Definition & Antagonism of Histamine H2-Receptors

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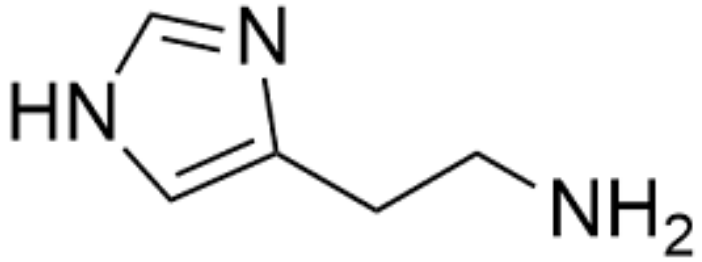
Black et. al 1972

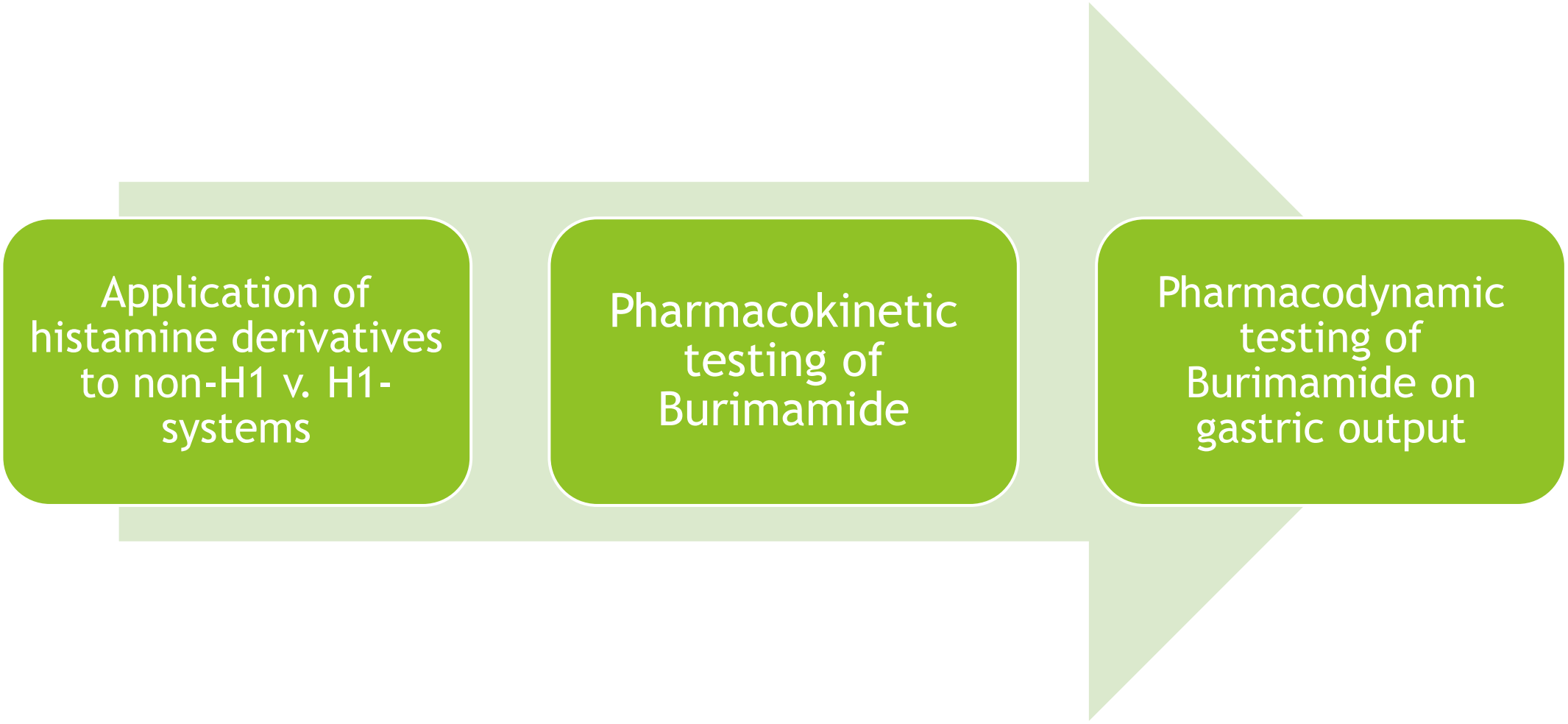
Introduction

- What is Histamine?
  - An endogenous, nitrogenous compound that regulates physiological functions in the gut, is involved in a local immune response, and acts as a neurotransmitter.
- Histamine also stimulates the contraction of smooth muscle (gut/bronchi), acid secretion (stomach), and increases heart rate.
- There are 4 types of Histamine receptors
  - H1- Allergic Inflammation
  - H2- Gastric Acid Secretion
  - H3- Neurotransmission
  - H4- Immunomodulation



Histamine

Experimental Design



Application of Histamine Derivatives

Methods

- Histamine response was measured in five tissue systems/assays
