The effect of anticholinergic drugs on the mucus content of gastric juice

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EDITORIAL SYNOPSIS Increasing suppression of gastric secretion by anticholinergic drugs is accompanied by a rising mucus concentration; the actual output of mucus shows little change despite a marked reduction in the secretory volume. The problems involved in the estimation of mucus secretion and the importance of the above findings in relation to the therapeutic use of anticholinergic drugs in peptic ulceration are discussed.

The exact control of mucus secretion has not been adequately determined though many workers consider it to be partially under vagal control (Mitchell, 1931; Jennings and Florey, 1940; Glass and Boyd, 1949). Consequently, if the latter concept is correct, anticholinergic drugs should reduce mucus secretion. The effect of anticholinergic drugs on gastric mucus secretion is also of importance because of their frequent use in the treatment of peptic ulceration; it would be disadvantageous if they reduced the secretion of mucus because mucus is considered a protection against peptic ulceration by its physical and chemical properties (Bradley, 1933; Hollander, 1951; Mitchell, 1931; Komarov, 1936, 1942). The present study was undertaken, therefore, to determine the effect of anticholinergic drugs on the mucus component of gastric juice, the latter being stimulated by hypoglycaemia.

METHODS AND MATERIALS

The patients studied were psychiatric patients having insulin coma therapy. All were free of gastrointestinal disease. Their repeated treatment enabled many observations to be made on the same patient. A Cleland tube was passed when the patient became comatose, coma being considered to be present when the patient no longer responded to painful stimuli and bilateral extensor plantar responses were present. Continuous suction was applied for about 15 minutes to remove any gastric residue and 15-minute specimens were collected during the last 30 to 45 minutes spent in coma. The last 15-minute specimen was the sample actually considered in this study. Blood sugars were done initially but were discontinued when it was found reproducible control results were obtained under the above conditions, whatever the actual blood sugar level found.

The series of anticholinergic drugs used included atropine 0.67 mg., propantheline 30 mg., oxyphenyclimine 10 mg., and propionyl atropine methyl nitrate 18 mg. These were administered orally two to two and a half hours before the onset of the coma.

The gastric juice was collected in tubes surrounded by ice and the visible mucus removed by centrifugation. Bile-stained specimens were discarded. The acid concentration was estimated using phenol red as indicator. The mucus was measured in terms of its total hexose content using Dreywood's anthrone reagent (Morris, 1948) as modified by Richmond, Caputto, and Wolf (1957).

RESULTS

The results are given in Table I, the volume after the anticholinergic drugs being listed in order of decreasing volumes of secretion for each patient.

These results show that with increasing anticholinergic suppression of gastric secretion there is a drop in acid concentration and a rise in mucus concentration. This response was observed in all the seven cases studied. The mucus concentration fell as the acid concentration decreased and the relationship between these two concentrations was more parabolic than linear (Fig. 1). The rise in mucus concentration was such that the total output of soluble mucus actually rose in three cases, showed a slight fall in three cases, and in one case showed no change. These changes represent variations in the dissolved mucus content of gastric juice under the circumstances of the study. It is difficult to interpret these results in terms of mucus secretion, because it is impossible to prove how much of the rise in mucus concentration was due to the presence of small fragments of insoluble mucus in what was

