CLINICAL ASSESSMENT OF ANTISECRETORY DRUGS IN MAN

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Therapeutic measures — drugs and operations — which reduce gastric secretion of acid and pepsin are of proven clinical value in diseases associated with ulceration and inflammation of the upper alimentary tract. Since illnesses of this type are very common, the potential market for safe and effective antisecretory drugs is so great that many pharmaceutical firms now test all newly developed compounds for antisecretory effects, irrespective of whether or not the drugs have been initially developed as potential inhibitors of gastric secretion. Indeed, even drugs which have been in clinical use for many years for non-gastrointestinal disorders are being restudied for antisecretory properties, sometimes because they are structurally similar to agents with proven inhibitory effects on gastric secretion. If animal studies of candidate gastric inhibitory drugs show even minor antisecretory effects, and freedom from toxicity, the studies are usually extended to man. The objective of these preliminary investigations is to provide answers to the following questions:

1. Does the compound exert any inhibitory effect on human gastric secretion and, if so, under what circumstances?
2. What are the pharmacokinetic and pharmacodynamic properties of the compound?
3. By what mechanisms is the antisecretory effect achieved?
4. Is the compound safe and well tolerated, or is its use associated with significant side effects or toxicity?

Since so many reports are currently appearing about drugs with potential for gastric inhibition, we have attempted to provide some background information to permit more satisfactory evaluation of studies involving gastric antisecretory drugs.

1. Does the compound have gastric inhibitory properties?

General considerations

a. Which subjects should be studied?

Healthy volunteers Healthy subjects are assumed to have normal physiological control of gastric secretion and to have unimpaired absorption, distribution, metabolism and excretion of administered drugs. Studies in healthy volunteers are, therefore, appropriate for establishing that an antisecretory effect does exist, as well as for defining the normal pharmacokinetic and pharmacodynamic properties of new compounds.

Patient volunteers Since antisecretory drugs will always be used therapeutically in patients with disease and since the physiological control of gastric secretion is abnormal in many of the disorders which have to be treated with antisecretory drugs, it is necessary to establish that new drugs also have gastric inhibitory effects in the different groups of potential patients, since differences in response may occur. For example, the ID_{50} of cimetidine for pentagastrin-stimulated gastric secretion in healthy subjects is 0.5 $\mu\text{g/ml}$ (Burland *et al.*, 1975), while the value for patients with duodenal ulcer is twice that amount (Bodemar & Walan, 1978). Similarly, it has been shown that gastric inhibition is more complete in patients with gastric than with duodenal ulcers (Thjodleifsson & Wormsley, 1975a), while some patients with gastric hypersecretion may be more 'resistant' than expected to antisecretory drugs (Danilewitz *et al.*, 1982).

Patients should not be studied immediately (within 1 week) of complications of ulcers such as haemorrhage or perforation, since the latter may markedly (but usually only temporarily) impair gastric secretory function.

Patients should not be receiving any other drug

therapy. No gastric antisecretory drug should have been used for at least 7 days before study and even antacids should preferably be stopped at least 24 h beforehand, because of possible residual effects on the gastric mucosa; on plasma levels of gastrin; and on the bioavailability of the test drug.

In view of the degradation of drugs in the liver, or excretion by the kidneys, and the increased occurrence of ulcers in diseases of these organs, it is often necessary to undertake additional studies to identify alteration in the kinetics and actions of drugs in patients with these types of diseases.

Effects of age, sex and ethnic group Gastric secretion tends to decrease with age (Baron, 1978), mainly as the result of increased degrees of gastritis, with associated loss of acid-secreting parietal cells. There is no evidence that the antisecretory effects of drugs are different in older patients, although the pharmacokinetic characteristics of the drugs may be affected by the age of the patients (Somogyi *et al.*, 1980).

In view of the ever-present possibility of teratogenicity, new antisecretory drugs should not be tested in females of child-bearing age.