  - Contractions of guinea pig Ileum suspended in solution (Fig. 1)
  - Contractions of the stomach of a rat measured by intragastric balloon
  - Contraction frequency of right Atrium (Fig. 1)
  - Electrically evoked contractions of uterine horn
  - Rat gastric acid secretion pH measurements
- Compared the “relative activity” pooled from several assays compared to histamine

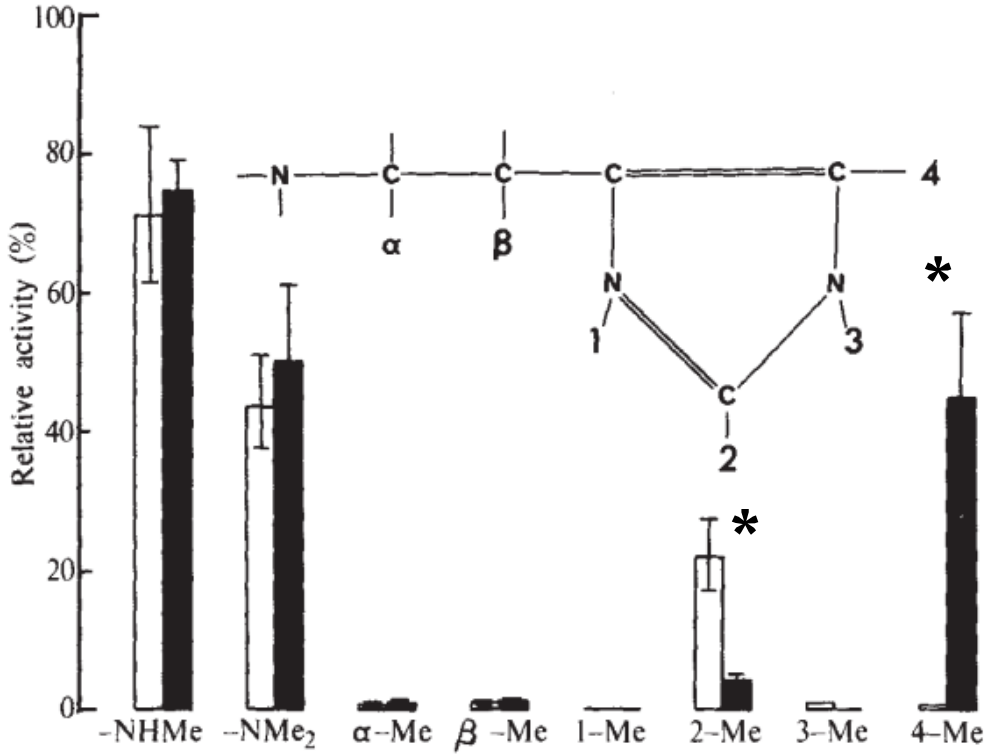


Figure 1. Bar chart showing activity of histamine derivatives relative to histamine on ileum (white) and atrium (black)

Application of Histamine Derivatives

Conclusions: 2- and 4-methylhistamine significantly differ between the H1 and non-H1 groups. 2-methylhistamine has greater activity in H1 assays and 4-methylhistamine has greater activity in non-H1 assays.