TABLE I
EFFECT OF ANTICHOLINERGIC DRUGS ON VOLUME OF SECRETION AND ACID AND MUCUS CONCENTRATIONS¹

1 Drug	Control	Control	Control	P.A.M.N.	Oxyphencyclimine	Propantheline			
Volume (ml.)	44	44	38	29	14	8			
Acid concentration (mEq./l.)	108	99	111	60	44	17			
Mucus concentration (mg. %)	26.5	30	46.5	58	144	286			
Mucus output (mg.)	11.7	13.2	17.7	16.8	20.2	22.9			
2 Drug	Control	P.A.M.N.	Atropine	Propantheline	Oxyphencyclimine	Propantheline			
Volume (ml.)	101	98	74	75	55	50			
Acid concentration (mEq./l.)	57	41	43	62	45	32			
Mucus concentration (mg. %)	42	64	35	43	63	92			
Mucus output (mg.)	42.4	62.7	25.9	32.2	34.6	46			
3 Drug	Control	Control	Control	Control	Control	P.A.M.N.	Oxyphencyclimine	Atropine	Propantheline
Volume (ml.)	21	19	14	22	17	19	15	14	6
Acid concentration (mEq./l.)	41	32	21	31	46	39	15	26	7
Mucus concentration (mg. %)	83	141	80	110	61	50	123	70	194
Mucus output (mg.)	17.5	26.7	11.2	24.2	10.4	9.5	18.4	9.8	11.6
4 Drug	Control	Control	Atropine	P.A.M.N.	Oxyphencyclimine	Propantheline			
Volume (ml.)	32	30	35	32	17	17			
Acid concentration (mEq./l.)	40	38	35	16	30	19			
Mucus concentration (mg. %)	61	56	83	60	62	146			
Mucus output (mg.)	19.5	16.8	30.8	19.2	10.5	24.8			
5 Drug	Control	Control	Atropine	Oxyphencyclimine	Propantheline				
Volume (ml.)	36	27	11	6	5				
Acid concentration (mEq./l.)	78	113	53	61	42				
Mucus concentration (mg. %)	48	49	66	70	204				
Mucus output (mg.)	10.1	13.2	7.26	4.2	10.2				
6 Drug	Control	P.A.M.N.	Atropine	Oxyphencyclimine					
Volume (ml.)	50	42	36	17					
Acid concentration (mEq./l.)	88	110	38	49					
Mucus concentration (mg. %)	36	36	67	72					
Mucus output (mg.)	18	15.1	24.1	15.1					
7 Drug	Control	Control	P.A.M.N.	Atropine					
Volume (ml.)	56	45	44	36					
Acid concentration (mEq./l.)	100	103	55	79					
Mucus concentration (mg. %)	46	50	84	96					
Mucus output (mg.)	26	22.5	37	34.5					

¹The mucus concentration is expressed in terms of a standard containing equal parts of mannose and galactose. The volumes, etc., represent those of the last 15-minute sample collected while the patient was in hypoglycaemic coma. The samples from each patient were collected during repeated tests on the same patient.

considered the soluble mucus component and how much to a contribution to the soluble mucus component from the dissolution of visible or insoluble mucus.

DISCUSSION

Two problems in the study of gastric mucus secretion have been the relationship of the dissolved to the visible mucus component and the development of a satisfactory method of measuring the mucus concentration. The relationship of visible mucus to dissolved mucus is of importance because the con-

centration of dissolved mucus could be an index of the amount of visible mucus that goes into solution in the acid-pepsin mixture in the stomach as well as of the rate of secretion of dissolved mucus. Also, as has been mentioned, it is technically difficult to get the dissolved mucus free from small fragments of visible mucus. Babkin (1950) felt that liquefied visible mucus did not make a significant contribution to the dissolved mucus component, though most workers (Glass and Boyd, 1954; Hollander and Janowitz, 1954) agree that visible mucus does liquefy spontaneously. In the present study, though the collections with the smallest volume contain the most

FIG. 1. Graph showing the relationship between mucus concentration and acid concentration in three patients when the volume of secretion is progressively reduced by anticholinergic drugs.

visible mucus, there was not a good correlation between the amount of visible mucus and the actual determined concentration of dissolved mucus, and therefore it is felt that the actual readings are an index of the dissolved mucus secretory rate.

Mucus is a conjugated protein which contains a polysaccharide as a prosthetic group. Grossberg, Komarov, and Shay (1950) considered that dissolved mucus consisted of at least two mucoproteins, one containing mucoitin sulphuric acid (which contains hexosamine and glucuronic acid) as its prosthetic group, and another containing hexosamine and galactose. Glass and Boyd (1949) divided dissolved mucus into gastric mucoprotein and gastric mucoprotease. The former was considered the secretion of the gastric glands and the latter liquefied surface epithelial cell secretion. They were differentiated by their solubility at pH 4 after acetone precipitation in the trichloroacetic acid filtrate of centrifuged gastric juice. The quantitative methods of estimating dissolved mucus have been based on the properties of either the protein or the polysaccharide component. The method of Glass and Boyd (1949) was based on the protein moiety and determined the tyrosine content of mucus by means of the Folin-Ciocalteu colorimeter reaction. The fractional precipitation method of Glass and Boyd (1949) and the deductions based on the tyrosine content of various fractions

