fig. 1.

Histamine and 5 - HT levels:—Table II shows histamine and 5 - HT levels in blood and serum respectively, before and after administration of the drug. Five out of seven cats which showed a rise in acid gastric secretion following administration of reserpine, there was a definite rise in blood histamine content. Thus on an average the initial blood histamine level was 0.053 μg/ml. whereas after reserpine it was 0.183 μg/ml. In one cat where there was a fall in acidity following intravenous reserpine there was a concomitant fall in the histamine content of blood. Since the blood samples for histamine estimations were obtained at the time of peak response after the drug administration, it is not possible to correlate effectively rise in blood histamine with a rise in gastric acidity.

TABLE II

Blood histamine and serum 5-HT levels before and after administration of reserpine intravenously

S. No.	*Blood histamine* μg/ml (base)		*Serum 5-HT*		*Percentage rise in Gastric Acidity.*
	Initial	Final	Initial	Final	
1.	0.036	0.037	1.4	2.3	60.86
2.	0.087	1.06	2.	3.5	100
3.	0.054	0.05	2.5	5	275
4.	0.005	0.009	1	1 2	470
5.	0.05	0.09	1.8	3.0	54.8
6.	0.015	0.045		—	420
7.			2	3.5	92.2
8.	0.01	0.03	1.0	1.0	500
Aver.	0.053	0.183	1.67	2.79	
S. D.	0.0061	0.30	0.517	1.28	
S.E.	0.0025	0.126	0.215	0.534	

In most of the cases there has been a rise of 5-HT content of serum following administration of reserpine. Thus, on an average initial serum 5-HT level was 1.67 μg/ml. while after reserpine it was 2.79 μg/ml.

Figure 2 shows histamine and 5-HT content of blood and serum respectively before and after reserpine on atropinised guinea pig ileum and rat colon.

Response of atropinised spinal cats: Table III shows the effect of 500 μg of intravenous reserpine on the gastric acidity in atropinized spinal cats.

In these preparations, reserpine action was more pronounced than in intact cats. Furthermore, although the onset of action came on in approxi-

mately the same time as in normal cats, the rise in acidity continued for a longer period.

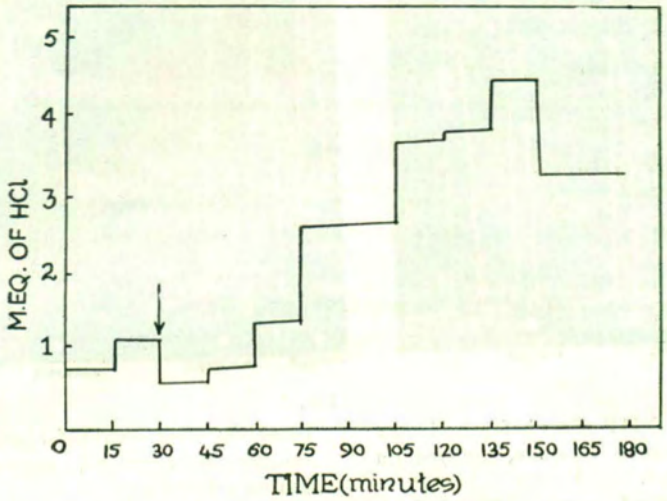

Fig. 2

TABLE III

Effect of reserpine on acid gastric secretion in spinal atropinized cats.

S. No.	*Gastric acidity* mEq HCl/litre Initial	Final	*Number of times rise over basal.*	*Time in minutes* Onset	Peak
1.	0.632	9.12	13.65	30 min.	150
2.	0.542	5.14	9.85	30 „	180
3.	0.365	5.11	14	30 „	180
4.	0.73	7.3	10	30 „	150

Figure 3 shows a typical response in atropinzed spinal cat following administration of reserpine 500 μg i.v.

Response of Dogs: In dogs, intravenous reserpine 500 μg was also found to produce an increased acid gastric response. Thus two dogs which were administered 2 mg/kg of atropine sulphate intravenously fifteen minutes prior to administration of reserpine, showed a marked rise in acid gastric secretion. In one dog hexamethonium bitartarate 2 mg/kg was given along with atropine sulphate. In this animal reserpine failed to produce an increased acidity although 50 μg of histamine produced the usual response.