Table 1 Activities Relative to Histamine (=100)

	H_1 group		Non-H_1 group			Statistical analysis					
	Guinea-pig ileum *in vitro*	Rat stomach contractions *in vivo*	Guinea-pig atrium *in vitro*	Rat uterus *in vitro*	Rat gastric acid secretion *in vivo*	Source of variation	DF	χ^2	MS	F	*P*
4-Methyl-histamine	0.2	0.3	43.0	25.3	38.9	Within assays	4	3.15	0.79	—	NS
						Within groups	3	39.56	13.19	16.7	0.01
						Between groups	1	6,350.96	6,350.96	481.6	0.001
2-Methyl-histamine	16.5	18.6	4.4	2.1	2.0	Within assays	5	5.38	1.08	—	NS
						Within groups	3	76.19	25.38	23.6	0.01
						Between groups	1	728.42	728.42	28.7	0.05
3-(2-Amino-ethyl)-1,2,4-triazole	12.7	10.5	6.8	9.5	13.7	Within assays	4	49.62	12.41	—	0.001
						Within groups	3	96.59	32.20	2.60	NS
						Between groups	1	46.61	46.61	1.45	NS

Table 1. results of individual assays analyzed by calculating heterogeneity for 3 separate contrasts

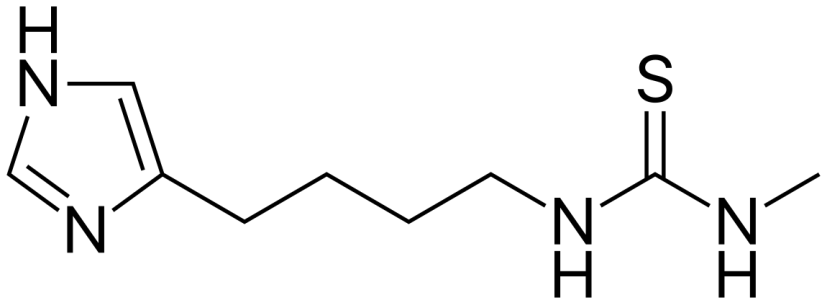
- Within-assays: heterogeneity due to differences between individual replicated assays on any one system
- Within groups: heterogeneity due to differences in mean relative activities within H1 or non-H1 groups.
- Between groups: heterogeneity due to differences between two groups of assays treated as a whole

Burimamide: Pharmacokinetic Analysis

Conclusion: Burimamide demonstrated a dose-dependent shift compared to histamine ("without antagonist") without significant changes in the shape of the curve.

Methods

- Measured the contraction frequency of right Atrium from guinea pig (% maximum)



