

# Absorption of Nicotine by the Human Stomach and Its Effect on Gastric Ion Fluxes and Potential Difference

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*We studied gastric absorption of nicotine and the effect of oral nicotine, intravenous nicotine, and cigarette smoking on ion fluxes and potential difference in the human stomach. Nicotine was well absorbed, mean  $18.6 \pm 3.4\%$  in 15 min, on intragastric instillation at pH 9.8. Absorption was accompanied by side effects of nausea and vomiting, and delay in gastric emptying. Gastric absorption of nicotine at pH 7.4 was less marked (mean  $8.2 \pm 2.9\%$ ), but was negligible at pH 1 (mean  $3.3 \pm 1.4\%$ ). Intragastric nicotine at pH 7.4 and 9.8 stimulated gastric acid output either during instillation (pH 9.8) or during subsequent acid instillation (pH 7.4). Rapid cigarette smoking and intravenous nicotine suppressed gastric acid output. Neither oral administration nor intravenous infusion of 4 mg nicotine base per hour nor smoking 3–5 cigarettes per hour significantly altered the gastric mucosal barrier as measured by gastric ionic fluxes and potential difference. In conclusion, (1) the base nicotine ( $pK_a 8.5$ ) is well absorbed from the human stomach at pH 9.8, but poorly absorbed at pH 1.0; (2) gastric absorption of nicotine delays gastric emptying; (3) intragastric nicotine at and above neutral pH appears to have a mild stimulating effect on gastric acid output, while rapid cigarette smoking or intravenous infusion of nicotine suppresses acid output; (4) nicotine does not alter the gastric mucosal barrier to sodium ion movement nor affect potential difference.*

Cigarette smoking has been implicated in the pathogenesis of gastric ulcer in man (1–3), but the data are by no means clear-cut (1). The effect of cigarette smoking on acid secretion is uncertain (4–6), and the mechanism of the damaging action, if any,

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This work was supported in part by grants from the Australian Tobacco Research Foundation, the National Health and Medical Research Council of Australia, and the Medical Research Service of the Veterans Administration. The technical assistance of Mr. P. Settree, BSc, is gratefully acknowledged.

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of cigarette smoking or nicotine on gastric mucosa is unknown. We studied the effect of cigarette smoking and its major constituent, nicotine, on the gastric mucosal barrier in man as measured by changes in ion fluxes and potential difference (PD) in an attempt to determine whether cigarette smoking and nicotine acted predominantly by altering the gastric mucosal barrier (7) in man.

Little data are available on the absorption of nicotine from the stomach in man (8). This may be of considerable importance in suspected poisoning from oral tobacco or nicotine ingestion (8), and in subjects who chew tobacco. In order to determine optimal therapy in nicotine poisoning by ingestion, we studied absorption of nicotine from the stomach at acid and alkaline pH.

TABLE 1. ORDER OF INTRAGASTRIC INSTILLATION OF TEST SOLUTIONS FOR IONIC FLUX STUDIES (GROUP 1.1)\*

Period	Control study at pH 1	Nicotine study at pH 1	Nicotine study at pH 7.4	Nicotine study at pH 9.8
1	Control pH 1	Nicotine pH 1	Nicotine in phosphate buffer	Nicotine in glycine buffer
2	Control pH 1	Nicotine pH 1	Nicotine in phosphate buffer	Nicotine in glycine buffer
3	Control pH 1	Nicotine pH 1	Nicotine in phosphate buffer	Control pH 1
4	Control pH 1	Nicotine pH 1	Control pH 1	Control pH 1

\*At pH 1 control acid solutions and nicotine in acid solutions were each instilled for 4 consecutive periods; nicotine in buffer at pH 7.4 or 9.8 was instilled for repetitive periods followed by control acid solution.

