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THE EFFECT OF ACETAZOLEAMIDE, AN INHIBITOR OF CARBONIC ANHYDRASE, ON GASTRIC SECRETION

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Sulphanilamide has a diuretic effect (Southworth, 1937 ; Strauss and Southworth, 1938) which is thought to be due to inhibition of the enzyme carbonic anhydrase, which catalyses the reversible reaction

$$CO_2 + H_2O \rightleftharpoons H_2CO_3$$

Acetazoleamide (2-acetylamino-1, 3, 4-thiadiazole-5-sulphonamide, " Diamox "), a derivative of sulphanilamide, is a more powerful inhibitor of carbonic anhydrase than sulphanilamide.

Davenport and Fisher (1938) demonstrated that carbonic anhydrase is present in large amounts in the gastric mucosa, and later (Davenport, 1939, 1940) that most of this enzyme in the stomach is present in the oxyntic cells. Further investigations have sought to prove that the enzyme plays an important part in gastric hydrochloric acid secretion. Janowitz, Colcher, and Hollander (1952) showed that histamine-induced secretion in dogs could be completely suppressed by acetazoleamide. The mechanism of gastric HCl secretion has been reviewed recently by Gray (1942), Davies (1951), Texter and Barborka (1955).

In view of the fundamental role played by carbonic anhydrase in gastric acid secretion it was suggested that an inhibitor of the enzyme might be of use in the treatment of the hyperacidity associated with peptic ulcers. The present study was undertaken to assess the effects of acetazoleamide on gastric acid secretion. Parallel studies on urinary volume, electrolyte excretion, and urinary *p*H were performed to make sure that the drug had reached an effective level.

METHODS

The drug was administered to twelve healthy normal adults isolated in a small hospital ward. They were kept on a fixed weighed diet for three days, additional fluid intake being restricted to 1,500 ml. On the first day they accustomed themselves to the diet, the second was the control day and the third the experimental day. The subjects were divided into two groups of 6, one of which received 250 mg. and the second 500 mg. acetazoleamide on the test day.

The effect of acetazoleamide on gastric secretion was compared with that of atropine, a known inhibitor of acid secretion. Two mg. of atropine was given subcutaneously an hour before gastric analysis to another group of six subjects treated under similar conditions.

If a standard volume of a non-absorbable dye such as phenol red is injected into and withdrawn from the stomach at a fixed interval, it is possible to calculate the volume of pyloric evacuation and the rate of gastric secretion (Brooks, Erskine, Gephart, Swain, and Moore, 1950; Gill and Jessup, 1950) on the assumption that the rate of pyloric evacuation is constant. Although the method is open to the errors inherent in this assumption, it provides a quantitative assessment of the volume of gastric secretion which cannot be obtained with fractional meal techniques.

The following investigations were performed on control and test days:

1. The phenol red method of gastric analysis of Brooks *et al.* (1950) was used. The procedure for gastric analysis was modified from Gill and Jessup (1950). Subjects were fasted for twelve hours. A Ryle's tube was passed and the resting juice aspirated. A solution of phenol red (100 ml. of 1.2 mg.%) warmed to 37° C. was injected into the stomach by way of the Ryle's tube; ten minutes later the gastric contents were completely aspirated. A further 100 ml. of phenol red solution was immediately injected and the procedure repeated for five 10-min. periods. The volumes of aspirates were recorded and the concentration of phenol red estimated in an EEL absorptiometer against a control sample of the injected solution (to allow for any concentration during warming to 37° C.).

2. The volume and specific gravity of the urine passed during the two 24-hr. periods covering the control and experimental days were measured.

3. A urine concentration test was made involving the collection of three urine specimens passed at hourly intervals in the early morning before gastric analysis and the determination of their volumes, specific gravity, and *p*H.

4. The 24-hour sodium and potassium excretion was measured on control and test days.

5. Plasma chlorides were determined by the method of Schales and Schales.

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Results

The rates of total gastric secretion, hydrochloric acid production and pyloric evacuation were calculated and the results for each of the three groups are presented in Table I. The statistical significance of differences between results on control and test days was calculated by students "paired" *t* test.

Table I

THE EFFECT OF ACETAZOLEAMIDE ("DIAMOX") ON VOLUMES OF PYLORIC EVACUATE, GASTRIC SECRETION AND FREE ACID SECRETION IN GROUPS OF 6 NORMAL ADULTS, CONTRASTED WITH THE EFFECT OF ATROPINE

