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Research Article

AMMONIA AS A SOURCE OF GASTRIC HYPOACIDITY IN PATIENTS WITH UREMIA *

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Ammonia is produced when urea passes from the blood into gastric secretion, a reaction catalyzed by a urease, present in the gastric mucosa of man and several animals (1–14). Fitzgerald and Murphy (15) have suggested that the ammonia formed in this process may have an important protective function by neutralizing gastric acidity. This concept was based on the observation in man that administration of urea in amounts sufficient to raise temporarily the blood urea level by 12 mg. per cent was followed by a decrease of gastric acidity. Burke and Page (16) were unable to confirm these findings, and Kornberg, Davies and Wood (17–19) presented evidence which suggested that, at least in the cat, the urease found in the stomach is of bacterial origin and does not influence gastric acid secretion.

This paper compares gastric ammonia and acid contents in normal and uremic subjects, the latter known to exhibit an elevated gastric ammonia concentration (20–22). Because of the influence of antibiotics on intestinal ammonia production (23–25), their effects on gastric ammonia and acid concentration were studied.

MATERIALS AND METHODS

Fifty hospitalized subjects were studied, 24 without evidence of renal dysfunction, 25 with uremia due to chronic renal disease, and one with azotemia due to obstructive uropathy. The blood urea concentration in the patients with uremia varied from 40 to 174 mg. nitrogen per cent with an average of 100.5 mg. N per cent. The patients were fasted for 16 hours and gastric juice collected by a Levine tube with the patients placed in the left lateral position, as proposed by Henning (26), to facilitate the quantitative recovery of gastric secretion (27). After a 45 minute period of stabilization, gastric juice was aspirated every 15 minutes and collected for examination. Basal secretion was studied using the four specimens collected during the first hour. At the end of this period, 0.005 mg. per Kg. histamine dihydrochloride was administered subcutaneously, and the effect of this drug on volume and composition of gastric secretion was determined on the four specimens collected during the second hour. This procedure was performed before and after administration of various antibiotics.[1] Twenty mg. per Kg. oxytetracycline was given orally for four to seven days to five nonuremic and six uremic subjects; 300 mg. of the same drug was injected intramuscularly daily for three to eight days to three nonuremics and three uremics. Five uremic and five nonuremic subjects received 20 mg. per Kg. chloramphenicol orally for four to seven days and six nonuremic and five uremic subjects were treated similarly with 20 mg. per Kg. erythromycin.

Venous blood urea was measured by the urease method (28), gastric juice was analyzed for chlorides (29) and free and total acid (dimethyl-aminoazobenzol and phenolphthalein as indicators). Ammonia and urea were measured (28) in neutralized gastric juice.

RESULTS

A. Comparison between gastric juice in uremic and nonuremic subjects

Increased blood urea was associated with high gastric urea and ammonia concentration. This was found both in the basal state and after administration of histamine. In addition, the free and the total acid concentrations were significantly lower ($p < 0.05$) in uremic patients as compared to nonuremic individuals (Table I).

B. Action of antibiotics on gastric ammonia and urea contents

Mean ammonia concentrations of basal and post-histamine gastric secretions were lowered significantly ($p < 0.05$) in the patients treated by oral oxytetracycline (Table II). In both non-

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[1] The authors wish to thank the following companies for making these antibiotics available: Lepetit (chloramphenicol), Lilly (erythromycin) and Pfizer (oxytetracycline).

TABLE I

Comparison between gastric secretion of uremic and nonuremic subjects

		Free acid	Total acid	Chlorides	Gastric ammonia	Gastric urea	Blood urea
		mEq. HCl/L.	*mEq. HCl/L.*	*mEq./L.*	*mMole/L.*	*½ mMole/L.*	*½ mMole/L. (or mg. N %)*
24 subjects without uremia	Basal secretion	22.0	39.6	102.3	5.7	2.8	
	S. D.	4.5	4.9	5.0	0.9	0.5	11.4 ± 0.6 (16.0 ± 0.8)
	Posthistamine secretion	51.5	65.3	121.9	5.1	2.5	
	S. D.	7.4	7.6	5.5	0.9	0.5	
26 subjects with uremia	Basal secretion	8.1	28.2	119.1	37.4	15.9	
	S. D.	4.1	4.3	5.1	5.2	3.7	71.8 ± 4.9 (100.5 ± 6.9)
	Posthistamine secretion	32.8	55.4	137.7	31.8	17.4	
	S. D.	6.0	6.6	2.5	5.0	4.0	

uremic and uremic subjects the ammonia concentration was reduced by about 80 per cent of the pretreatment level. An increase of gastric juice urea concentration was associated with the change in ammonia. Both changes were of the same order of magnitude. In five of the six patients with uremia receiving oxytetracycline the drop of ammonia was accompanied by a rise of acidity, while in subjects without renal dysfunction no change in acidity was detectable. Similar results were obtained when the values were calculated on the basis of hourly gastric output (Figure 1). No change in