## MATERIALS AND METHODS

### Studies

Forty-six studies were carried out on 13 healthy volunteers (ten males, three females), aged 19–26 years, after obtaining informed consent and institutional approval from the Human Experimentation Committee. All subjects were nonsmokers except for two subjects in the cigarette-smoking studies. Subjects were divided into three groups as follows:

**Group 1—Intragastric Nicotine at pH 1, 7.4, 9.8.** In this group were eight subjects. The eight subjects were divided into two groups of four:

1. One half of the group had ionic flux measurements only. Each study consisted of four consecutive 15-min study periods in the order shown in Table 1 for studies at pH 1, pH 7.4, and pH 9.8. Changes in ion fluxes were looked for in all periods in control observations, during administration of solutions which contained nicotine at pH 1, 7.4, and 9.8, and after administration of nicotine in buffer solutions at pH 7.4 and 9.8.

2. The second half of the group of four subjects had both ionic flux and PD measurements simultaneously. So that large changes in pH would not interfere with PD measurements, for example by producing liquid-junction potentials, the order of instillation of solutions for studies at pH 7.4 and 9.8 shown in Table 2 was used.

The PD study itself had no effect on the parameters measured. Flux data from studies with and without PD recordings were therefore combined in each group. Within each group no significant differences appeared between individual periods 1 through 4 when the same test solution was instilled, so that all such periods in each study were combined and mean values  $\pm$  standard errors (SE) shown in tables and figures.

**Group 2—Cigarette Smoking.** In this group were five subjects who were each studied twice to determine the effect of cigarette smoking on ionic fluxes and PD. The control study consisted of four consecutive periods of instillation of control acid solution (as in group 1 studies). During the next study on a separate date, each subject was encouraged to smoke as many cigarettes (3–5) as he could tolerate immediately before and during the study. Three subjects were nonsmokers and two smoked 5–10 cigarettes per day. During this study, the intragastric solution again consisted of the control acid test solution (160 mM HCl) instilled for four consecutive 15-min periods.

In addition, in two subjects (one smoker, one nonsmoker) 32 mg nicotine acid tartrate was added to the test solution during an additional two periods of their study to test the effect of oral and systemic nicotine combined.

**Group 3—Intravenous Infusion of Nicotine.** In this group were four subjects who had already taken part in the group 2 studies. In them, the effect of intravenous infusion of nicotine on ionic fluxes and PD was studied. Nasogastric intubation and instillation of fluid began after nicotine infusion was stopped. Each study consisted of four consecutive periods of instillation of control test solution as in group 1. Data were compared with control studies without nicotine infusion done on a separate date.

In addition, in two subjects 32 mg nicotine was added to the test solution in a final two periods to study the effect of combined intravenous and intragastric nicotine on ionic fluxes.

### Test Solutions

**Oral Acid Solution.** The control test solution at pH 1 was 160 mM HCl with a mean osmolality of 307 mOsm/kg containing radioactive chromium chloride ( $^{51}\text{CrCl}_3$ , 25

TABLE 2. ORDER OF INSTILLATION OF TEST SOLUTIONS FOR CONCOMITANT MEASUREMENT OF IONIC FLUX AND POTENTIAL DIFFERENCE (GROUP 1.2)

Period	Control study at pH 1	Nicotine study at pH 1	Nicotine study at pH 7.4	Nicotine study at pH 9.8
1	Control pH 1	Nicotine pH 1	Phosphate buffer	Glycine buffer
2	Control pH 1	Nicotine pH 1	Phosphate buffer	Glycine buffer
3	Control pH 1	Nicotine pH 1	Nicotine in phosphate buffer	Nicotine in glycine buffer
4	Control pH 1	Nicotine pH 1	Nicotine in phosphate buffer	Nicotine in glycine buffer

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$\mu\text{Ci/liter}$ ) as nonabsorbable indicator. Preliminary studies comparing  $^{51}\text{Cr}$  with phenol red, 50 mg/liter, and polyethylene glycol, 2 g/liter, at various pH levels showed so little difference under the conditions of our study that  $^{51}\text{Cr}$  was used for all calculations (unpublished data).

A concentration of nicotine acid tartrate of 32 mg/200 ml was used in all nicotine solutions. The nicotine base concentration of each of our solutions was approximately 25% or 8 mg/200 ml test solution.