Burimamide

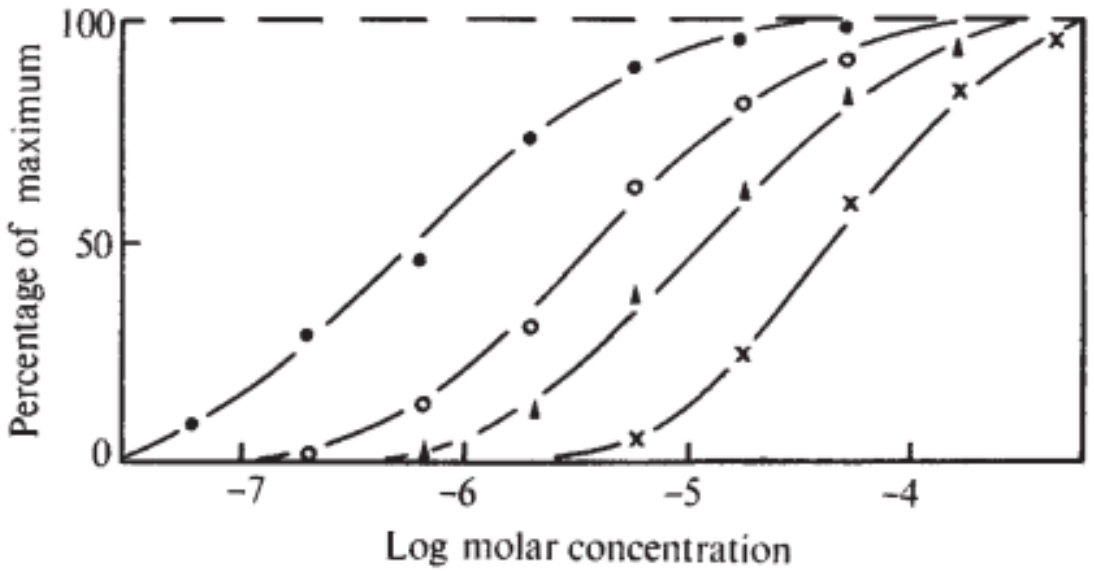


Fig. 2 Histamine cumulative log-dose response curves from guinea-pig atrium: without antagonist (●) and after equilibration with burimamide 2×10^{-5} M (○), 4×10^{-5} M (▲) and 2.7×10^{-4} M (×). Using Marquardt's algorithm[9] for non-linear least-squares curve-fitting, each dose-response curve could be fitted to the logistic function[10]

Burimamide: Pharmacokinetic Analysis

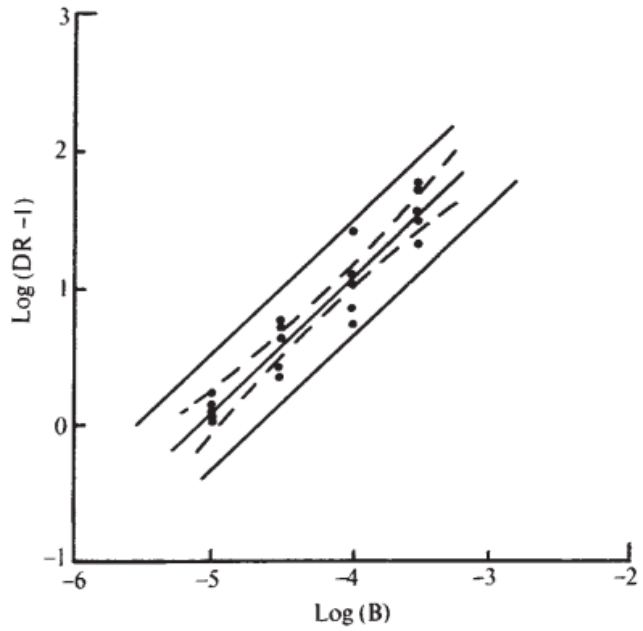


Fig. 3 Antagonism of histamine by burimamide on guinea-pig atrium. Antagonism is expressed by histamine dose-ratios (DR) needed for equal responses before and after burimamide (B) equilibration. If burimamide and histamine compete for a common site (and certain assumptions hold) then log (DR-1) = log (B) − log K_B, where K_B = (apparent) dissociation constant for the antagonist-receptor interaction[11]; the data are plotted to test this relationship. Each DR was calculated from the ratio of ED_{50} values estimated from fitting a logistic function to each of a separate pair of dose-response curves. Twenty pairs of dose-response curves were obtained from eleven tissue preparations. Concentrations of burimamide were 1×10^{-5} M, 3×10^{-5} M, 1×10^{-4} M and 3×10^{-4} M. Regression of log (DR-1) on log (B) was calculated by method of least squares and 95% confidence limits for the regression (dashed lines) and for a single estimation (continuous lines) are shown. K_B (apparent) = 7.8×10^{-6} M (6.4–9.6); $pA_2 = 5.11$ (5.02–5.19). Slope = 0.98 (0.90–1.06).