TABLE II

Gastric secretion before (I) and after (II) oral administration of oxytetracycline

	Case number	Free acid		Total acid		Chlorides		Ammonia		Urea		Blood urea	
		I	II	I	II	I	II	I	II	I	II	I	II
		mEq. HCl/L.		*mEq. HCl/L.*		*mEq./L.*		*mMole/L.*		*½ mMole/L.*		*½ mMole/L. (or mg. N %)*	
Nonuremic subjects													
Basal secretion	1	32	2	62	23	81	97	11.7	2.0	6.2	11.2	17.4 (24.4)	22.0 (30.8)
	2	84	112	102	120	140	134	4.0	1.8	0.6	3.6	10.5 (14.7)	12.8 (17.9)
	3	26	23	37	36	107	119	1.9	1.2	2.4	3.5	16.6 (23.3)	
	4	0	0	10	15	94	112	11.9	1.0	1.9	10.3	14.0 (19.6)	11.9 (16.7)
	5	0	4	5	14	72	81	2.7	0.8	3.5	6.6	8.2 (11.5)	11.4 (16.0)
	Mean	28.4	28.2	43.2	41.6	99	109	6.4	1.4	2.9	7.0	13.3 (18.6)	14.5 (20.3)
Posthistamine secretion	1	89	61	108	78	143	128	7.6	1.2	8.6	7.8		
	3	51	66	62	78	116	137	2.2	0.7	2.1	2.9		
	4	0	3	10	26	108	119	14.3	0.9	1.2	9.8		
	5	31	34	43	44	100	126	2.6	0.8	2.4	4.8		
	Mean	43	41	56	57	117	128	6.7	0.9	3.6	6.3		
Uremic subjects													
Basal secretion	6	0	26	24	47	127	119	79.0	12.0	0.6	70.0	110 (154)	124 (174)
	7							74.0	3.4	0	48.6	103 (144)	108 (151)
	9	0	0	10	13	98	96	27.6	14.0	5.2	45.6	52 (73)	82 (115)
	10	0	17	14	34	128	119	61.0	25.6	2.7	15.1	75 (105)	73 (102)
	11	0	10	13	20	122		32.9	2.0	0.3	22.4	54 (76)	33 (46)
	Mean	0	13	15	29	119	111	54.9	11.4	1.8	40.3	78.8 (110.3)	84 (117.6)
Posthistamine secretion	6	0.6	44	42	74	136	136	71.0	10.0	0.6	68.0		
	7	67	129	97	138	156	145	65.0	3.0	0.5	39.4		
	8	81	109	98	128	134	145	3.9	0.7	23.2	35.1	52 (73)	73 (102)
	9	51	87	73	108	139	148	34.7	14.4	1.2	27.1		
	10	45	37	64	60	136	134	42.0	24.8	0.5	13.1		
	11	0	7	11	13	133	84	30.5	1.9	1.5	23.5		
	Mean	41	69	64	87	139	132	41.2	9.1	4.6	34.3		

chloride content or volume of gastric juice was observed. Intramuscular administration of oxytetracycline was less effective than when given by mouth, both in reducing gastric ammonia and increasing acidity.

Neither gastric ammonia, acid, nor chloride was significantly influenced by chloramphenicol ($p > 0.05$) (Table III). Individual responses to erythromycin varied (Table IV); in some subjects gastric ammonia fell considerably, while in others there was no change. The differences were not found to be statistically significant ($p > 0.05$).

The observed antibiotic effect on gastric secretion was reversible. In four patients with uremia whose gastric ammonia had been reduced by antibiotics, it rose again after cessation of the treatment.