**Oral Solutions—pH 7.4.** They consisted of 200 ml phosphate buffer containing 32 mg nicotine acid tartrate (8 mg nicotine base) plus 25  $\mu\text{Ci/liter}$   $^{51}\text{CrCl}_3$ . The control pH 7.4 buffer solution consisted of 161.6 ml of 21.3 g/liter disodium hydrogen phosphate plus 38.4 ml of 23.4 g/liter anhydrous sodium dihydrogen phosphate ( $\text{NaH}_2\text{PO}_4$ ).

The phosphate buffer solution without indicator or nicotine was used as a wash solution. The mean electrolyte composition and osmolality of the phosphate buffer solution were: sodium 258 mEq/liter, potassium 0.2 mEq/liter, chloride 10 mEq/liter, osmolality 320 mOsm/kg. Phosphate ion made up the anion balance.

**Oral Solutions—pH 9.8.** They consisted of 200 mg glycine buffer containing 32 mg nicotine acid tartrate (8 mg base) and nonabsorbable indicators  $^{51}\text{Cr}$ . The glycine-sodium hydroxide buffer solution consisted of glycine 7.505 g/liter + sodium chloride 5.85 g/liter made to 1 liter with distilled water. 120 ml of this solution were mixed with 80 ml 0.1 N NaOH to make a 200 ml solution of pH 9.8. This solution contained:  $\text{Na}^+$  97 mEq/liter,  $\text{K}^+$  0.2 mEq/liter,  $\text{Cl}^-$  65 mEq/liter with a mean osmolality 206 mOsm/kg.

### Cigarette Smoking

Cigarettes were provided by British Tobacco Co., Australia, from the one production batch of a commercially available filter-tip brand. This batch had been assayed and shown to yield on smoking an average of 2 mg nicotine (base) per cigarette (9).

### Intravenous Nicotine

Ampoules (5 ml) of nicotine acid tartrate for intravenous use contained the equivalent of 4 mg nicotine base aseptically prepared in water for injection. The contents of an ampoule were dissolved in 100 ml isotonic saline and infused over 45 min (80  $\mu\text{g/kg/hr}$ ). Attempts to run the solution any faster produced nausea.

### Experimental Technique, Laboratory Measurements, and Calculations

The technique has been previously described (10) with the modification that the stomach was first bathed with control test solution at the appropriate pH level for 15 min before beginning the first period (11, 12). Volumes secreted and emptied (13), and net ion fluxes (10) were calculated, and  $\text{H}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  concentrations, osmolality, radioactivity  $^{51}\text{Cr}$  (12), and pepsin were measured by methods previously described (10). In this technique the volume emptied refers to emptying of gastric contents, that is, instilled solution plus secretion (10, 13).

### Potential Difference (PD)

Gastric PD was recorded continuously by standard methods utilizing intravenous peripheral electrodes (14), as previously described (15, 16). For statistical analysis, PD data were analyzed at 3-min intervals throughout each 15-min study period (0, 3, 6, 9, 12, and 15 min).

### Nicotine Assay

Nicotine assayed by gas chromatography as previously described (17).

### Statistical Analysis

Results were analyzed statistically by Student's *t* test for paired and unpaired values.

## RESULTS

### Nicotine Absorption by the Stomach

The percentage absorption of nicotine instilled into the stomach at pH 1, 7.4, and 9.8 was measured in group 1.1 studies. Practically no absorption (mean  $3.3 \pm 1.4\%$ ) occurred at pH 1. With increase in pH to 7.4 which nears the  $\text{pK}_a$  value for nicotine of 8.5, absorption increased to  $8.2\% \pm 2.9\%$ , but the difference was not significant compared to pH 1. Above the dissociation constant for nicotine at pH 9.8, nicotine was well absorbed (mean  $18.6 \pm 3.4\%$ ). This was significantly greater than absorption at pH 1 ( $P < 0.01$ ) or pH 7.4 ( $P < 0.05$ ).