Drug and Dose	Subject	Pyloric Evacuate (ml./min.)		Gastric Secretion (ml./min.)		Free Acid (mMol./min.)	
		Before	After	Before	After	Before	After
Acetazoleamide 500 mg. by mouth	A	10	8·4	1·8	1·3	0·005	0·007
	B	3·2	8·0	1·6	0 66	0·029	0·013
	C	3·4	3·9	0·56	1·8	0·001	0·011
	D	9·7	2·0	1·6	0·68	0·042	0·008
	E	7·5	4·6	2·4	2·5	0·028	0·008
	F	5·6	5·8	3·1	0·2	0·005	0
	Mean	6·6	5·4	1·8	1·2	0·018	0·008
	P	50%		30%		<20%	
Acetazoleamide 250 mg. by mouth	G	12	7·6	2·6	1·1	0·048	0·035
	H	7·8	0·78	6·0	2·3	0·092	0·012
	J	11	7·5	4·1	4·1	0·045	0·013
	K	8·4	3·5	4·0	2·8	0·110	0·047
	L	0·5	5·0	1·9	1·6	0·017	0·014
	M	9·1	9·9	1·6	0·65	0·019	0·071
	Mean	8·3	5·7	3·4	2·1	0·055	0·032
	P	20%		5–10%		30%	
Atropine 2 mg. s.c.	N	10	2·3	2·7	0·8	0·019	0
	O	11	2·1	3·6	0·6	0·062	0·003
	P	6·8	5·0	1·9	0·4	0·034	0
	Q	11	2·1	4·6	0·86	0·12	0
	R	11	4·1	6·0	1·1	0	0
	S	8·4	8·7	3·2	1·0	0·042	0
	Mean	9·7	4·1	3·7	0·72	0·046	0
	P	<25%		<1%		<5%	

Gastric Function.—The rate of gastric secretion, the production of acid and the rate of pyloric evacuation were all slightly diminished after the administration of acetazoleamide, but the decrease was small and not statistically significant. Furthermore, a dose of 500 mg. acetazoleamide produced no greater effect than a dose of 250 mg. By contrast 2 mg. atropine produced a significant diminution of gastric secretion and motility.

Urine Output and Urinary Electrolytes.—In all instances the total volumes of the three morning specimens and the volumes of the 24-hour output were greater after the administration of the drug. The volumes of the 24-hour specimens increased on an average by a factor of 1.86 on 500 mg. and 1.7 on 250 mg. acetazoleamide. The concentration of the urine was reduced and the urine became alkaline in all cases. The effect of acetazoleamide on the excretion of sodium and potassium is shown in Figs. 1, 2, and 3.

The increase in sodium excretion over the 24-hour period corresponded closely with the increase in 24-hour volume. All subjects likewise showed an increased potassium excretion which was greater on the experimental day by a factor of 1.7 on 500 mg. and 1.6 on 250 mg. acetazoleamide. The plasma chlorides showed no significant change.

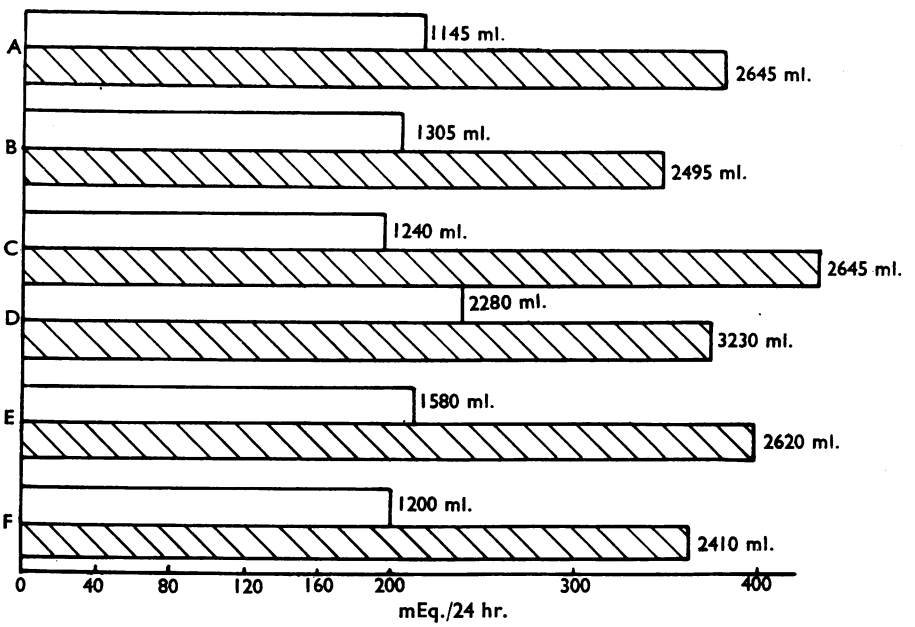

FIG. 1.—The effect of oral administration of 500 mg. of acetazoleamide on the total daily urinary excretion of sodium in 6 healthy adults. Plain rectangles before, and hatched rectangles after, acetazoleamide.