Marked differences in gastric secretory function have been observed between different ethnic groups. As a rule, gastric output of acid and pepsin is greater (about twice as high) in West Europeans and Americans compared with African and Asian individuals (Baron, 1978). However, there is no evidence that the gastric inhibitory effects of drugs are altered, other than relatively, in different population groups.

No evidence is available that preceding diet influences the gastric inhibitory properties of drugs. However, we have recently shown that smoking prevents, wholly or in part, the inhibitory effects of antisecretory drugs on nocturnal gastric secretion (Boyd *et al.*, 1981a), although the inhibition of pentagastrin-stimulated secretion is not altered. The potential effects of smoking must therefore be taken into consideration when designing protocols for study of antisecretory drugs.

Ethical considerations Studies should only be carried out after obtaining the fully informed consent of volunteer subjects.

b. Intubational methodology

Gastric intubation For studies in which complete aspiration of gastric contents is required, a naso-gastric tube with a terminal air vent (14FG or larger) must be used. The air vent is essential to ensure adequate recovery of gastric contents. Intubation through the nose is preferable to peroral intubation, since the latter route is often associated with persistent nausea and stimulates salivation. Correct

positioning of the tube in the stomach can be confirmed by a water-recovery test (Hassan & Hobsley, 1970), or radiologically. Aspiration is best performed by continuous mechanical suction and the subjects are encouraged to take occasional deep breaths and to make minor changes in position to ensure that gastric juice does not pool between the gastric rugae. Saliva should be expectorated. Infusion of markers to assess completeness of recovery is not necessary and may falsely increase basal secretory rates (Venables, 1972).

Duodenal intubation Intubation of the duodenum may be necessary for intraduodenal infusion of antisecretory drugs. An enteric feeding tube with mercury weight and syringe attachment (Dobhof) is commercially available and satisfactory for duodenal intubation. Correct siting in the duodenum is confirmed radiologically or by aspiration of alkaline bile-stained juice and is associated with a characteristic change in transmitted pressure profile on passage from stomach into duodenum. Following the duodenal intubation, a naso-gastric tube is positioned in the stomach, as above. Absence of duodeno-gastric reflux must be confirmed by instilling 10 ml of a solution of phenol red down the duodenal tube, while continuous suction is applied to the gastric tube. If no phenol red appears in the gastric aspirate, the drug being studied (together with a further 5–10 ml phenol red solution) is administered slowly (during about 2 min) down the duodenal tube. Appearance of marker in the gastric aspirate at any time during the study invalidates that test.

24-h profiles of gastric contents The most suitable tube for sampling gastric contents (as compared with complete aspiration) is also an enteric feeding tube, passed so that the mercury bag is sited 55 cm from the nares. This position makes it unlikely that the tube will accidentally enter the duodenum during a prolonged study. Since the tube is made of soft polyvinyl (3 mm diameter), discomfort to the patient is minimal and there is no interference with eating or daily activities. Sampling is usually performed at hourly intervals. Three ml of gastric juice is sufficient to permit measurement of pH, hydrogen ion concentration and peptic activity. Samples should not be withdrawn within 1 h of ingestion of drugs, because significant amounts of the drug may be aspirated.

How should the drug be administered?

Oral administration While it is usually necessary to study how effective a new drug is after oral administration (or after introduction directly into the stomach through a naso-gastric tube, if the drug has a taste which prevents experimental 'blinding'), it may be very difficult to evaluate antisecretory effects

because the actual techniques involved in measuring changes in gastric secretion may interfere with the action of the test drug. The technical problems depend partly on whether the drug exerts its antisecretory effects locally either within the lumen of the stomach or duodenum (by altering, in some way, gastric juice which has been secreted); or by direct topical action on the gastric mucosa, or parenterally, after absorption from the small intestine.