**Group 1.1 and 1.2—Intragastric Nicotine at pH 1, 7.4, and 9.8 on Ion Fluxes.** In Figure 1 are shown mean net flux values  $\pm$  SE for  $\text{H}^+$  and  $\text{Na}^+$  ions during acid instillation studies at pH 1 (for order of in-

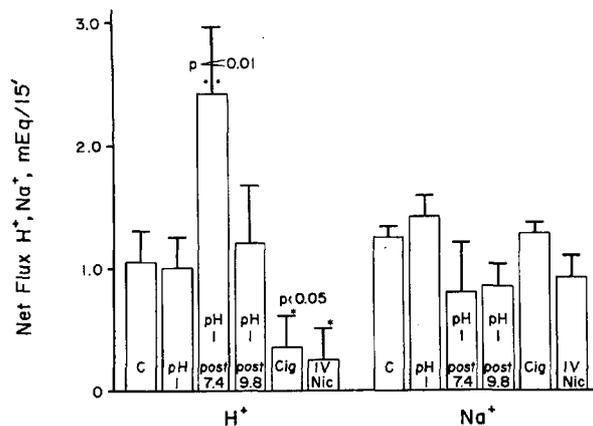


Fig 1. Mean  $\pm$  SE net  $\text{H}^+$  and  $\text{Na}^+$  flux values during acid instillation: for control (C) and nicotine (pH 1) studies at pH 1; after instillation of nicotine in buffer at pH 7.4 (pH 1 post 7.4) and pH 9.8 (pH post 9.8); during cigarette smoking (Cig) and intravenous nicotine (IV Nic) studies. Statistical analyses were made to control (C) values.

TABLE 3. IONIC MOVEMENT AND VOLUMES SECRETED AND EMPTIED IN RESPONSE TO NICOTINE SOLUTIONS AND ALKALINE BUFFERS

	N*	Net flux (mEq/15 min)		Volume (ml/15 min)	
		H <sup>+</sup>	Na <sup>+</sup>	Secreted	Emptied
Control pH 1	8	1.05 ± 0.22	1.26 ± 0.12	17.9 ± 2.6	17.2 ± 4.2
Nicotine pH 1	8	0.96 ± 0.23	1.53 ± 0.14	24.9 ± 2.1	20.6 ± 2.9
pH 7.4 buffer	4	1.31 ± 0.42	2.05 ± 0.46	21.1 ± 1.9	70.5 ± 17.9
Nicotine pH 7.4	8	2.23 ± 0.29	2.24 ± 0.55	21.1 ± 2.8	21.7 ± 5.5b†
pH 9.8 buffer	4	2.05 ± 0.26	0.44 ± 0.21	9.0 ± 2.7	79.9 ± 25.2
Nicotine pH 9.8	8	3.08 ± 0.27a†	1.49 ± 0.25	25.6 ± 2.8	15.4 ± 5.4b†

\*On this and next table, *N* refers to number of subjects studied and values are mean ± SE.

†a *P* < 0.05 For values between nicotine and corresponding control pair at each pH level.

†b *P* < 0.01 Only values significant by paired as well as unpaired *t* test are marked.

stillation, see Table 1). Nicotine in acid caused no alteration in fluxes compared to the control acid solution. Compared to acid control, net hydrogen flux into the gastric lumen was significantly increased when acid was reinstalled into the stomach after instillations of nicotine in buffer at pH 7.4. Net H<sup>+</sup> flux into the lumen was significantly reduced during cigarette smoking and after intravenous infusion of nicotine. In no study was Na<sup>+</sup> movement into the gastric lumen significantly affected.

In Table 3 are compared net ion fluxes and volumes secreted and emptied each 15 min, for control and nicotine solutions at each pH level. There were not significant differences between control and nicotine solutions for net H<sup>+</sup> or Na<sup>+</sup> flux values at pH 1 and pH 7, although mean net H<sup>+</sup> flux was greater with nicotine in buffer at pH 7.4 than control buffer. Mean net H<sup>+</sup> flux into the lumen was significantly greater (*P* < 0.05) for intragastric nicotine at pH 9.8 than buffer at pH 9.8. Nicotine in the stomach at pH 7.4 and 9.8 each reduced gastric emptying (*P* < 0.01).