Table 2 Dissociation Constant (K_B) for Burimamide estimated on Guinea-pig Ileum using Three Agonists

	Agonist ED_{50}/ 10^{-6} M With 95% confidence limits	Burimamide K_B/ 10^{-6} M With 95% confidence limits
Histamine	1.1 (0.9–1.4)	7.8 (6.4–9.6)
4-Methylhistamine	3.1 (2.0–4.3)	7.2 (5.2–9.2)
2-Methylhistamine	19.8 (9.7–29.9)	6.9 (5.7–8.2)

Activities of each agonist are expressed as ED_{50} values obtained from fitting the logistic function to complete dose-response curves.

Table 3 Burimamide Antagonism on Isolated Tissues

Tissue	Agonist	Slope of log (DR-1) on log (B) regression With 95% confidence limits	Burimamide K_B/ 10^{-6} M With 95% confidence limits
Atrium	Histamine	0.98 (0.90–1.06)	7.8 (6.4–9.6)
Uterus	Histamine	0.96 (0.80–1.12)	6.6 (4.9–8.3)
Ileum	Histamine	1.32 (1.11–1.54)	288 (95–870)
Ileum	Carbachol	1.44 (1.16–1.72)	174 (60–500)

Conclusion:

Burimamide is a specific competitive antagonist of H2-receptors with no significant interaction with catecholamine-β-receptors, H1-receptors, or acetylcholine receptors.

Histamine Receptors & Gastric Acid Secretion

Methods

- Rats were given potential inhibitors via rapid I.V. injection of Burimamide during the plateau of gastric secretion.
  - Indicated by arrow in Figure 4
- Secretion stimulated by Infusion of histamine or pentagastrin at a rate of 2.5 x 10-7 mol/kg per min = ~70% max response (histamine)

Results

- Burimamide injection increased the pH above 4.1
  - Inhibition maxes out after 30 minutes

Conclusion: Burimamide is a surmountable inhibitor of histamine stimulated gastric secretion.

