Measurement of gastric secretion as a student teaching exercise

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Teaching gastrointestinal physiology to preclinical medical students presents problems in finding suitable practical exercises to demonstrate the physiology of gastric acid secretion. In our course, students measure their own gastric secretory activity by the use of nasogastric tubes. Gastric secretion can be stimulated by insulin-induced hypoglycemia or by pentagastrin, a synthetic gastrin analogue. The time course of the secretory responses, i.e., volume, acid output, and pH, are followed by collecting control and poststimulatory secretions into 15-min samples. The effect of antulcer drugs, such as cimetidine, can be easily studied in such experiments. The results of these experiments are very reproducible, allowing year-to-year comparisons of treatments. Examples of results of various experimental protocols are shown. We believe this to be a useful class exercise not only because of the excellent results it yields but because of the experience and insights it produces.

gastric acid secretion; cimetidine; pentagastrin; insulin; student exercise

Basic physiology and pharmacology of gastric secretion

Figure 1 shows a simplified summary of the factors controlling acid secretion in the stomach. Acid production by the parietal cells may result from vagal stimulation of muscarinic (M1) receptors (cephalic phase of gastric secretion). Vagal activity may also stimulate release of the neurocrine gastrin-releasing peptide, which acts on the G cells of the antrum, stimulating gastrin release. Gastrin is also released by protein breakdown products in the gastric lumen (gastric phase). Somatostatin cells in the antrum produce the paracrine somatostatin, which inhibits gastrin release from the G cells; somatostatin release is inhibited by vagal activity but is stimulated by a high hydrogen ion concentration in the gastric lumen. Gastrin is carried by the circulation to the parietal cells where it stimulates gastrin receptors.

A third receptor type on the parietal cell membrane binds histamine. Histamine is secreted in the fundic mucosa by mastlike cells or histaminocytes (2). Although there is evidence from some species of increased histamine secretion in response to activation of acetylcholine (M1) receptors, and probably also gastrin receptors, there is no evidence in humans that the amount of histamine acting on the parietal cell increases during the stimulation of acid secretion, and it appears that there is an ever-present background secretion of histamine. The activation of the parietal cells by the histamine thus released is of great significance in the production of gastric acid. The three receptor types on the parietal cell membrane all activate the proton pump on the luminal membrane but via different intracellular pathways. There is a very strong interdependence of these actions, and it is because of this that H2 blockers such as cimetidine inhibit the secretory response to gastrin and acetylcholine, as well as to histamine. The involvement of histamine in gastric acid secretion was first demonstrated in 1920 by Popielski (8). After Komarov (5) showed histamine and gastrin to be separate secretagogues, MacIntosh (6) suggested that histamine was the final common mediator by which acetylcholine and gastrin stimulated the parietal cells. However, experiments on isolated parietal cell preparations (10) demonstrated that the receptors for the three secretagogues, acetylcho-
The discovery that analogues of 4-methylhistamine antagonize gastric histamine receptors (1) led to the development of the H₂-receptor antagonists. This provided the possibility for reducing histamine-induced gastric secretion by specific H₂-receptor antagonism. The recognition of two populations of histamine receptors, H₁ and H₂, with the latter being found predominantly in the stomach, led to wide clinical use of the H₂-receptor antagonist cimetidine and cogenors for the reduction of gastric acid secretion.

**Experimental Procedure**

Although all medically fit students are encouraged to participate, they must give their informed consent before they can act as subjects. The class extends over 2 wk; students are paired, with each participant acting as a subject 1 wk and as a “carer” the 2nd wk. All subjects must fast overnight. Subjects are divided into various treatment groups, e.g., for the 1988 data shown in Figs. 3 and 4, the groups were control and insulin, cimetidine and insulin, control and pentagastrin, and cimetidine and pentagastrin. With a class size of 48, this produces treatment groups of 12, which allows reasonable statistical analysis. In this experiment the cimetidine groups were administered cimetidine (800 mg on the previous night and 800 mg 2 h before intubation). In 1990 (see Fig. 6) the class was divided into three treatment groups: no cimetidine, low cimetidine (400 mg taken the night before the experiment), and high cimetidine (800 mg taken the night before the experiment and 800 mg on the morning of the experiment). As a point of reference, the recommended dose for acute treatment of acute gastric or duodenal ulceration is 800 mg at bedtime or 400 mg night and morning. The recommended maintenance dose is 400 mg at bedtime.