**Group 1.2—Intragastric Nicotine at pH 1, 7.4, and 9.8 on Potential Difference.** No significant differences occurred between PD values for the control solutions with those containing nicotine at the corresponding pH.

**Group 2—Cigarette Smoking and Ion Fluxes.** The only significant alteration was a smaller net H<sup>+</sup> flux after cigarettes (Table 4). Sodium output was not significantly increased. There were no significant differences between electrolyte concentration and osmolality changes in the two studies.

In the two subjects in whom intragastric nicotine was given in the final two periods of the cigarette study, there was a small net loss of H<sup>+</sup> ions, mean of the four periods being  $-0.16 \pm 0.27$  mEq/15 min, but no increase in net sodium flux, mean  $1.07 \pm 0.24$  mEq/15 min.

**Group 2—Cigarette Smoking and Potential Difference (Figure 2).** No significant differences between control PD values and values during cigarette smoking were evident.

In subjects given intragastric nicotine during the last two periods of the cigarette smoking (two subjects) study there were no differences in PD compared to control studies.

**Group 3—Intravenous Nicotine and Ion Fluxes.** The results for ionic fluxes after intravenous infusion of nicotine were similar to those for cigarette smoking (Table 4). Net H<sup>+</sup> flux was significantly less than controls, but Na<sup>+</sup> flux was not increased.

In the two subjects in whom intragastric nicotine was given in the final two periods of the study,

TABLE 4. IONIC MOVEMENT AND VOLUMES SECRETED AND EMPTIED IN RESPONSE TO CONTROL ACID SOLUTION WHILE SMOKING AND WITH INTRAVENOUS (IV) NICOTINE

	N	Net flux (mEq/15 min)		Volume (ml/15 min)	
		H <sup>+</sup>	Na <sup>+</sup>	Secreted	Emptied
Control pH 1	5	1.06 ± 0.31	1.15 ± 0.16	19.6 ± 2.5	17.9 ± 6.0
Cigarettes pH 1	5	0.33 ± 0.24**	1.28 ± 0.08	25.3 ± 6.7	24.4 ± 8.9
IV nicotine pH 1	4	0.25 ± 0.25**	0.98 ± 0.14	16.3 ± 2.5	12.1 ± 4.3

\*\**P* < 0.05.

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mean net  $H^+$  ( $0.75 \pm 0.25$  mEq/15 min) and  $Na^+$  ( $0.81 \pm 0.23$ ) fluxes were similar to those without intragastric nicotine.

**Group 3—Intravenous Nicotine and Potential Difference (Figure 2).** No significant differences between control PD values and values during intravenous infusion of nicotine were evident.

In subjects given intragastric nicotine during the last two periods of intravenous nicotine infusion (two subjects) study there were no differences in PD compared to control studies.

### Pepsin

Nicotine caused no change in pepsin output ( $35 \pm 3$  mg/15 min control,  $36 \pm 3$  nicotine) or concentration ( $216 \pm 16$   $\mu$ g/ml control,  $215 \pm 16$  nicotine).

## DISCUSSION

Little data has previously been available on the absorption of nicotine from the human stomach. Goodman and Gilman (8) list nicotine as one of the most toxic of all drugs and report that an oral dose of 60 mg may be fatal—they did not specify if this referred to the base or hydrogen tartrate. Nicotine is a moderately strong base with a  $pK_a$  of 8.5. Its absorption might therefore be expected to follow that of the pH-partition hypothesis proposed by Hogben and associates (18). This indeed is what we found. At pH 1 nicotine is not absorbed, as it exists in the dissociated ionized state and is not lipid soluble. At pH 9.8 a considerable proportion of the drug is in the undissociated un-ionized state which is lipid soluble and hence well absorbed.