Drugs which exert local effects (e.g. antacids, antipeptic agents, 'cytoprotective' compounds) must, of course, be administered in a form which ensures release of the active agent within the stomach or duodenum. The drug must also be given enough time to exert its local effects and gastric aspiration must be discontinued after administration of the drug as long as is necessary for the drug to exert its effects (since otherwise the drug will be removed from the stomach in the aspirate). The study then becomes difficult to interpret, because for quite a long time (e.g. an hour or more) intragastric events cannot be monitored and subsequent evaluation of alterations in gastric secretory patterns in terms of drug-induced effects is difficult or impossible. Although studies of this type are often reported, because they are simple to perform, the results are really not worth very much. In order to assess the antisecretory efficacy of drugs with local intragastric effects, it is therefore necessary to employ alternative and technically more difficult methods (such as intragastric titration, or studies with multiple indicators) to monitor immediate, as well as more persistent, changes in the composition of the gastric contents after administration of the drugs.

When antisecretory drugs exert their effects after absorption, technical problems arise usually because the protocol of the study is defective. One of the principal determinants of absorption of a drug is the rate of its delivery to the site of absorption (usually the small intestine). The rate of absorption therefore depends particularly on the rate of gastric transit which, in turn, differs unpredictably between individuals and may also be affected by the drug itself. After oral or intragastric administration, it therefore becomes necessary to wait for some time for the drug to empty from the stomach and enter the circulation. As a result, the study usually depends on some form of discontinuous protocol (a period of 'control' aspiration of gastric contents: cessation of aspiration for some time: restart of aspiration) in order to assess the antisecretory effects of the absorbed drug. Alternatively, the test drug may be administered orally some arbitrary time (e.g. 30 (Bajaj & Hirschowitz, 1976) to 180 (Boyd *et al.*, 1981b) min) before starting to aspirate gastric juice. Unfortunately, these experimental schedules introduce at least three uncontrolled variables into the test situation, since it is not possible to measure the (changing) rates of

emptying of the drug from the stomach; or the changing rates of secretion of gastric juice during this time; or the consequently variable rates of emptying of gastric juice into the small intestine.

One can, of course, obtain approximate estimates of the amount of drug available for absorption by measuring the residual drug aspirated from the stomach (Barbezat & Bank, 1976) or by serial measurements of blood levels of the drug (Myren *et al.*, 1979). However, the other variables cannot easily be measured and become even more serious problems when orally or intragastrically administered drugs are tested against the gastric secretory response to exogenous secretagogues. In this type of study, the output of gastric juice is permitted to attain a steady rate (plateau) of secretion during a 'control' period, the rate of gastric secretion being measured by continuous aspiration of gastric contents from the start of stimulation. When the drug is administered, orally or by instillation down the aspiration tube, gastric aspiration is stopped for a specified period of time, to permit absorption of the drug (Barbezat & Bank, 1976). A fundamental source of error is introduced when gastric aspiration ceases in the middle of a study, because acid in the upper small intestine inhibits gastric secretion (and emptying) (Wormsley, 1971), so that inhibition attributed to the anti-secretory drug may, in fact, be caused by the small intestinal acidification which necessarily accompanies gastric discharge of the drug into the small intestine.

Intraduodenal administration The problems arising from the variable rate of gastric emptying of an orally administered drug and from small intestinal acidification can be totally avoided by introducing the drug directly into the small intestine, because intraduodenal administration of drugs permits accurate, continuous measurement of changes in gastric secretion, while also preventing duodenal contamination with acid. Absorption of many drugs is rapid after intraduodenal administration, with the result that the time course of the gastric inhibitory effect is very similar to that of the drug administered intravenously (Thjodleifsson & Wormsley, 1974).

Intraduodenal administration of drugs is undoubtedly the method of choice for testing drugs which inhibit gastric secretion after absorption into the circulation.