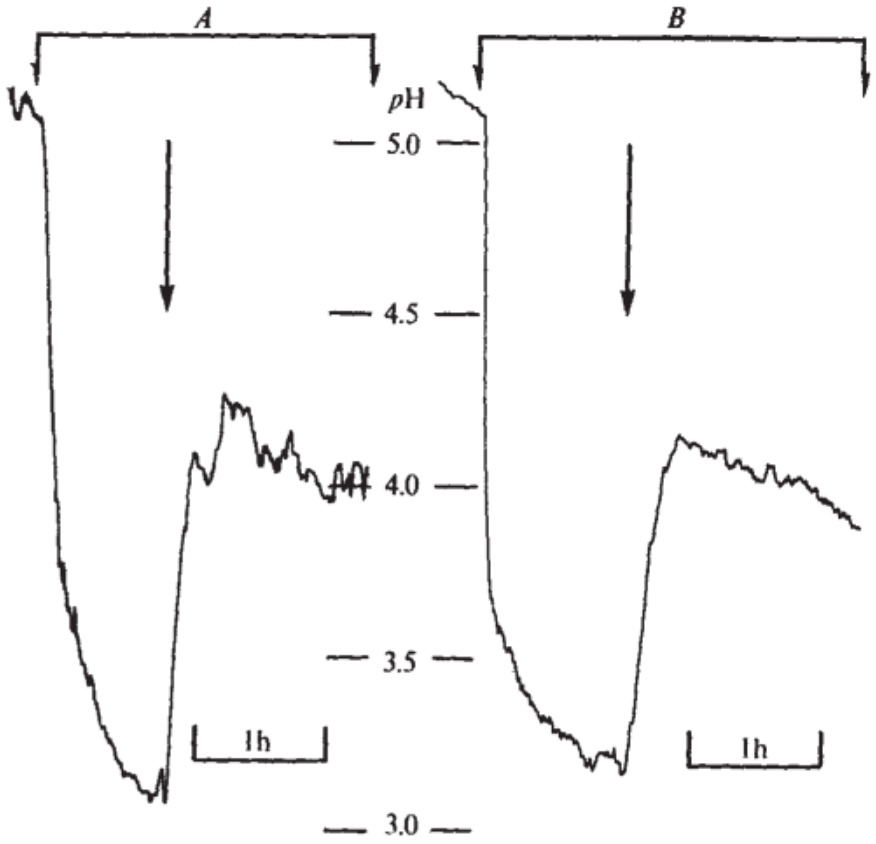


Fig 4. **Inhibitory response of single Burimamide injection**
A. stimulated by histamine
B. stimulated by pentagastrin

Histamine Receptors & Gastric Acid Secretion

Methods

- Subjects: six male dogs prepared with Heidenhain pouches
- Measuring of gastric output as a measure of H+ ion concentration output per minute after Burimamide injection (i.v.) under multiple conditions:
  - Top 3 curves with continuous I.V. histamine, bottom 2 curves with continuous I.V. pentagastrin

Results

- Half life estimated ~90 minutes
- Pentagastrin only generated ~60% of Histamine's maximum secretions

Not Shown:

- Effect of burimamide on gastric secretion evoked by feeding examined in each dog. Large meals evoked less secretion than Histamine.
- Burimamide produced a ~64.4% inhibition of food-stimulated secretions

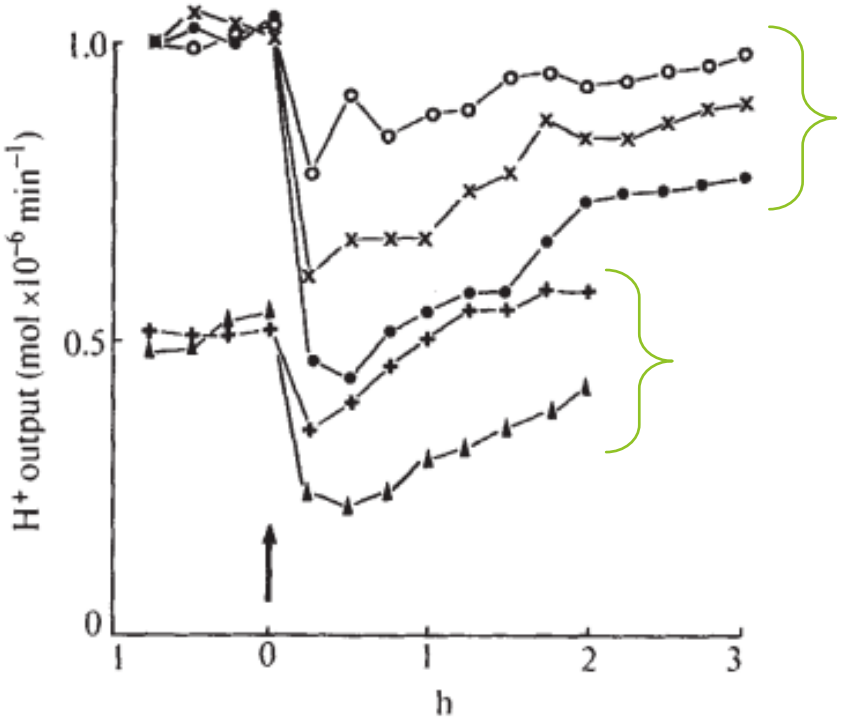


Fig. 5 Gastric acid output from dogs prepared with Heidenhain pouches. Burimamide was given intravenously at zero time (arrow). Each output curve is the mean of six experiments; the upper three curves were obtained with histamine 2×10^{-5} mol h^{-1} intravenously, and the lower two curves with pentagastrin 8×10^{-6} g kg^{-1} h^{-1} intravenously. Doses of burimamide, mol kg^{-1}, were as follows: during histamine, ○, 1×10^{-5}; ×, 2×10^{-5}; ●, 4×10^{-5}; and during pentagastrin, +, 2×10^{-5}; ▲, 4×10^{-5}.