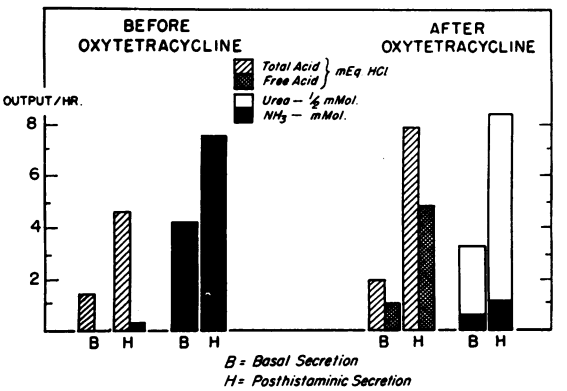

FIG. 1. GASTRIC SECRETION BEFORE AND AFTER SEVEN DAYS OF ORAL OXYTETRACYCLINE TREATMENT (20 MG. PER KG. DAILY)

Uremic patient (blood urea, 154 to 174 mg. N per cent).

C. Relationship between changes in ammonia and acid concentrations in gastric secretion

The relationship between spontaneous changes in gastric ammonia and acid concentration was studied in the patient in whom azotemia due to obstructive uropathy was relieved by cystostomy. The gastric ammonia content was lowered proportionally and gastric acidity rose to a similar extent with the fall of blood urea (Figure 2). Ad-

TABLE III

Gastric secretion before (I) and after (II) oral administration of chloramphenicol

	Case number	Free acid		Total acid		Chlorides		Ammonia		Urea		Blood urea	
		I	II	I	II	I	II	I	II	I	II	I	II
		mEq. HCl/L.		*mEq. HCl/L.*		*mEq./L.*		*mMole/L.*		*½ mMole/L.*		*½ mMole/L. (or mg. N %)*	
Nonuremic subjects													
	12	54	26	72	41	130	124	11.1	5.1	0.4	2.3	13.9 (19.5)	12.7 (17.8)
	13	21	16	46	22	126	124	11.5	5.4	1.5	3.0	15.4 (21.6)	10.0 (14.0)
Basal	14	36	60	47	68	105	123	3.5	3.1	1.8	0.4	10.0 (14.0)	6.0 (8.4)
secretion	15	0	7	6	22	55	107	2.6	3.0	3.9	3.3	14.0 (19.6)	10.9 (15.3)
	16	0	0	11	4	72	146	4.8	0.5	8.9	9.3	15.9 (22.3)	14.5 (20.3)
	Mean	20	22	36	31	97	125	6.7	3.4	3.3	3.7	13.8 (19.3)	10.8 (15.1)
	12	92	99	110	111	155	160	7.1	3.8	1.2	0.9		
	13	63	44	78	73	143	134	9.4	6.3	0.7	2.1		
Posthistamine	14	61	75	70	91	128	143	3.1	2.5	1.7	0.4		
secretion	15	48	53	58	73	128	135	5.1	2.5	3.0	2.5		
	16	0	0	12	10	60	138	3.6	1.8	9.1	10.2		
	Mean	53	54	66	72	123	142	5.7	3.4	3.1	3.2		
Uremic subjects													
	17	0	18	14	42	128	138	61.0	52.1	2.7	0.2	75.0 (105.0)	62.5 (87.5)
	18	0	0	4	12	140	134	47.0	48.0	18.0	20.0	74.0 (104.0)	81.0 (113.4)
Basal	19	6	35	22	56	107	158	8.6	12.0	20.5	22.6	45.5 (63.7)	50.0 (70.0)
secretion	38	0	20	12	40	122	105	34.7	3.4	2.2	31.2	48.5 (67.9)	50.1 (70.1)
	39	0	3	7	23	113	130	23.3	14.2	1.8	4.4	30.0 (42.0)	28.6 (40.0)
	Mean	1.2	15.2	11.8	34.6	122	133	34.9	25.9	9.0	15.7	54.6 (76.4)	52.4 (73.4)
	17	45	57	64	78	136	154	42.0	45.0	0.5	0.3		
	18	0	0	8	14	150	146	48.0	46.0	25.0	28.0		
Posthistamine	19	46	74	66	95	141	160	10.9	8.5	13.2	15.9		
secretion	38	0	25	11	38	122	106	34.6	3.8	3.5	35.8		
	Mean	22.8	39.0	37.3	56.3	137	142	33.9	25.8	10.6	20.0		