Intravenous administration Intravenous dosing assures complete bioavailability, whether rapid bolus injection or continuous intravenous infusion is used, so that a satisfactory evaluation of the inhibitory potency of the drug can be obtained. Intravenous infusion has the advantage that constant plasma levels of the drug can be obtained, so that accurate dose-response relationships can be defined.

The use of continuous intravenous infusion of anti-

secretory drugs also permits identification of the type of gastric inhibition which is followed by 'rebound' hypersecretion (to levels greater than in the pre-treatment control period) (Wormsley, 1970) when infusion of the inhibitory drug is stopped. This type of gastric 'inhibition-rebound' response is difficult to interpret but is important to identify, because it is probably of no therapeutic value.

What should be measured?

The principal components of gastric juice are water, hydrochloric acid, pepsin, intrinsic factor and mucus. As a rule, it is only necessary to measure the rate of secretion of gastric juice and acid, since the other components (pepsin, intrinsic factor) are usually secreted more or less in parallel with acid. The concentration of these components, multiplied by the rate of secretion of water (that is, the volume of gastric juice secreted into the stomach in unit time) provides a measure of the output of that component.

Gastric juice is secreted at rates ranging from zero to the maximal response to specific exogenous stimulants (such as pentagastrin or histamine). The latter responses may differ in magnitude and, in turn, often differ from the gastric response to the (endogenous) stimulus of food. When the stomach is not being obviously stimulated, it is considered to be in a 'basal' state.

Both basal and stimulated gastric secretion may be markedly abnormal in disease, being characteristically increased in many patients with duodenal ulcer and decreased in patients with gastric ulcer (Baron, 1978). It is not known against which of these indices of gastric secretory function new antiseecretory drugs should be tested in order to provide maximal information about clinical antiseecretory efficacy. Since the degree of inhibition of basal and stimulated secretion is often different, antiseecretory drugs should probably be tested against both types of secretion.

The inhibition of gastric secretion produced by drugs manifests usually as decrease in the rate of secretion of gastric juice without change in the concentration of acid. When the concentration of acid is also decreased, it may be necessary to check that the integrity of the gastric mucosa has not been compromised (see below).

A special problem arises when the gastric contents are not aspirated continuously, but are only sampled during the determination of a 24 h profile. Alterations in the composition (that is, decrease in concentration) of the sampled gastric contents following administration of an antiseecretory drug are usually interpreted as showing that gastric secretion has been inhibited, on the basis of the (unstated) assumption that decreased concentration of acid in the gastric contents implies decrease in the secretion

of acid (e.g. in response to food), while the amounts of diluent (e.g. saliva, food, drink, &c.) remain similar to those in the control test (without treatment).

Design of studies of antiseecretory drugs

New drugs should have their antiseecretory effects assessed in double blind, controlled studies (Modell & Houde, 1958). Since gastric secretion (both basal and stimulated) may alter (and especially diminish) with repeated testing (Thjodleifsson & Wormsley, 1975b), the order in which secretory studies are performed must be randomised. Studies must be performed on separate days, which should not be consecutive since the effects of the test itself, as well as the residual effects of the test drug, may alter gastric function. On the other hand, the interval between tests should not be too long, since gastric secretion may decrease markedly with time (Ramsey *et al.*, 1979). The most satisfactory interval seems to be 2 to 4 days. Tests should be performed at the same time of day, to preclude the effects of diurnal variations in gastric secretion.

The environmental circumstances should be kept as constant as possible, since (for example) the preparation or intake of food by someone in the vicinity of the test subject may stimulate gastric secretion. More important, venepuncture may inhibit gastric secretion for up to 30 min, so that if blood samples are to be taken, or intravenous infusions are scheduled during the study, indwelling cannulae should be inserted before the study starts and an equilibration period of 30 min allowed after inserting the needle (Saunders *et al.*, 1975).

Does the compound under study inhibit gastric secretion?

a. Inhibition of basal and nocturnal gastric secretion.