Gastric Acid Output from Human Volunteers

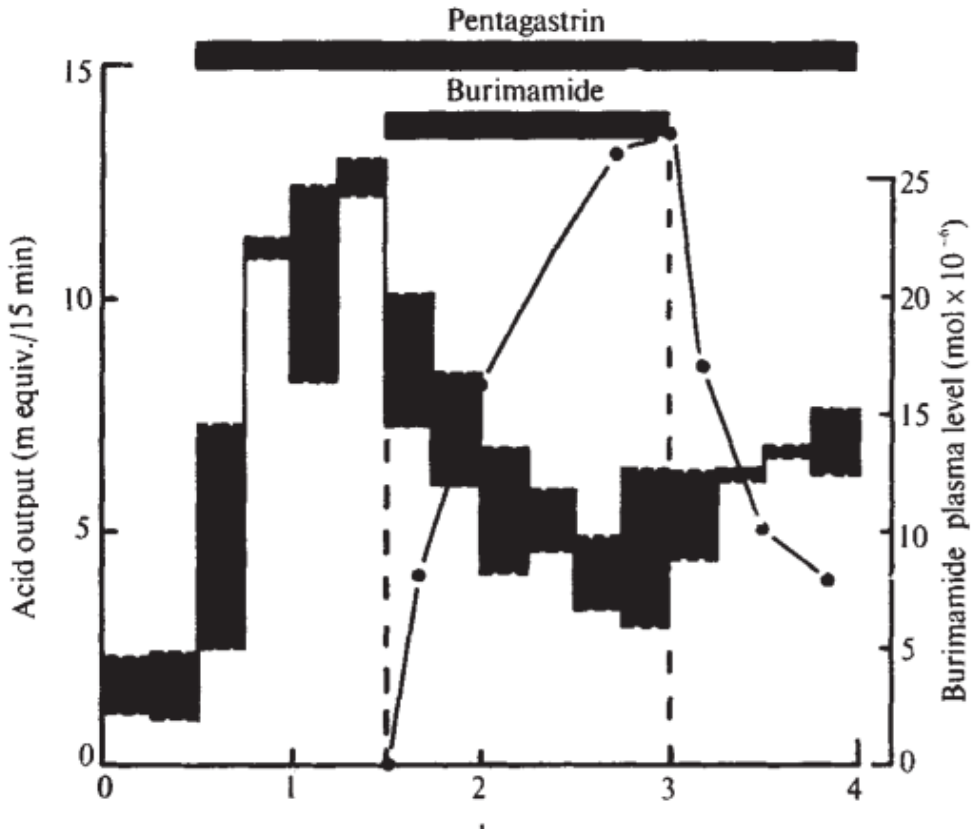


Figure 6. Mean output from 2 subjects given continuous pentagastrin and burimamide for 1.5 hours.

Methods

- Subjects: 2, Human
- Pentagastrin infused intravenously (6x10^-6 g/kg per hr)
- Burimamide administered continuously after 1.5 hours of pentagastrin administration (rate: 0.3 g/hr)
- Acid output measured at 15-minute intervals
  - Gastric fluid aspirated from an intragastric tube

Results

- Burimamide reduced acid output 80% after 90 minutes
- Decline in acid output corresponded to increase in plasma burimamide

Conclusions

- Burimamide can antagonize responses to histamine which cannot be blocked by H1-antagonist Mepyramine
- Histamine activates H2-receptors to produce gastric acid secretions
- Histamine responses like hypotension can be completely blocked by a combination of Mepyramine (H1) and Burimamide (H2), but neither alone
- Burimamide inhibits pentagastrin-stimulated acid secretion without altering cholinergic secretion

50 Years Later…

- Since this paper was publish, it has been cited over 1700 times
- Many H2-antagonists have entered the market to treat GI conditions such as gastric ulcer, GERD, heartburn, etc.