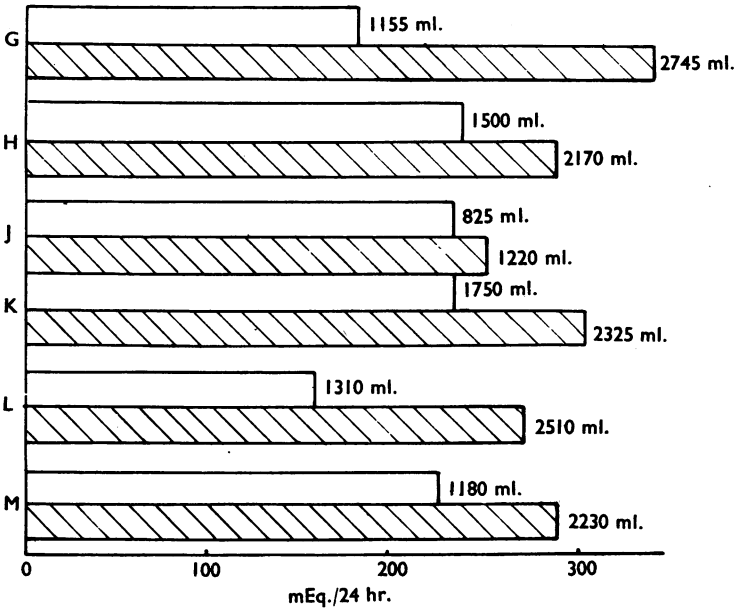

FIG. 2.—The effect of oral administration of 250 mg. of acetazoleamide on the total daily urinary excretion of sodium in 6 healthy adults. Plain rectangles before, and hatched rectangles after, acetazoleamide.

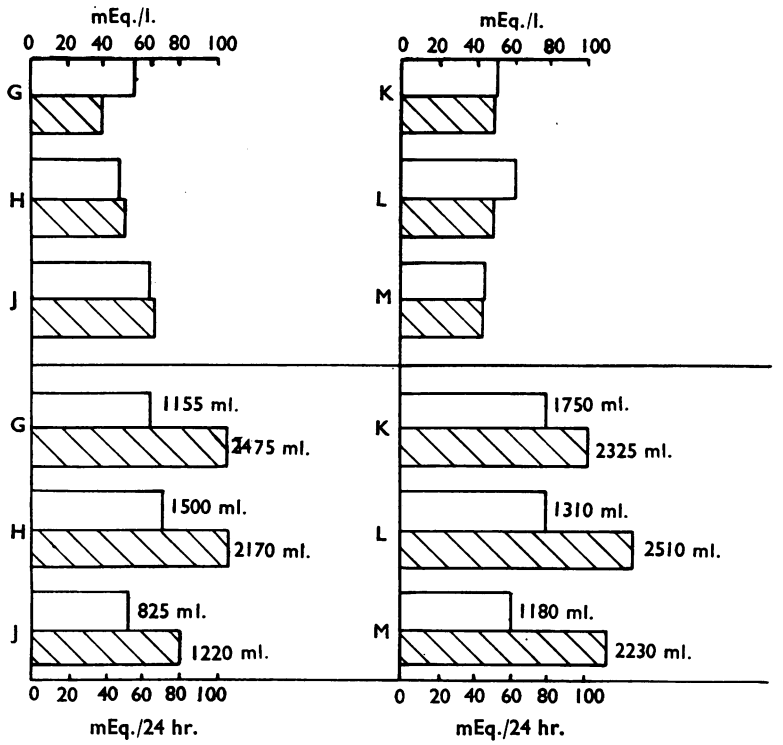

FIG. 3.—The effect of oral administration of 250 mg. of acetazoleamide on urinary potassium excretion in 6 healthy adults. Plain rectangles before, and hatched rectangles after, acetazoleamide.

Discussion

Acetazoleamide in the usual therapeutic doses did not abolish gastric hydrochloric acid secretion. Counihan, Evans, and Milne (1954) consider that renal carbonic anhydrase activity is not completely suppressed by therapeutic doses of acetazoleamide. Failure to reduce gastric function significantly is probably due to the same cause, as the concentration of carbonic anhydrase in the oxyntic cells is relatively high (Davies and Edelman, 1951).

The present experiment is the first in which the effects of acetazoleamide have been studied in a relatively large group of normal adults. The use of the drug as an oral diuretic in congestive heart failure and emphysema has been the subject of recent clinical reports (Belsky, 1953; Ruskin, 1955). The paper by Counihan, Evans, and Milne (1954) described the action in two normal adults and a group of patients. In our twelve subjects we have confirmed the marked diuretic action of acetazoleamide, and parallel effects on soduim and potassium excretion, in the first twenty-four hours after administration.

Acetazoleamide does not appear to possess any advantages over conventional methods for the treatment of hyperacidity; its other important physiological effects, such as the production of systemic acidosis, would make prolonged therapy of such gastric disorders unnecessarily hazardous.

Summary

1. The effect of acetazoleamide ("Diamox"), an inhibitor of carbonic anhydrase, on gastric secretion has been studied in twelve healthy (normal) adults on a similar diet under hospital conditions.

2. In therapeutic doses acetazoleamide does not appear to have a marked effect on gastric hydrochloric acid secretion; it has a much less significant effect on total gastric secretion than atropine. Marked diuresis, increased sodium and potassium excretion, and alkalinization of the urine, were observed in all subjects, in the first twenty-four hours after administration.

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