Basal gastric output of acid and pepsin is variable and poorly reproducible when measured over short periods of time, so that little value has been attached to the inhibitory effects of antiseecretory drugs on basal secretion (White & Juniper, 1973). However, if basal secretion is going to be studied, aspiration must be continued for a minimum period of one hour (in four batches of 15 min) and the results from the first 30 min after intubation should be excluded from analysis (Faber & Hobsley, 1977). More prolonged (2-3 h) collections of basal secretion tend to be more reproducible and therefore provide a more satisfactory basis for testing inhibitory effects. However, the most satisfactory measure of 'unstimulated' gastric secretory activity involves collection of gastric juice for 12 h during the night. Measurement of nocturnal

gastric secretion of acid and pepsin is particularly important because 'inappropriate' nocturnal secretion is thought to play a pathogenetic role in duodenal ulceration while, in addition, inhibition of overnight gastric secretion is known to afford symptomatic relief for patients with duodenal ulcer and with oesophagitis.

b. Inhibition of stimulated gastric secretion

Antisecretory drugs have usually been tested for their effects on gastric secretion stimulated maximally by a gastric secretagogue because this criterion of gastric function is reproducible and easy to measure. However, there are experimental and theoretical reasons for preferring submaximal rates of stimulation when assessing the antisecretory activity of drugs.

The secretory stimulant should be administered by constant-rate intravenous infusion, which permits a constant rate of stimulation (and, usually, of secretion) (Wormsley, 1972) to be achieved, so that any changes in secretory rate elicited by antisecretory drugs can be easily detected. The time taken to reach a constant rate of secretion depends on the stimulant which is used and should be taken into account in planning the duration of stimulation, since the secretory stimulus should continue for a minimum of 60 min after constant rates of secretion are achieved.

Histamine Histamine has recently come into use again as a stimulant of gastric secretion because many of the newly developed antisecretory drugs have H_2 receptor blocking effects, or have to be tested for such effects. An intravenous infusion of $0.014 \text{ mg kg}^{-1} \text{ h}^{-1}$ of the base (or $0.4 \text{ mg kg}^{-1} \text{ h}^{-1}$ histamine acid phosphate) produces a maximal gastric response in most subjects (Lawrie *et al.*, 1964). The peak secretory rate occurs quite late (up to 60 min after the start of stimulation). Unwanted effects, such as flushing, nausea, palpitations, abdominal cramps and occasional circulatory collapse can occur and can be minimised by prior administration of a histamine H_1 receptor antagonist. However, adverse reactions of some severity occur in 5% of test subjects despite the antihistaminic drug (Johnston & Robinson, 1967).

Pentagastrin Pentagastrin, in doses ranging from $1.5\text{--}6 \text{ } \mu\text{g kg}^{-1} \text{ h}^{-1}$, normally produces maximal stimulation of secretion (Baron, 1978), while a dose of $0.2 \text{ } \mu\text{g kg}^{-1} \text{ h}^{-1}$ provides a satisfactory submaximal stimulus for assessing the effects of antisecretory drugs. Constant secretory rates are usually achieved after 30 min. Pentagastrin gives rise to side effects only rarely, although nausea, faintness and hypotension have been reported.

Insulin Infusion of soluble insulin ($0.04 \text{ U kg}^{-1} \text{ h}^{-1}$) produces prolonged hypoglycaemia of constant degree, which in turn results in maximal secretory rates 30 to 60 min after the start of stimulation (Baron, 1978). Insulin is used as a gastric stimulant because the effect of insulin on the stomach is thought to be mediated by the vagal nerves and insulin-stimulated gastric juice therefore reflects the relationship between gastric innervation and the individual's gastric function. However, the gastric effects of insulin can be difficult to reproduce and since insulin gives rise to serious, and even lethal, side effects there is no good reason for using insulin to test antisecretory drugs.