TABLE IV

Gastric secretion before (I) and after (II) oral administration of erythromycin

	Case number	Free acid		Total acid		Chlorides		Ammonia		Gastric urea		Blood urea	
		I	II	I	II	I	II	I	II	I	II	I	II
		mEq. HCl/L.		*mEq. HCl/L.*		*mEq./L.*		*mMole/L.*		*½ mMole/L.*		*½ mMole/L. (or mg. N %)*	
Nonuremic subjects													
Basal secretion	21	0	0	16	17	102	138	6.7	2.3	1.1	5.2	10.6 (14.8)	10.0 (14.0)
	22	32	31	44	46	102	116	1.3	1.7	4.4	7.1	8.3 (11.6)	9.9 (13.9)
	23	0	1	7	13	98	89	8.5	3.5	0.8	1.4	11.5 (16.1)	9.0 (12.6)
	24	0	0	5	7	80	90	3.5	2.1	4.9	5.8	9.3 (13.0)	10.0 (14.0)
	25	28	22	45	35	120	77	18.3	6.2	0.2	0.5	15.2 (21.3)	12.6 (17.6)
	36	5	34	15	45	94	104	4.3	7.3	1.8	1.1	7.2 (10.1)	9.2 (12.9)
	Mean	10.8	14.5	22.0	27.2	99	102	7.1	3.9	2.2	3.5	10.4 (14.6)	10.1 (14.1)
Posthistamine secretion	21	0	30	27	57	108	136	5.3	0.8	1.0	3.4		
	22	67	86	74	95	126	146	0.9	0.9	3.5	4.5		
	23	27	50	43	67	109	119	8.8	3.5	0.1	1.4		
	24	0	0	4	10	73	90	3.7	1.7	4.3	5.8		
	25	48	55	61	77	122	121	16.2	6.0	0.1	0.6		
	36	53	87	65	96	115	125	5.0	6.8	0.8	0.3		
	Mean	32.5	51.3	45.7	67	109	123	6.7	3.3	1.6	2.7		
Uremic subjects													
Basal secretion	26	2	1	28	17	145	74	64.2	12.5	0	13.7	70 (98)	29 (41)
	27	0	0	15	33	128	107	32.5	0.5	1.5	29.5	69 (97)	40 (56)
	28	10	58	32	98	117	151	54.7	7.9	23.5	76.1	96 (134)	113 (158)
	29	0	0	5	3			7.8	6.3	24.4	14.3	39 (55)	30 (42)
	49	7	6	33	22	138	107	15.2	8.6	20.6	20.5	46 (64)	46 (64)
	Mean	3.8	13	23	35	132	110	34.9	7.2	14.0	30.8	64.0 (89.6)	51.5 (72.1)
Posthistamine secretion	26	40	54	69	70	142	111	46.6	9.4	0	10.3		
	27	0	55	32	84	134	153	23.0	1.4	17.7	22.8		
	28	54	68	81	102	136	152	32.0	8.9	46.0	83.5		
	29	0	0	10	8			8.2	6.0	12.4	12.6		
	49	38	46	58	66	150	141	15.5	10.9	14.4	13.2		
	Mean	26.4	44.6	50.0	66.0	141	139	25.1	7.3	18.1	28.5		

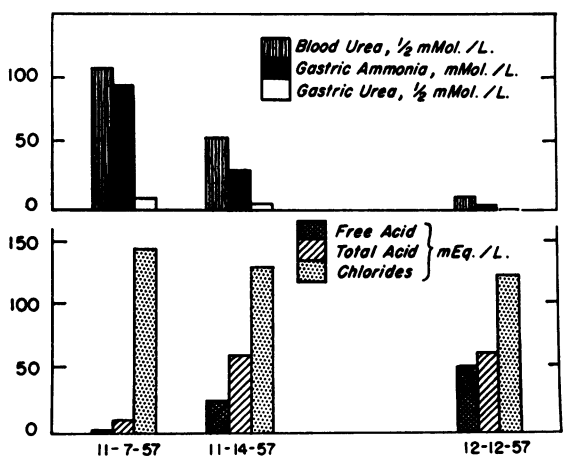

FIG. 2. EFFECTS OF A DECREASE IN BLOOD UREA ON GASTRIC AMMONIA AND ACIDITY (POSTHISTAMINE SECRETION)

ministration of antibiotics resulted in a significant drop of gastric ammonia ($p < 0.01$) and a significant increase of gastric acidity ($p < 0.05$) in eight patients with uremia due to a chronic glomerulonephritis in whom no change in blood urea occurred during the period of investigation (Table V, Group A). In a similar group (Table V, Group B) of nine patients with uremia, where no marked reduction of gastric ammonia occurred, no change of acidity was observed.