While a class such as this requires supervision by a medically qualified member of the staff, who can provide help immediately should a problem arise, we have found that the best results (in terms of successful intubations) are achieved when the procedure is explained and demonstrated by a hospital nurse, who is involved in the regular intubation of patients. A successful and nontraumatic demonstration on a volunteer does a lot to reduce class tension and give others an incentive to succeed.

A small-diameter (3 mm) Ryles tube (FG-10) is inserted nasogastrically in seated subjects, the intubation being performed by the subject, partner, or, if necessary, by the supervising nurse or practitioner. The position of the tube can be verified by injecting air while listening over the stomach with a stethoscope. Any residual fluid is withdrawn and discarded, and timed collection is begun. Fluid is aspirated continuously and segregated into 15 min samples. The volume of each sample is measured, and then it is filtered through gauze. A 5-ml aliquot is pipetted into an automatic titrator, pH is measured, and then the aliquot is titrated against 0.05 M NaOH to an end point of pH 7.4. After 1 h of basal collection the subject receives an injection of pentagastrin (Peptavlon, 6 µg/kg body wt sc) or insulin (0.20 units/kg sc or iv; see DISCUSSION). Pentagastrin treated subjects collect gastric secretions for a further 1 h, while subjects receiving insulin must continue for a further 2 h.

Gastric secretion can be stimulated experimentally by a subcutaneous injection of pentagastrin (Peptavlon; ICI), a gastrin analogue, and by insulin. The development of pentagastrin led to the replacement of the augmented histamine test to assess a patient’s acid secreting capacity with the much safer pentagastrin secretory test. The advent of H₂-blocking agents has now dramatically reduced the need for this test. Insulin stimulates acid secretion by producing a hypoglycemia, which acts on hypothalamic receptors to cause an increase in vagal activity. This test can be used clinically to test the completeness of surgical vagotomy.
RESULTS

Figures 2–6 summarize some of the results from four years of class experiments. They show the acid output in millimoles per 15 min, pH, and volume secreted every 15 min. Figure 2 (1987 class) shows the effects of intravenous insulin injection, whereas Fig. 3 (1988 class) shows that subcutaneous insulin has a much less dramatic effect. Pentagastrin at the recommended dose levels produces a faster, larger response than intravenous insulin (Fig. 4; 1988 class). When the dose of pentagastrin was halved in an attempt to reduce unpleasant side effects (nausea, vomiting), maximal secretion rates were not reached (Fig. 5; 1989 class). In all of these cases the effects of cimetidine are very marked; Fig. 6 (1990 class) shows the effects of two levels of cimetidine dosage on the response to pentagastrin. While a variety of statistical analyses may be carried out on the data, a number of important conclusions are apparent on examination of the graphs. 1) Cimetidine produces a significant reduction in basal acid output but a nonsignificant reduction in the volume secreted. 2) Cimetidine produces a very large and significant rise in gastric pH during the basal period. 3) Pentagastrin produces a more rapid increase in gastric secretion than does intravenous insulin (30 min to peak output compared with 45 min) and a higher peak. 4) Insulin given intravenously produces a more rapid and a greater increase in acid secretion than when it is given subcutaneously. 5) Cimetidine reduces both hormonally (pentagastrin) and vagally (insulin) stimulated acid secretion.

DISCUSSION

This experiment can be used to demonstrate a number of physiological and pharmacological points.

1) Gastric secretion can be stimulated both vagally and hormonally, and an H₂ blocker will reduce the response to both types of stimuli.

2) The slower and weaker response to subcutaneous insulin compared with intravenous insulin can be related to the slower absorption from the injection site and a consequent smaller reduction in blood glucose. Although it was accepted for many years that gastric acid secretion is initiated and stimulated maximally below a specific threshold concentration of blood glucose, i.e., that there is an "all or none" relationship, it has been demonstrated more recently that there is a graded acid secretory response to hypoglycemia, beginning at normoglycemic levels (7). The results in Figs. 2 and 3 are in accord with this.

3) It suggests that interdigestive gastric pH can be elevated sufficiently to reduce peptic ulceration, without preventing acid production during the physiological stimulus of a meal.

4) While the actions of the various drugs are readily apparent from the mean values shown in Figs. 2–6, there is a very large degree of variation in gastric acid secretion and in the response to stimulation in normal individuals.
Cimetidine. Most reported side effects from cimetidine are associated with long-term, high-dose treatment. Under these circumstances cimetidine may produce nonspecific blockade of nongastric H₂ receptors (3), with possible neuropsychiatric effects. From some 100 subjects we have seen one possible adverse reaction: headache, tiredness, dizziness, and rash. A slightly higher incidence of rashes has been reported in cimetidine-treated patients than in those given a placebo (9).