Modified sham feeding Modified sham feeding involves chewing food and then spitting it out, with resultant stimulation of gastric secretion through reflex vagal effects. The acid response to modified sham feeding attains values which are about 50% of the maximal response to pentagastrin (Stenquist *et al.*, 1978). Peak rates of secretion are achieved after about 30 min. The secretory response is not constant and is not as reproducible as the response to exogenous secretagogues. The test is not associated with adverse reactions.

Food-stimulated gastric secretion The secretory response to a meal varies with the composition of the meal. The response to a meal containing protein, carbohydrate and fat lasts approximately 4 h, with the greatest fall in intragastric pH occurring about 90 to 120 min after eating, when most of the meal has emptied into the duodenum and the buffering effect of the proteins has been lost from the stomach (Malagelada *et al.*, 1976).

The gastric response to feed can be measured by allowing digestion to proceed for a specified period of time after ingestion and then evacuating the stomach, following which the residual stimulant effect of the food on gastric secretion can be measured by continuous aspiration from the stomach for a further period. This type of experimental schedule gives rise to a complex physiological and experimental situation; is poorly reproducible; and is therefore suitable only for qualitative evaluation of antisecretory drugs.

Alternatively, the gastric secretory response to food can be measured by the technique of intragastric titration (Richardson *et al.*, 1976). Aliquots of gastric contents are aspirated from the stomach every 2 min; the pH is measured and sodium hydroxide or sodium bicarbonate are infused into the stomach, with continuous vigorous mixing, so that the intraluminal contents are maintained at a pH which is preselected (e.g. pH 5). The secretion of acid can be calculated from the amount of alkali introduced into the

stomach in order to maintain the pH constant. The secretory response to food, as measured by intragastric titration, tends to be greater than the response to exogenous secretagogues, because intragastric titration overestimates the gastric secretory response to a meal (Spenny, 1979). Consequently, the effects of antisecretory drugs may be spuriously exaggerated. The fact that intragastric pH and intragastric pressure can be maintained at constant values during the test meal makes possible the reliable measurement of the effects of the antisecretory drugs on the release of gastrin in response to the meal.

Gastric secretion following a meal can also be measured without manipulating intragastric pH. Techniques are now available by which gastric secretion of acid and pepsin, and the rate of discharge of gastric contents into the duodenum can be measured by using multiple nonabsorbed markers to estimate the degree and rate of dilution of the meal by gastric and duodenal secretions, as well as the transfer of components of the meal and of the endogenous secretions from one compartment (e.g. stomach) to another (e.g. duodenum) and *vice versa* (Longstreth *et al.*, 1977; Moberg *et al.*, 1977).

c. 24-h intragastric profiles

Measurement of the 24 h profiles of intragastric pH, hydrogen ion concentration and peptic activity can be used to evaluate the effects of antisecretory drugs in subjects who are eating and drinking normally and who participate in normal daily activities (Pounder *et al.*, 1976). Test and control days involve identical activities, the latter being recorded in diaries. Meals on the two days are also identical and are prepared beforehand from the same (frozen) batches of food. Gastric contents are monitored hourly, or more frequently, by aspiration of small amounts of gastric contents through a naso-gastric tube, which is left in place during 48 h. This type of monitoring can be combined with complete aspiration of overnight gastric secretion (Walt *et al.*, 1981).

d. Which stimulant should be used to test antisecretory drugs?

The question cannot be answered unequivocally. In our opinion, it is desirable to test the antisecretory effects of drugs against nocturnal secretion, in view of the possible pathophysiological significance of this criterion of gastric function in ulcer disease. Similarly, monitoring 24 h intragastric conditions during treatment seems valuable in order to determine whether an antisecretory drug affects the postprandial and nocturnal peaks of intragastric acidity. Study of the inhibition of pentagastrin-stimulated secretion is useful as an index of the antisecretory action of a drug in a well-defined and reproducible experimental

situation, provided that the test is carried out properly by administering the drug directly into the duodenum.