by these workers have been severely criticized by Schrager (1961). He found that the tyrosine estimation used by Glass to determine the mucoprotein and mucoprotease content was a measure of the proteinous material only, and the tyrosine of the mucoprotein related chiefly to the pepsin content of that fraction. Grossberg *et al.* (1950) determined the hexosamine and glucuronic acid content of dissolved mucus and thereby they felt that they could determine the proportion derived from the mucoid cells of the glands and the surface epithelium, the surface epithelium secretion not containing glucuronic acid. The anthrone reagent depends upon the fact that on the addition of strong sulphuric acid hexoses are converted to hydroxy methyl furfural which gives a blue colour to the anthrone. It will thus measure the total hexose content of the polysaccharides of gastric juice without reference to the conjugated protein to which they are attached; consequently, it will give an index of the total dissolved mucoprotein secretion of gastric juice, assuming that the soluble mucus can be adequately separated from the insoluble mucus. Ignoring Schrager's objection to the method of Glass and Boyd (1949), the method of estimating mucus used in their study has given in our hands more reproducible results than the method of the latter group of workers.

The different origin of the two components of mucus studied by Grossberg *et al.* (1950) was based on indirect evidence, and other workers have found mucoitin sulphuric acid in surface epithelium mucus. Though the mucus within these two groups of cells, the surface epithelial cells and the gland mucoid cells and the pyloric gland cells and cardiac gland cells, stain differently with mucicarmine (Jennings and Florey, 1940), there does not appear to be enough information yet to enable one to differentiate their secretory products by chemical means.

As hypoglycaemic stimulation was used in the present study, it is necessary to know the effect of vagal stimulation on mucus secretion. Vineberg (1931) measured it by the volume of visible mucus and found electrical stimulation of the vagus stimulated mucus secretion. Grossberg *et al.* (1950) found that sham feeding increased considerably the uronic acid containing mucin but only slightly and transiently the uronic acid free mucin; the increase in the output of the mucins was accompanied by a considerable decrease in the concentration when compared with their basal concentration. Glass and Boyd (1949) found insulin stimulated the secretion of both components of dissolved mucus, both the output and concentration rising, the mucoprotein showing the most marked rise. Jennings and Florey (1940), using a histochemical technique, found that vagus stimulation stimulated secretion from the

mucoid cells of the neck of the glands, the cardiac glands, and the pyloric glands, whereas it had no effect on the activity of the surface epithelial cells. Our observations on the effect of hypoglycaemic stimulation on mucus secretion agree with those of Grossberg *et al.* (1950), namely, that the increased secretory volume resulting from hypoglycaemia was accompanied by a falling concentration of dissolved mucus. Hence the rise in concentration of mucus observed after anticholinergic drugs is probably due to the latter reducing the volume of secretion during hypoglycaemia with relatively little effect on mucus secretion.

The only comparable study of the effect of an anticholinergic agent on gastric secretion has been made by Plummer, Burke, and Bradford (1951). They found that methantheline bromide (Banthine) reduced the volume of secretion slightly and there was a considerable drop in mucoprotein concentration and a slight rise in mucoproteose concentration. Except in the 80-minute specimen there was no drop in volume after Banthine in their studies, meaning that an adequate dose of the anticholinergic drug was not used. Their experimental design did not permit repeated observations to be made on the same patient as in the present study. It is difficult to be sure that a comparable stimulus is being applied in each case unless the maximal stimulus is applied, as is indicated by the presence of hypoglycaemic coma. Also, they used the tyrosine colorimetric method of Glass and Boyd (1949) in estimating the mucus concentration, which depends upon a different biochemical component of mucus to that estimated in our study.

In the present investigation it was found that apart from reducing the volume and acid concentration of gastric juice, anticholinergic drugs result in an increase in the concentration of mucus. Apart from its mechanical protective action, mucus has an inhibiting action on peptic digestion by virtue of its sulphated polysaccharide content (Komarov, 1936, 1942), and there is evidence that it may absorb pepsin (Bradley, 1933; Hollander, 1951); it has a slight acid neutralizing capacity (Mitchell, 1931; Glass, Pugh, and Wolf, 1951). Hence, in the treatment of peptic ulceration, anticholinergic drugs would have a beneficial effect because of their action on the mucus secretion as well as because of their action on acid secretion. The little effect of anticholinergic drugs on vagally stimulated mucus secretion could mean that this secretion is not under vagal control, or alternatively, the mucus cell response, though under vagal control, cannot be

blocked by anticholinergic agents. It is known that the extent to which certain parasympathetically innervated organs can be blocked by the atropine series varies, and this has been explained by the fact that the mediator, acetylcholine, may be liberated intracellularly instead of extracellularly as usually (Goodman and Gilman, 1955). If liberated intracellularly, anticholinergic agents cannot prevent the mediator reaching the receptor cell and consequently lose their inhibiting effect on a vagally stimulated response.

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