Pentagastrin. Although we have seen no serious adverse reaction to pentagastrin, a large percentage experiences some transient but unpleasant side reactions. In 1990, when 39 subjects received the recommended dose of 6 µg/kg, 23 reported some degree of nausea, with 11 retching or actually vomiting. Of the 16 subjects who did not experience nausea, 11 experienced dizziness and a slight weakness. These reactions, which normally last <3 min, occur some 15–20 min after administration of the pentagastrin and are presumably associated with peak blood pentagastrin levels.

Insulin. As the stimulatory effect of insulin on gastric secretion is due to the hypoglycemia it induces, a dose of insulin sufficient to stimulate gastric secretion will often produce the symptoms of hypoglycemia, e.g., sweating and cutaneous vasodilation, followed by vasoconstriction and shivering, and then tiredness. Although insulin-induced hypoglycemia presents little danger to healthy subjects, there is still some risk involved, and these subjects must be supervised closely and 50% dextrose solution must be available. Severe hypoglycemia can be rapidly reversed by injecting this down the tube, but if necessary it can be given intravenously. We have never found it necessary to do more than give a glucose tablet.

FIG. 4. Acid secretory response of control (n = 11) and cimetidine-treated subjects (n = 9) to subcutaneous injection of pentagastrin (6 µg/kg). Values are means ± SE. Arrow indicates time of pentagastrin injection.

The extent of physiological variability in normal subjects is often not appreciated by students, who should be involved in the analysis of the data.

The good quality of the data allows various approaches to be used. Students may be simply given the collated raw data and asked to summarize the results statistically and graphically; this approach stresses the skills of data handling and presentation rather the specifics of gastrointestinal physiology. Alternatively, statistical and graphical summaries may be provided, and the students may be asked to discuss specific questions that place more stress on the interpretation of data, e.g., 1) Why does insulin take longer to have an effect on gastric secretion than pentagastrin? 2) Although pH of cimetidine subjects is high during the basal period, during stimulation pH falls to near normal levels. Do you think this might affect the usefulness of cimetidine in preventing peptic ulceration? and 3) Would these results be of any help in deciding whether the role of histamine in gastric secretion is better described by the final common mediator or potentiation theory?

Dangers, Problems, and Adverse Reactions

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Such problems are reduced when the insulin is administered subcutaneously, but the secretory response is then
slower and much reduced. Because of the possibility of problems and the necessity to have a total of 3 h of intubation to see the effects of insulin, we have discontinued the use insulin in this exercise.

Intubation. The process of intubation, while generally well tolerated by the majority of students, is quite stressful for some, who find the tube increasingly uncomfortable as the experiment proceeds. Thus all subjects must be told that they may remove the tube if necessary.

Conclusions

Overall, this experiment is quite unpleasant for the participants: they must do without breakfast, suffer a nasogastric tube for up to 3 h, and then, in the case of pentagastrin treatment, have up to 2 ml injected subcutaneously. Both pentagastrin and insulin may also produce effects that add to the subject’s discomfort. Against this must be balanced the positive aspects: the results obtained are extremely good, and retrospectively most students report a feeling of satisfaction and achievement. The results are sufficiently reproducible to allow year-by-year variation of protocol and comparison of the results. In future years, for example, we plan to investigate the acid inhibitory effects of a new drug, omeprazole, which reversibly reduces gastric acid secretions by specifically inhibiting the H⁺-K⁺-ATPase proton pump in the parietal cell (see Fig. 1).

While such experiments cannot demonstrate all the complexities of the control of gastric secretion as shown in Fig. 1, they do indicate the importance of H₂ receptors in the stimulation of gastric secretion. Data obtained from an experiment such as this do not allow students to decide between the various receptor models that have been suggested for activation of acid secretion (sequential, parallel, or single receptor). However, attempting to reconcile the various models with the class data is a great aid to understanding the various models and gives an appreciation of the complexity of model formation. The experiment also provides a dramatic demonstration of the efficacy of a very important class of drugs used to reduce acid secretion. Perhaps the most positive aspect that we can list is the attitude of the students after they have completed the experiment. For those who complete the experiment there is a feeling of achievement from having voluntarily submitted to an unpleasant experience and having been rewarded with good data. They also appreciate the clinical relevance of this particular exercise. Because students have the responsibility for supervising and caring for their partners, we believe this is a useful introduction to having to deal with patients subjected to similar invasive procedures. There can be little doubt that students learn more from practical exercises in which they actively participate. This exercise demands complete involvement from students, both when they act as subject and when they act as carer, and is an effective learning experience for medical students.

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