Pharmacokinetic and pharmacodynamic studies

Study of absorption, distribution, metabolism and excretion of antisecretory drugs is necessary both to define rational dosage schedule and to determine the conditions for altering such schedules (e.g. the necessity to reduce the dosage frequency of a drug in patients with renal failure if the drug is mainly excreted in the urine). The principles and techniques of pharmacokinetic analysis are the same for antisecretory as for any other drugs and will not be discussed in detail here.

Two aspects warrant further comment. The peak plasma levels, and therefore the duration of action of antisecretory drugs, may be significantly influenced by relation of intake to meals. For example, when cimetidine is taken by a fasting subject, peak plasma levels are achieved within 45 min (Bodemar *et al.*, 1981). When taken with food, absorption of cimetidine is delayed, so that peak plasma levels (and maximal antisecretory effects) are not attained until 120 min after administration. The bioavailability of about 70% remains unchanged whether cimetidine is taken with food or not. Therapeutically, therefore, the maximal antisecretory efficacy of cimetidine is determined by the time of administration relative to meals. When given before meals, the maximal inhibition of gastric secretion occurs during the course of the meal — an effect which is required, for example, for the treatment of pancreatic insufficiency with enzyme supplements (Regan *et al.*, 1978). On the other hand, if cimetidine is given with a meal (Spence *et al.*, 1976), the maximal antisecretory effect is achieved at a time when intragastric pH is falling — a therapeutic effect which is desirable in the management of peptic ulcer disease.

In addition, the duration of action (the biological effect half-life) of antisecretory drugs should be determined. When drugs have an antisecretory effect which is closely correlated with plasma levels, the elimination half-life may be useful in predicting dosage schedules. For example, it has been suggested that the dose of cimetidine should be sufficient to provide sustained blood levels greater than 0.5 microgram per ml, since this value is the ID₅₀ for maximally stimulated gastric secretion (Burland *et al.*, 1975). However, in this connection it must be emphasized that we do not know to what extent and how long gastric secretion must be inhibited in order to permit successful treatment of ulcers. Some drugs (such as ranitidine (Berstad *et al.*, 1982) and benzimidazoles (Olbe *et al.*, 1982)) have antisecretory effects which do not correlate well with

plasma levels, since gastric inhibition may persist after the drug has been cleared from the circulation. In an attempt to establish directly the (clinically significant) 'duration of action' of this type of drug, studies with faulty design have often been carried out. Following a control test (e.g. with pentagastrin) in an untreated individual, the response to the same stimulant is measured at different times (e.g. 3, 6, 9 or 12 h) after administration of the drug (Damman & Simon, 1981). However, comparison with pre-treatment control values does not provide a valid measure of the degree of residual (i.e. drug-induced) gastric inhibition, because the response to a gastric stimulant may vary considerably at different times of day or night, particularly when repeated tests carried out during the same 24 h. In order to obtain valid information about the duration of action, the drug should be tested with prolonged sampling studies, carried out during separate (but identical) control and test periods.

Mode of action of antisecretory drugs

When a drug manifests gastric antisecretory effects, it is necessary in the first place to determine whether the decreased output of gastric juice is attributable to pharmacological inhibition of gastric secretion or to damage to the gastric mucosa. The latter phenomenon may not be endoscopically or histologically obvious and may then involve 'breaking the gastric mucosal barrier' — a functional term which indicates that the surface cells of the gastric mucosa have been so injured that instead of presenting an impermeable barrier to acid, the mucosa has become 'leaky' and permits the 'back diffusion' of acid into the mucosa (Davenport, 1976). Decreased amounts of acid in the gastric aspirate then reflect loss of secreted acid from the luminal contents into the mucosa, rather than inhibition of gastric secretion. The integrity of the gastric mucosal barrier after the administration of antisecretory drugs in man is studied by observing the flux of hydrogen ions and electrolytes out of, and into, the gastric lumen after a solution of known acidity and electrolyte content is introduced into the stomach (Thjodleifsson & Wormsley, 1975c). Such solutions contain an inert marker substance, which allows measurement of the magnitude of 'back diffusion' of acid, as well as loss of instilled solutions into the duodenum and dilution within the stomach. Coincident infusion of a different marker into the duodenum also permits estimates to be made of the degree of duodeno-gastric reflux (which may also decrease the amount of acid aspirated from the stomach, as a result of neutralisation by the bicarbonate in the regurgitated duodenal contents). Using this technique, it was demonstrated that