Side effects occurred promptly after intragastric instillation of 32 mg nicotine hydrogen tartrate (8 mg base) at pH 9.8. Nausea and vomiting induced were similar to but not as severe as that experienced by the same subjects during intravenous infusion of nicotine and/or rapid cigarette smoking studies. Mean absorption was also increased at pH 7.4. Most commercially available antacids have a pH value at this value or higher. For example, pH of Mylanta I and II is 8.4, Maalox 8.0, and a teaspoonful of baking soda in 100 ml water 8.5. Hence, subjects chewing tobacco could expect increased gastric absorption of nicotine if they were achlorhydric because of disease, eg, pernicious anemia; gastric surgery; or peptic ulcer therapy, eg, intense antacid regimen or H-2-receptor antagonists (18). Con-

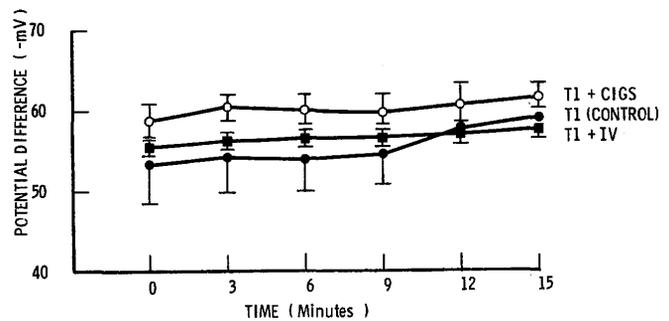


Fig 2. Comparison of effect of intragastric instillation of acid solution during cigarette smoking and intravenous infusion of nicotine with control studies on gastric PD.

versely, in cases of suspected oral nicotine or tobacco poisoning, acidification of the stomach with a solution of a weak acid may be useful as an emergency measure. Certainly antacids should never be given.

Gastric emptying is not delayed in the human stomach at neutral pH. Intragastric nicotine significantly slows gastric emptying at both the pH 7.4 and pH 9.8 levels. Thus, therapy of acute nicotine ingestion by nasogastric aspiration or washing the stomach with a solution of a weak acid may still be effective, although some time has elapsed since the nicotine was swallowed.

Our studies of net ion fluxes have failed to show an effect of nicotine administered orally, systemically, or both combined, on the gastric mucosal barrier to  $H^+$  or  $Na^+$  ions. This was true at intragastric pH levels below (pH 1 and 7.4) and above (pH 9.8) the dissociation constant of nicotine ( $pK_a$  8.5). There was a suggestion that acid secretion was stimulated during nicotine in buffer instillation at pH 7.4 and 9.8 (Table 1). This was more clearly seen in the significant increase in acid secretion seen with acid instillation after nicotine in buffer at pH 7.4 compared to control acid instillation (Figure 1).

Nicotine, a moderately strong base, diffuses readily into the stomach from the plasma where it is trapped in the acid environment of the stomach (18, 19). In our studies doses of intravenous nicotine and rates of cigarette smoking were encouraged to the limit of tolerance. The resultant nausea itself presumably contributed to or caused the inhibition of gastric acid secretion (20), although an inhibiting effect of nicotine itself through some central mechanism is also possible. This re-

duced acid secretion is reflected in the significant reduction in net H<sup>+</sup> flux seen in these studies (Table 4). Sodium fluxes and concentration changes were not increased, indicating alteration of the gastric mucosal barrier had not occurred in man, so confirming studies in Heidenhain pouch dogs (21).

Changes in potential difference have been shown to follow alteration in the gastric mucosal barrier to ionic fluxes. In previous studies, we have shown that reduction in PD induced by aspirin correlates closely with mucosal damage induced by the drug (15). In the current studies, nicotine produced no significant reduction in PD during or after intragastric instillation at pH 1, 7.4, or 9.8. Neither intravenous infusion nor cigarette smoking reduced PD during instillation of acid test solution with or without intragastric nicotine. Thus, PD and ion flux studies give no support to the concept that nicotine induces gastric mucosal damage in man by alteration of the gastric mucosal barrier.

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