DISCUSSION

Several authors (14, 15, 22, 30) have shown that the concentration of ammonia in gastric juice is roughly proportional to the blood urea level; this has been confirmed by our results.

Anemia, lowered blood carbon dioxide content,

TABLE V

Seventeen patients with stable uremia: Gastric secretion before and after antibiotic treatment with (A) and without (B) significant reduction in gastric ammonia

		Before antibiotic treatment		After antibiotic treatment		Difference	
		Gastric ammonia	Free acid	Gastric ammonia	Free acid	Gastric ammonia	Free acid
		mMole/ L.	*mEq. HCl/ L.*	*mMole/ L.*	*mEq. HCl/ L.*	*mMole/ L.*	*mEq. HCl/ L.*
Group A (8 uremic patients)	Basal secretion	49.8	1.4	7.6	18.7	−42.2	+17.3
	S. D.	6.6	1.4	3.4	7.5	5.2	6.3
	Posthistamine secretion	41.0	21.6	5.6	52.2	−35.4	+30.6
	S. D.	6.1	10.6	1.7	15.0	6.0	7.7
Group B (9 uremic patients)	Basal secretion	26.7	12.8	23.1	12.7	− 3.6	− 0.1
	S. D.	6.9	9.8	6.7	6.7	2.1	12.3
	Posthistamine secretion	24.0	46.2	19.2	47.4	− 4.8	+ 1.2
	S. D.	5.9	10.6	5.7	11.6	2.0	7.0

disturbances of water and electrolyte balance (31) and gastritis (32) have been suggested previously as causes for gastric hypoacidity in uremia. Although it is possible that these factors may contribute to the encountered low gastric acidity, no experimental proof that they are responsible has been presented.

The hypothesis that gastric ammonia reduces acidity (15) seemed more plausible but has not been supported previously by experimental evidence in uremic patients.

The demonstration that reduction of gastric ammonia after antibiotic treatment increased acidity of patients with uremia and *in vitro* addition of ammonia decreased acidity (33) clearly relates hypoacidity to ammonia.

In uremic patients, reduction of gastric ammonia causes gastric acidity to rise to a level similar to that of nonuremic subjects. In the basal state, where gastric acid secretion is normally low, the decrease in ammonia may be greater than the increase of acidity. After histamine stimulation, the ammonia decrease parallels the increased acidity.

Administered antibiotics did not influence gastric acidity in the absence of marked changes of ammonia. This was seen in both control subjects and uremic patients in whom antibiotics had little or no effect on gastric ammonia. The encountered differences in ability of oxytetracycline, erythromycin and chloramphenicol to influence gastric ammonia are unexplained; they may be related to the different antibiotic spectra or pharmacodynamic effects. Since bacteria reside in the stomach under physiological conditions (34, 35) and urease activity of gastrointestinal organism is reduced by antibiotics (36–39), it seems probable that the ammonia-reducing effect of oxytetracycline and erythromycin is related to their antibiotic properties rather than to a pharmacodynamic effect.

After use of oxytetracycline, an increased incidence of blood in gastric juice was noted and may be attributed to the occurrence of gastric ulcerations after such treatment (40). Theoretically, return of normal acidity coupled with the effects of retained urinary excretory products on mucous membranes may predispose to ulcerations and gastroduodenal bleeding (41).

Effects of therapy on gastric ammonia and acidity may also be of practical importance in patients with liver disease and azotemia who exhibit an elevated gastric ammonia. Reduction of gastric ammonia in patients with cirrhosis can be achieved with oxytetracycline (42) or neomycin (43).

SUMMARY

Twenty-six patients with uremia had high gastric ammonia and low free and total acid concentrations, compared with 24 control subjects without evidence of renal dysfunction.

Spontaneous and induced reduction of gastric ammonia in patients with uremia was accompanied by an equivalent increase in gastric acidity, indicating the contribution of ammonia to hypoacidity in uremia.

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