metiamide was a true inhibitor of gastric acid secretion (Thjodleifsson & Wormsley, 1975c) but that some prostaglandins reduced the apparent secretion of hydrogen ions by increasing transmucosal loss (O'Brien & Carter, 1975).

When an antisecretory drug is a true inhibitor of gastric secretion, it becomes necessary to determine whether the drug acts directly on the stomach — either through a specific effect on the parietal cells or by blocking the action of endogenous or exogenous stimulants on the respective parietal cell receptors.

The interaction of stimulants of gastric secretion with receptors on the parietal cells is assumed to follow Michaelis-Menten kinetics, so that if the secretory response is plotted against the rate of stimulation (dose of stimulant) a hyperbolic curve is obtained, the asymptotic rate of secretion representing $V_{\max}$ (the maximal rate of secretion) (Adam *et al.*, 1954). At high rates of secretion, large changes in the rate of stimulation produce only small changes in secretory rate, so that the effects of antisecretory drugs should be studied at levels of stimulation which provide less than about 50% of the maximal rate (Öbrink, 1980).

The secretory $V_{\max}$ is usually calculated by using one of the linear transformations of the Michaelis-Menten equation (Dowd & Riggs, 1965). If log-dose curves are then calculated for an inhibitor, the ED_{50} can be calculated. If a drug produces an increase in the ED_{50} (that is, more stimulant is required to elicit half-maximal response) while the CMR (calculated maximal response) remains unchanged, the inhibition is considered to be competitive. If the CMR is reduced (that is, if no amount of stimulation will produce as much secretion as can be obtained under normal (untreated) conditions) the drug is stated to show non-competitive inhibition. Thus, cimetidine competitively inhibits histamine-stimulated gastric secretion, but inhibits pentagastrin-stimulated secretion in a non-competitive manner (Aadland & Berstad, 1979).

It seems probable that some drugs act indirectly to inhibit gastric secretion by interfering with the production of endogenous gastric secretagogues. Such drugs may inhibit the release of gastrin, an effect which is easily established by serially monitoring blood levels of gastrin during the respective secretory studies. Alternatively, antisecretory drugs have been supposed to exert 'central' effects (e.g. sulpiride (McGuigan, 1978)), indirectly affecting gastric secretion by modulating central nervous control of gastrin release or parietal cell function; or have been proposed as 'mast cell stabilisers' (Davies *et al.*, 1981), preventing the release of histamine (supposedly necessary for parietal cell function) in the gastric mucosa. No systematic tests are available for examining these types of inhibitory effect.

Conclusions

Evaluation of new antisecretory drugs should now follow standardised protocols (as do randomised controlled clinical trials). Many published studies have had serious methodological flaws, attributable to lack of consideration of the physiological and kinetic factors which influence the gastric secretory response to stimulants and inhibitors. We suggest that candidate antisecretory drugs be investigated for their effects on nocturnal secretion and gastric secretion stimulated by a submaximal dose of pentagastrin, administered by intravenous infusion, with

the drug administered intraduodenally. Inhibition of gastric secretion under physiological circumstances should be studied by monitoring the effects of the drug on 24 h profiles of gastric luminal contents. Since the degree to which gastric secretion must be inhibited in order to exert a therapeutic effect in peptic ulceration and related disease is not known, any drug which shows antisecretory effects in man merits evaluation in clinical trials, providing that the drug is safe.

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