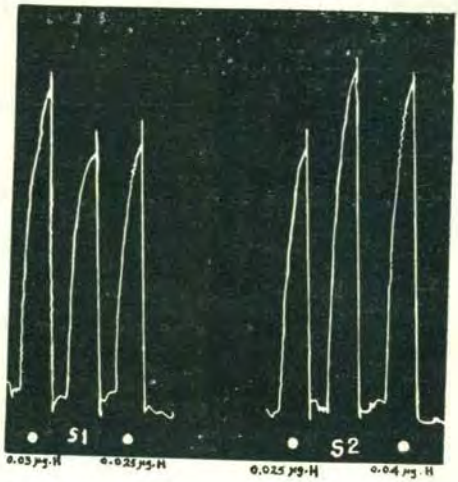

Fig. 2

Serum 5-HT of cat before and after intravenous reserpine, assayed on rat colon.
S_1 : 0.2 ml. serum (1:10) (Before)
S_2 : 0.2 ml. serum (1:10) (After)
5-HT : 5-hydroxytryptamine

Blood histamine of cat before and after intravenous reserpine, assayed on guinea pig ileum.
S_1 : 0.5 ml. blood (Before)
S_2 : 0.5 ml. blood (After)
H : Histamine base.

DISCUSSION

Reserpine given intravenously produced a pronounced increase in acid gastric secretion of majority of animals used. This has been reported by previous workers (Bein, 1956). There is a lag period averaging 45 minutes before the acidity starts rising. In fact immediately following reserpine administration, there is some amount of fall in acidity before the subsequent rise.

Rise in acid gastric secretion may be due to direct action on oxyntic cells. Such a response can also be due to liberation of an active substance in blood. Since reserpine action persisted in spinal atropinised cats it could be assumed that the action is not exerted through the intervention of central or peripheral parasympathetic system unless one assumes that astropinization does not effectively eliminate parasympathetic influences on gastric secretion. It has recently been shown by Popoy and Sokol' Skia (1959) that the secretory activity of gastric glands could be maintained in spinal dogs with central nervous connections completely cut off. Thus they showed that peripheral nerve structures function independently and could provide for the secretory activity of the gastric glands. It may, therefore, be assumed that reserpine produces acid gastric response either through humoral mechanism or by acting on these peripheral nervous structures. In one of our experiments in

dogs hexamethonium blocked the response to reserpine given i.v. Further work along this line is in progress.

We have found that intravenous administration of reserpine produces a fair amount of increase in blood histamine content as well as increase in 5-HT content of serum. In fact immediately following reserpine there is a transient fall in gastric acidity which may be due to increased level of 5-HT in blood. 5-HT has been shown to produce inhibition of acid gastric response in dogs by Haverbach *et al.* (1957). The rise in acid gastric secretion came after a latent period of 45 minutes and was associated with an increased blood histamine level. It may, therefore, be possible that part of this stimulant action of reserpine on acid gastric secretion is due to liberation of histamine in blood, which secondarily affects the oxyntic cells.

It has recently been shown by Waalkes *et al.* (1959) that a definite rise in histamine content follows incubation of reserpine with blood. It is, therefore, presumable that the increased level of blood histamine following reserpine may be due to liberation of histamine from formed elements of blood.

Clinically one does not see a very consistent rise in acidity following administration of reserpine. It may be that reserpine produces an equivocal response in acid gastric secretion depending upon whether action of liberated histamine or 5-HT is predominant.

SUMMARY

1. Action of reserpine (500 μg intravenous) on acid gastric secretion of cats and dogs was studied.

2. Reserpine was found to produce a marked rise in acid gastric secretion after a latent period of 45 minutes, maximum action being obtained after about 1 hour.

3. This effect was also seen in spinal cats.

4. Blood histamine and 5 - HT were found to rise after administration of reserpine.

5. Possible mechanism of reserpine in causing increased acid gastric secretion is discussed.

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